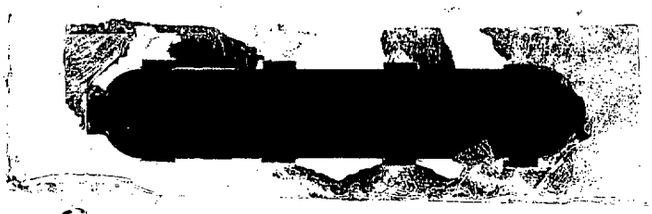
ISSUE CLASSIFICATION		
424	Class	468 Subclass



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U.S. UTILITY Patent Application

O.I.P.E.	PATENT DATE
SCANNED 8/2 Q.A. AG.	MAR 15 2005

APPLICATION NO.	CONT/PRIOR	CLASS	SUBCLASS	ART UNIT	EXAMINER
09/705630		~~514~~ 424	468	~~1614~~ 1615	~~WARE~~ YOUNG

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TITLE
Controlled release metformin compositions

PTO-2040
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ORIGINAL CLASS	ORIGINAL SUBCLASS	CROSS REFERENCE(S) CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					
424	468	424	457	474	480			

INTERNATIONAL CLASSIFICATION	
A61K	9/22
A61K	9/52

☐ Continued on Issue Slip Inside File Jacket

12/7/04 Formal Drawings (8 shts) set 11/3/00

☑ TERMINAL DISCLAIMER	DRAWINGS			CLAIMS ALLOWED	
	Sheets Drwg.	Figs. Drwg.	Print Fig.	Total Claims	Print Claim for O.G.
	8	8	1	~~25~~ 24	1

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☐ The term of this patent shall not extend beyond the expiration date of U.S Patent No. _____

☐ The terminal ___ months of this patent have been disclaimed.

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Chih-Ming Chen, Davie, FL;
Steve Jan, Coral Springs, FL;Joseph Chou, Manassas, VA;

** CONTINUING DATA **********

** FOREIGN APPLICATIONS **********

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** 02/01/2001

Foreign Priority claimed	STATE OR	SHEETS	TOTAL	INDEPENDENT
35 USC 119 (a-d) conditions met	COUNTRY	DRAWING	CLAIMS	CLAIMS
Verified and Acknowledged: Examiner's Signature Initials	FL	8	42	2

☐ yes ☒ no
☐ yes ☒ no ☐ Met after Allowance

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10018

TITLE
Controllec release metfo·min compositions

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PATENT APPLICATION

09705630

JC925 U.S. PTO
09/705630
11/03/00

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NOV 29 2004

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29.			70.	
30.			71.	
31.			72.	
32.			73.	
33.			74.	
34.			75.	
35.			76.	
36.			77.	
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38.			79.	
39.			80.	
40.			81.	
41.			82.	

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US006866866B1

(12) **United States Patent**
Chen et al.

(10) **Patent No.: US 6,866,866 B1**
(45) **Date of Patent: *Mar. 15, 2005**

(54) **CONTROLLED RELEASE METFORMIN COMPOSITIONS**

(75) Inventors: **Chih-Ming Chen**, Davie, FL (US); **Xiu-Xiu Cheng**, Davie, FL (US); **Steve Jan**, Coral Springs, FL (US); **Joseph Chou**, Manassas, VA (US)

(73) Assignee: **Andrx Labs, LLC**, Davie, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 162 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/705,630**

(22) Filed: **Nov. 3, 2000**

(51) **Int. Cl.**[7] **A61K 9/22**; A61K 9/52

(52) **U.S. Cl.** **424/468**; 424/457; 424/474; 424/480

(58) **Field of Search** 424/473, 468, 424/474, 475, 479, 480, 482; 514/635, 588, 591, 592, 593

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,845,770	A *	11/1974	Theeuwes et al.	424/427
5,688,518	A	11/1997	Ayer et al.	424/422
5,691,386	A	11/1997	Inman et al.	514/691
5,858,398	A	1/1999	Cho	424/450
5,955,106	A *	9/1999	Moeckel et al.	424/464
6,010,718	A	1/2000	Al-Razzak et al.	424/464
6,099,859	A *	8/2000	Cheng et al.	424/464
6,099,862	A *	8/2000	Chen et al.	424/473
6,284,275	B1 *	9/2001	Chen et al.	424/473
6,475,521	B1	11/2002	Timmins et al.	424/469

FOREIGN PATENT DOCUMENTS

WO	WO 99/47125 *	9/1999	
WO	WO 9947125 A1 *	9/1999	A61K/9/20
WO	9947125	9/1999	A61K/9/20
WO	WO 00/28989 *	5/2000	
WO	WO 0028989 A1 *	5/2000	A61K/31/353

OTHER PUBLICATIONS

Chiao, C. Sustained-Release Drug Delivery Systems Remington: The Science and Practice of Pharmacy, 1995, Mack Publishing Company, Easton, PA pp. 1660–1669.*

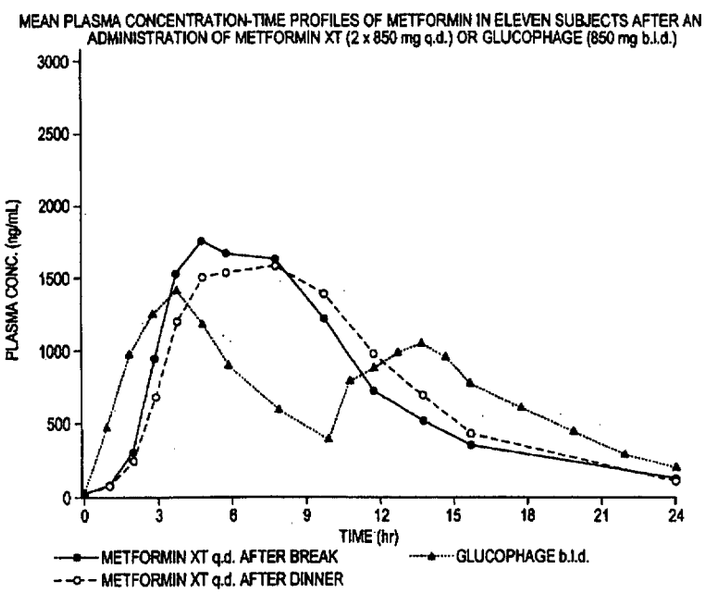
* cited by examiner

Primary Examiner—Thurman K. Page
Assistant Examiner—Micah Paul Young
(74) *Attorney, Agent, or Firm*—Davidson, Davidson & Kappel, LLC

(57) **ABSTRACT**

A composition for treating patients having non-insulin-dependent diabetes mellitus (NIDDM) by administering a controlled release oral solid dosage form containing preferably a biguanide drug such as metformin, on a once-a-day basis. The dosage form provides a mean time to maximum plasma concentration (T_{max}) of the drug which occurs at 5.5 to 7.5 hours after oral administration on a once-a-day basis to human patients. Preferably, the dose of drug is administered at dinnertime to a patient in the fed state.

25 Claims, 8 Drawing Sheets



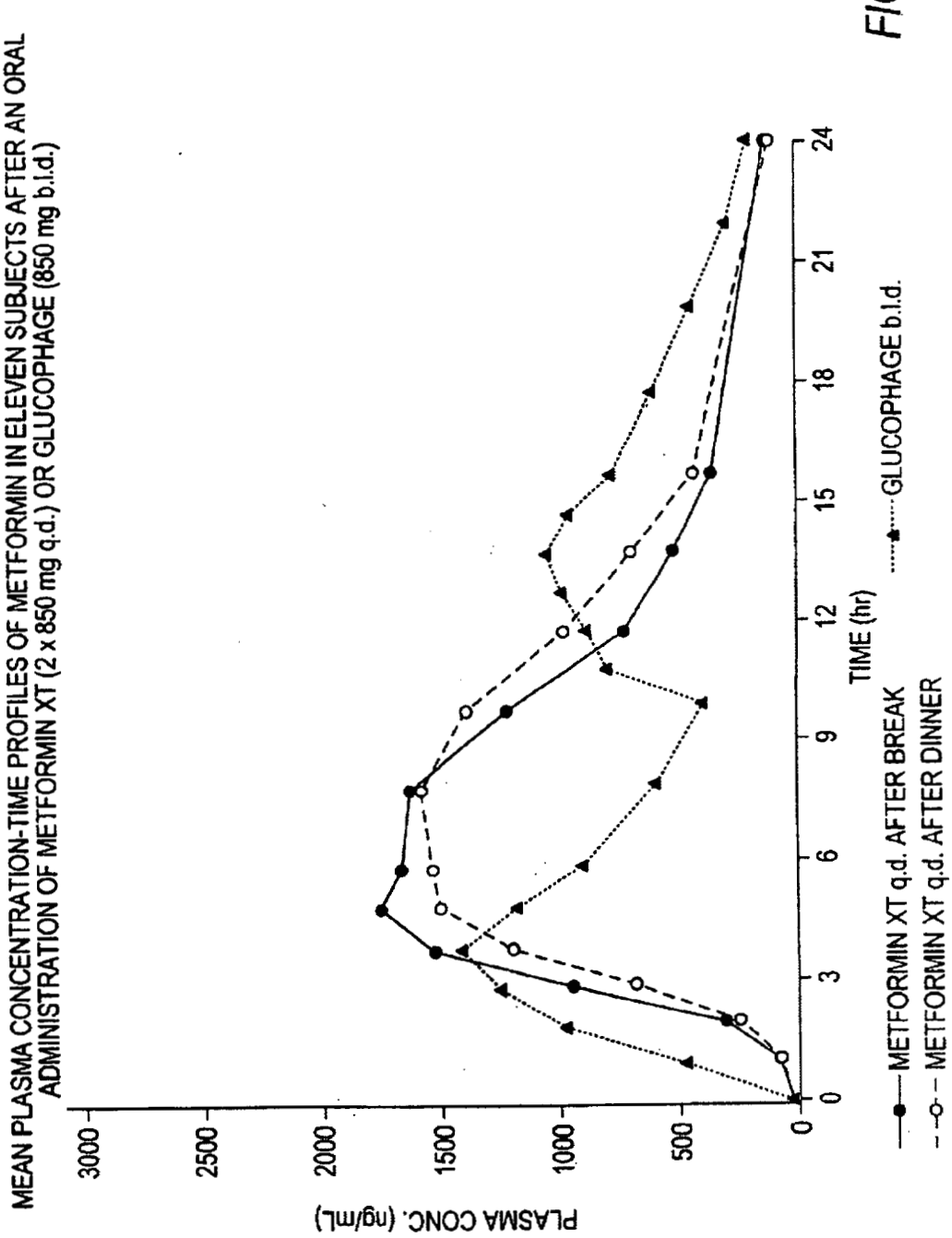

MEAN PLASMA CONCENTRATION-TIME PROFILES OF METFORMIN IN ELEVEN SUBJECTS AFTER AN ORAL ADMINISTRATION OF METFORMIN XT (2 x 850 mg q.d.) OR GLUCOPHAGE (850 mg b.i.d.)
PLASMA CONC. (ng/mL)
3000
2500
2000
1500
1000
500
0
0
3
6
9
12
15
18
21
24
TIME (hr)
METFORMIN XT q.d. AFTER BREAK
METFORMIN XT q.d. AFTER DINNER
GLUCOPHAGE b.i.d.

FIG. 1

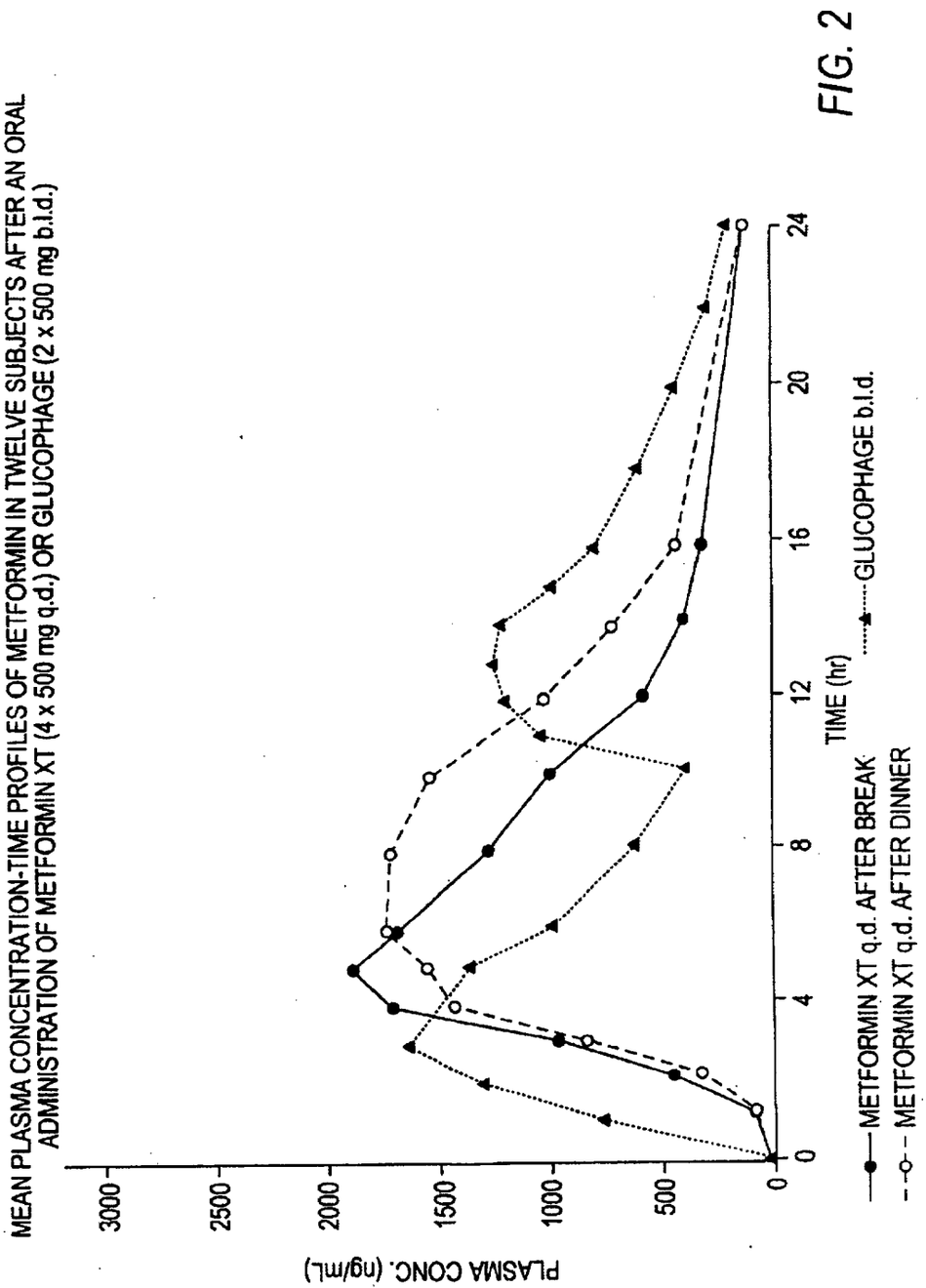

MEAN PLASMA CONCENTRATION-TIME PROFILES OF METFORMIN IN TWELVE SUBJECTS AFTER AN ORAL ADMINISTRATION OF METFORMIN XT (4 x 500 mg q.d.) OR GLUCOPHAGE (2 x 500 mg b.i.d.)
PLASMA CONC. (ng/mL)
3000
2500
2000
1500
1000
500
0
0
4
8
12
16
20
24
TIME (hr)
METFORMIN XT q.d. AFTER BREAK
METFORMIN XT q.d. AFTER DINNER
GLUCOPHAGE b.i.d.

FIG. 2

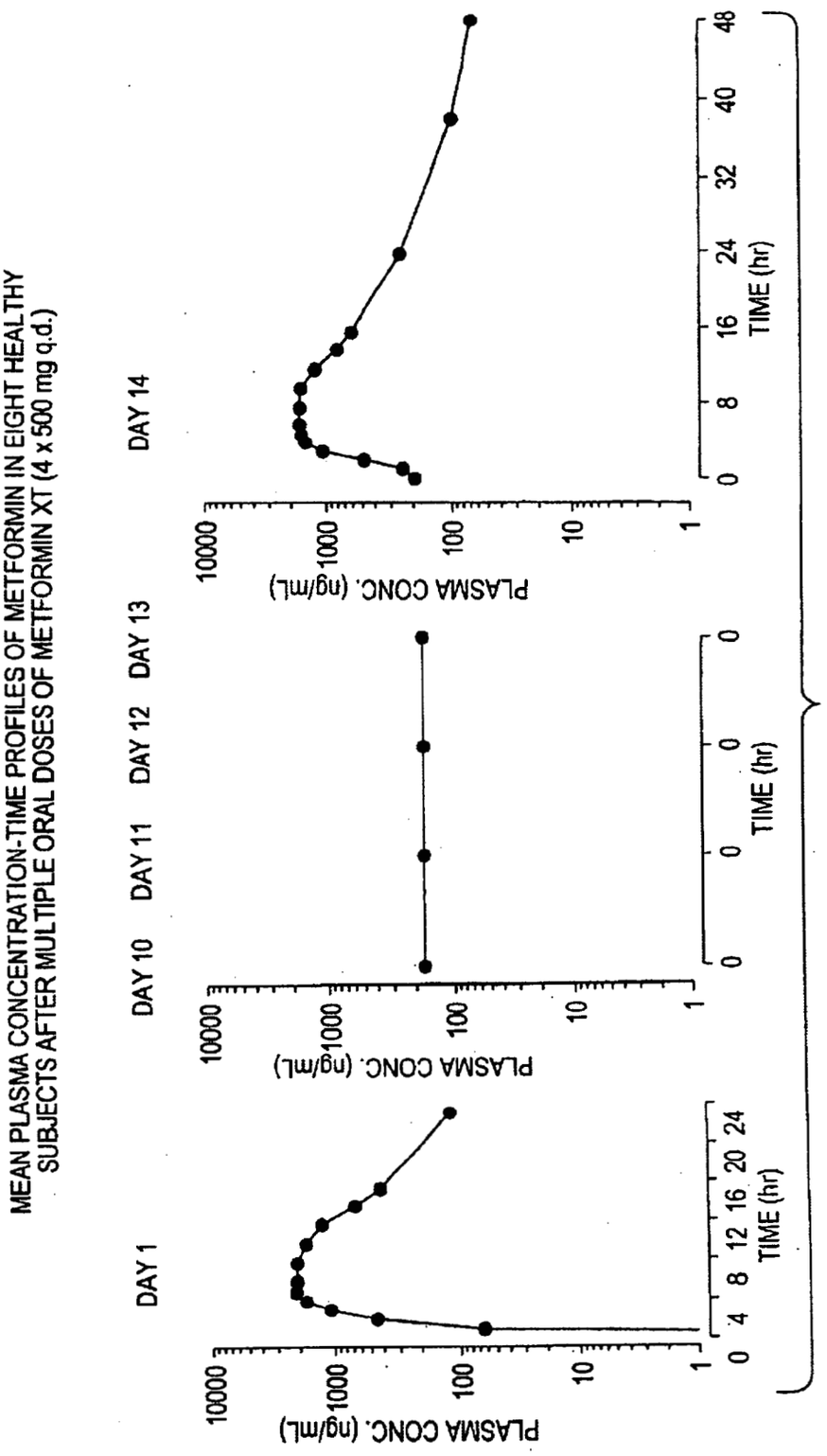

MEAN PLASMA CONCENTRATION-TIME PROFILES OF METFORMIN IN EIGHT HEALTHY SUBJECTS AFTER MULTIPLE ORAL DOSES OF METFORMIN XT (4 x 500 mg q.d.)
DAY 1
DAY 10
DAY 11
DAY 12
DAY 13
DAY 14
PLASMA CONC. (ng/mL)
TIME (hr)
10000
1000
100
10
1
0
4
8
12
16
20
24
32
40
48

FIG. 3

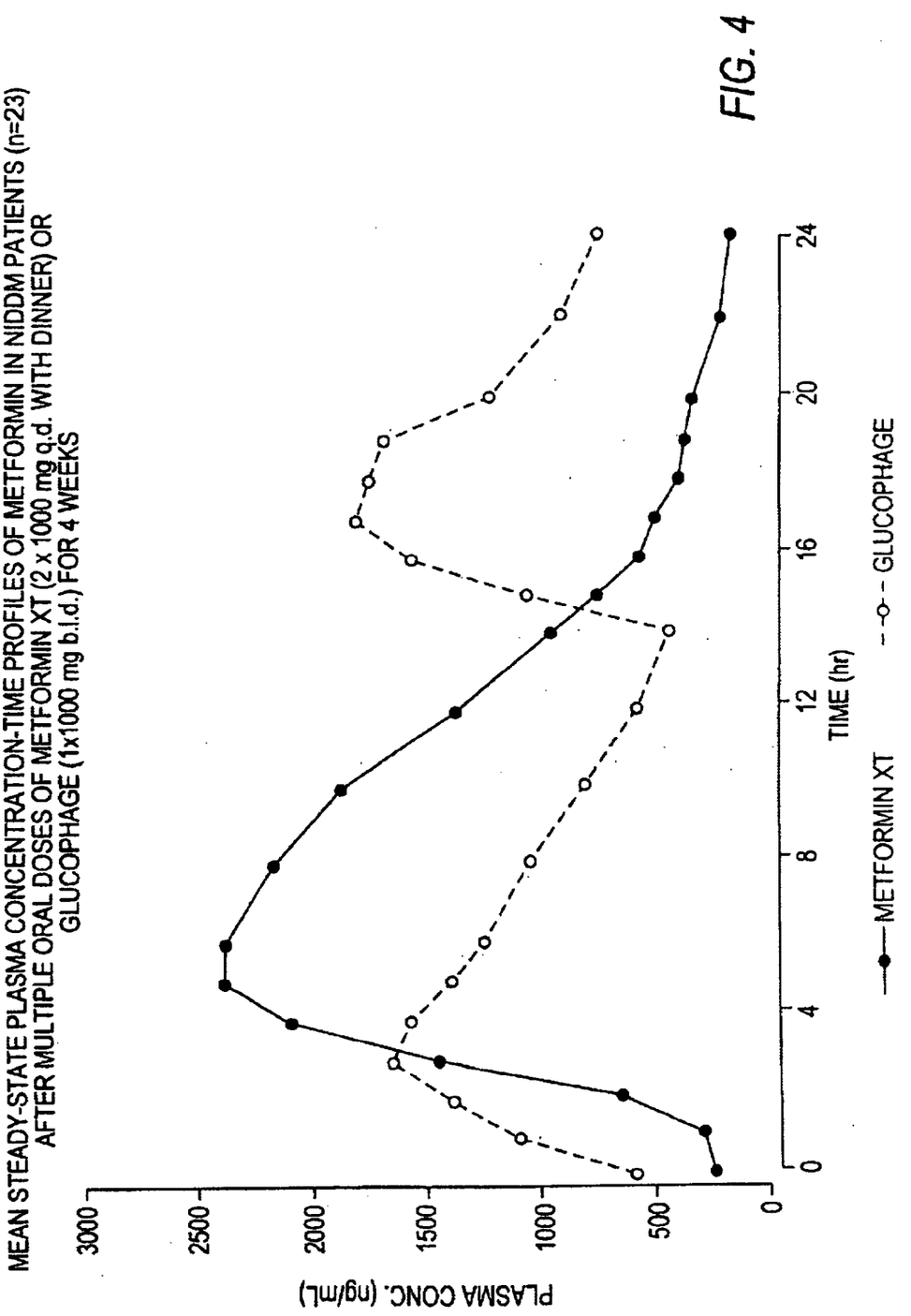

MEAN STEADY-STATE PLASMA CONCENTRATION-TIME PROFILES OF METFORMIN IN NIDDM PATIENTS (n=23)
AFTER MULTIPLE ORAL DOSES OF METFORMIN XT (2 x 1000 mg q.d. WITH DINNER) OR
GLUCOPHAGE (1x1000 mg b.i.d.) FOR 4 WEEKS
PLASMA CONC. (ng/mL)
3000
2500
2000
1500
1000
500
0
0
4
8
12
16
20
24
TIME (hr)
METFORMIN XT
GLUCOPHAGE

FIG. 4

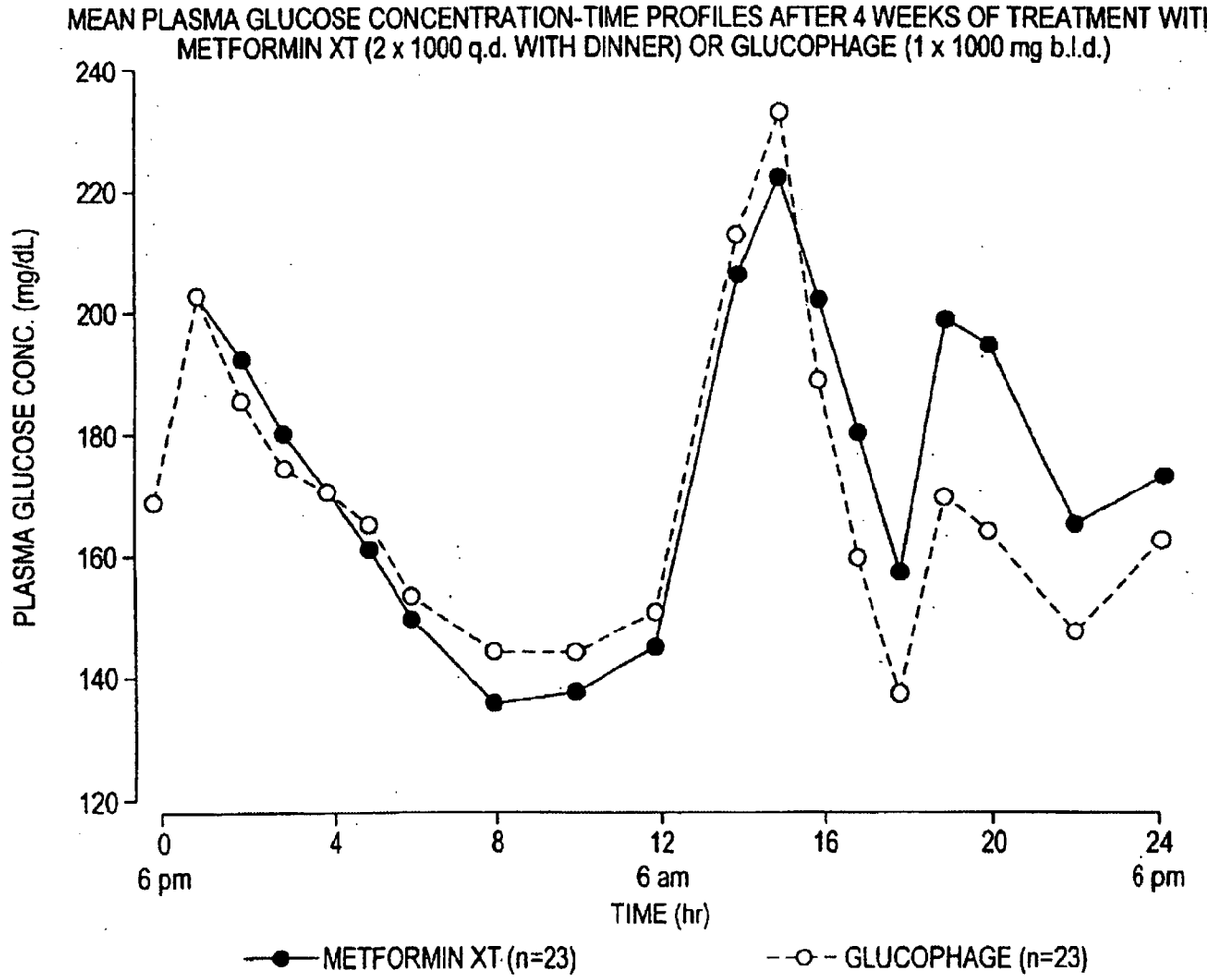

MEAN PLASMA GLUCOSE CONCENTRATION-TIME PROFILES AFTER 4 WEEKS OF TREATMENT WITH METFORMIN XT (2 x 1000 q.d. WITH DINNER) OR GLUCOPHAGE (1 x 1000 mg b.l.d.)
PLASMA GLUCOSE CONC. (mg/dL)
240
220
200
180
160
140
120
0
6 pm
4
8
12
6 am
16
20
24
6 pm
TIME (hr)
METFORMIN XT (n=23)
GLUCOPHAGE (n=23)

FIG. 5

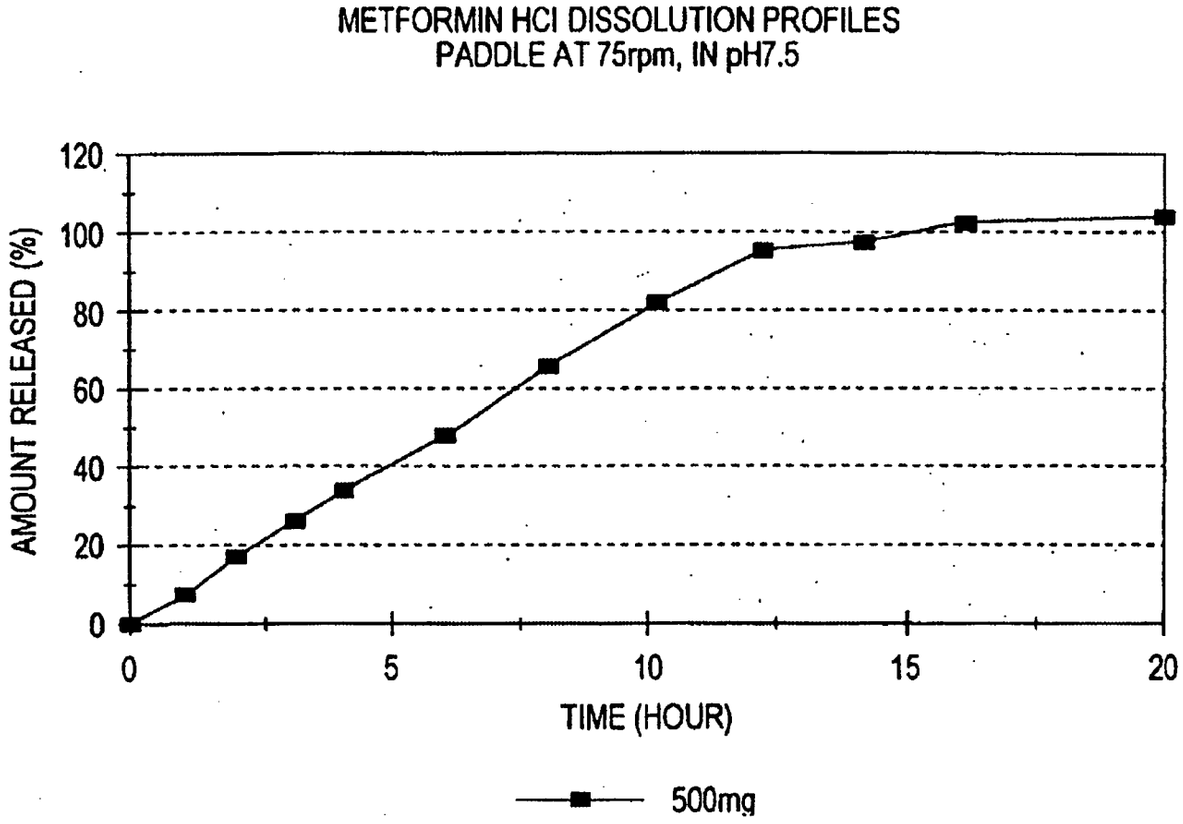

METFORMIN HCl DISSOLUTION PROFILES
PADDLE AT 75rpm, IN pH7.5
AMOUNT RELEASED (%)
120
100
80
60
40
20
0
0
5
10
15
20
TIME (HOUR)
500mg

FIG. 6

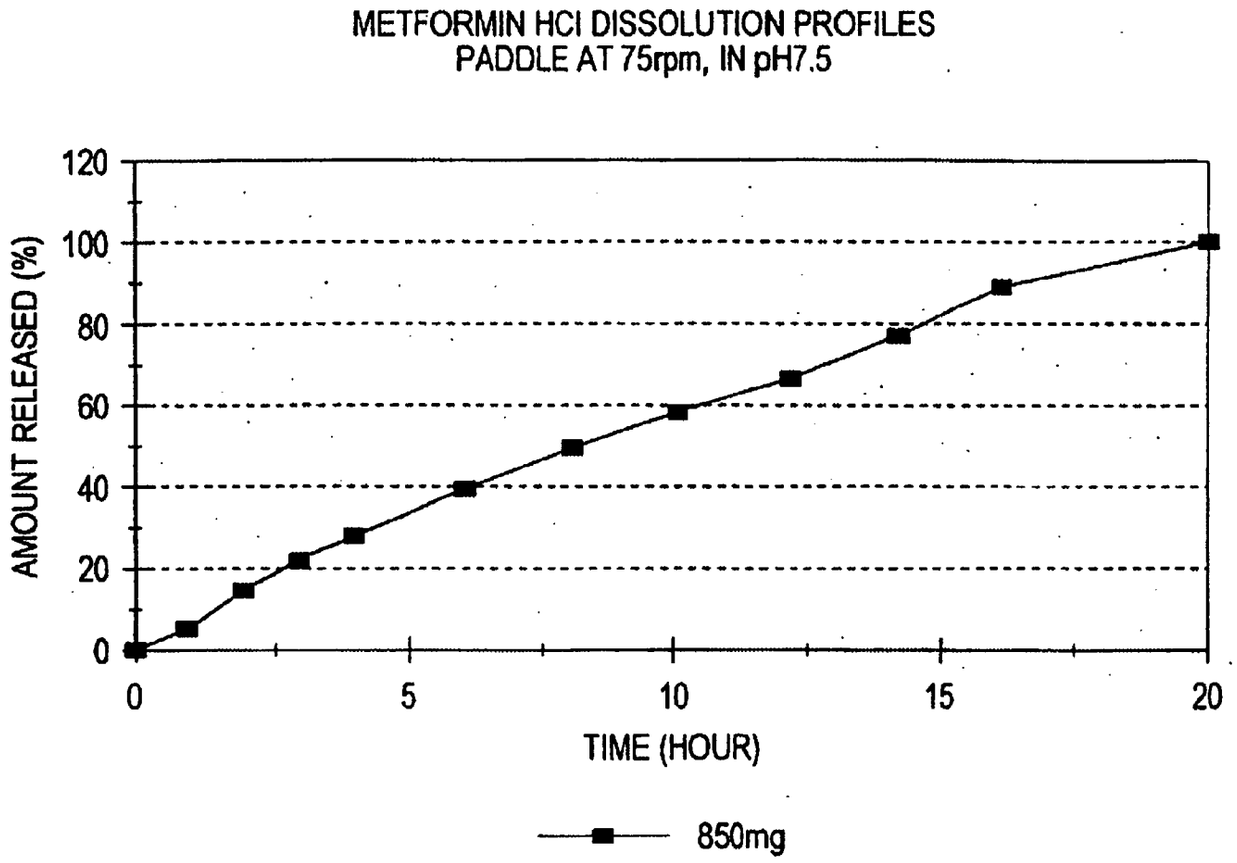

METFORMIN HCl DISSOLUTION PROFILES
PADDLE AT 75rpm, IN pH7.5
AMOUNT RELEASED (%)
120
100
80
60
40
20
0
0
5
10
15
20
TIME (HOUR)
850mg

FIG. 7

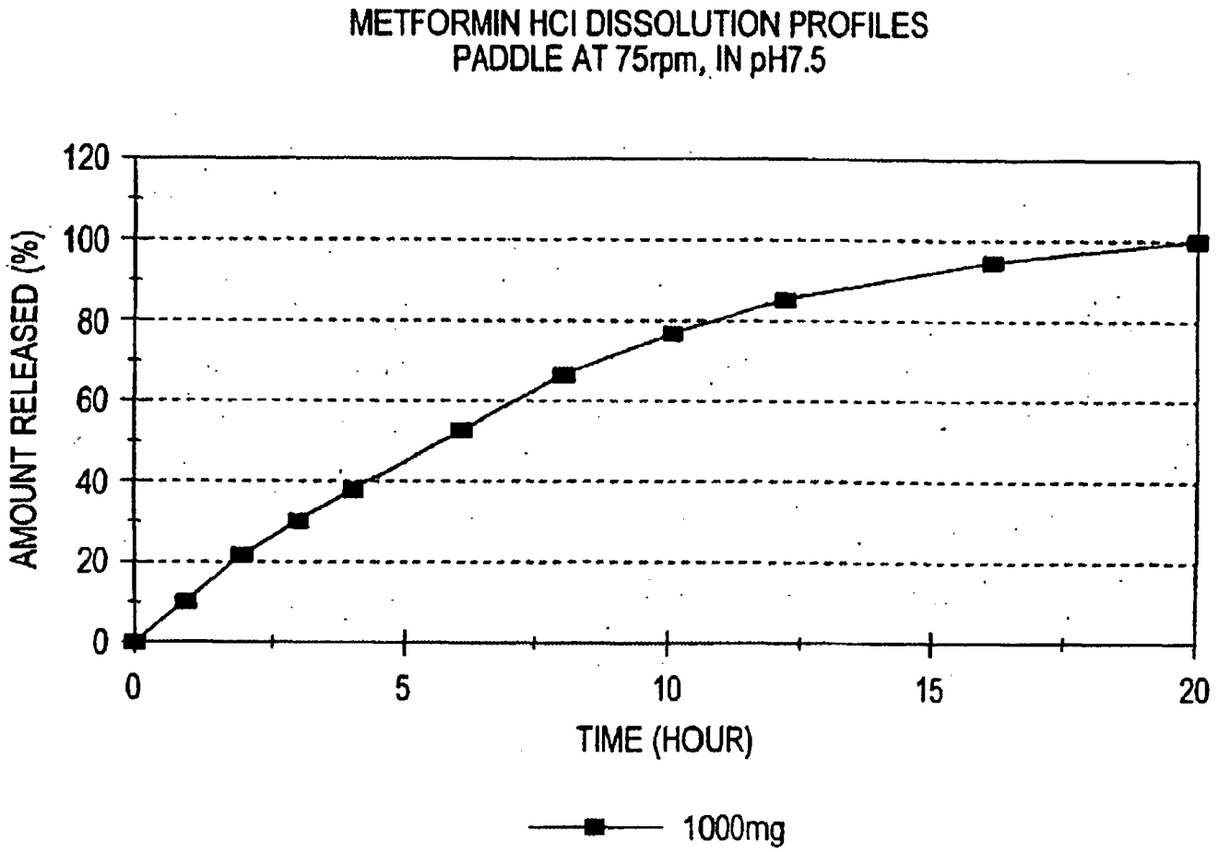

METFORMIN HCl DISSOLUTION PROFILES
PADDLE AT 75rpm, IN pH7.5
AMOUNT RELEASED (%)
120
100
80
60
40
20
0
0
5
10
15
20
TIME (HOUR)
1000mg

FIG. 8

CONTROLLED RELEASE METFORMIN COMPOSITIONS

BACKGROUND OF THE INVENTION

The present invention relates to controlled release unit dose formulations containing an antihyperglycemic drug. More specifically, the present invention relates to an oral dosage form comprising a biguanide such as metformin or buformin or a pharmaceutically acceptable salt thereof such as metformin hydrochloride or the metformin salts described in U.S. Pat. Nos. 3,957,853 and 4,080,472 which are incorporated herein by reference.

In the prior art, many techniques have been used to provide controlled and extended-release pharmaceutical dosage forms in order to maintain therapeutic serum levels of medicaments and to minimize the effects of missed doses of drugs caused by a lack of patient compliance.

In the prior art are extended release tablets which have an osmotically active drug core surrounded by a semipermeable membrane. These tablets function by allowing a fluid such as gastric or intestinal fluid to permeate the coating membrane and dissolve the active ingredient so it can be released through a passageway in the coating membrane or if the active ingredient is insoluble in the permeating fluid, pushed through the passageway by an expanding agent such as a hydrogel. Some representative examples of these osmotic tablet systems can be found in U.S. Pat. Nos. 3,845,770, 3,916,899, 4,034,758, 4,077,407 and 4,783,337. U.S. Pat. No. 3,952,741 teaches an osmotic device wherein the active agent is released from a core surrounded by a semipermeable membrane only after sufficient pressure has developed within the membrane to burst or rupture the membrane at a weak portion of the membrane.

The basic osmotic device described in the above cited patents have been refined over time in an effort to provide greater control of the release of the active ingredient. For example U.S. Pat. Nos. 4,777,049 and 4,851,229 describe an osmotic dosage form comprising a semipermeable wall surrounding a core. The core contains an active ingredient and a modulating agent wherein the modulating agent causes the active ingredient to be released through a passageway in the semipermeable membrane in a pulsed manner. Further refinements have included modifications to the semipermeable membrane surrounding the active core such as varying the proportions of the components that form the membrane; i.e., U.S. Pat. Nos. 5,178,867, 4,587,117 and 4,522,625 or increasing the number of coatings surrounding the active core; i.e., U.S. Pat. Nos. 5,650,170 and 4,892,739.

Although vast amounts of research has been performed on controlled or sustained release compositions and in particular on osmotic dosage forms, very little research has been performed in the area of controlled or sustained release compositions that employ antihyperglycemic drugs.

Metformin is an oral antihyperglycemic drug used in the management of non-insulin-dependent diabetes mellitus (NIDDM). It is not chemically or pharmacologically related to oral sulfonylureas. Metformin improves glucose tolerance in NIDDM patients by lowering both basal and postprandial plasma glucose. Metformin hydrochloride is currently marketed as GLUCOPHAGE® tablets by Bristol-Myers Squibb Co. Each GLUCOPHAGE® tablet contains 500, 850 or 1000 mg of metformin hydrochloride. There is no fixed dosage regimen for the management of hyperglycemia in diabetes mellitus with GLUCOPHAGE®. Dosage of GLUCOPHAGE® is individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended dose of 2550 mg per day.

Metformin has been widely prescribed for lowering blood glucose in patients with NIDDM. However, being a short acting drug, metformin requires twice-daily (b.i.d.) or three-times-a-day (t.i.d.) dosing. Adverse events associated with metformin use are often gastrointestinal in nature (e.g., anorexia, nausea, vomiting and occasionally diarrhea, etc.). These adverse events may be partially avoided by either reducing the initial and/or maintenance dose or using an extended-release dosage form. Another clear advantage of an extended release dosage form is a reduction in the frequency of administration. All of these findings suggest that an extended-release dosage form of metformin may improve the quality of therapy in patients with NIDDM and the safety profile relative to a conventional dosage form.

The limited work on controlled or sustained release formulations that employ antihyperglycemic drugs such as metformin hydrochloride includes the combination of the antihyperglycemic drug and an expanding or gelling agent to control the release of the drug from the dosage form. This research is exemplified by the teachings of WO 96/08243 and by the GLUCOPHAGE® metformin HCl product.

It is reported in the 50th Edition of the Physicians' Desk Reference, copyright 1996, p. 753, that food decreases the extent and slightly delays the absorption of metformin delivered by the GLUCOPHAGE® dosage form. This decrease is shown by approximately a 40% lower peak concentration, a 25% lower bioavailability and a 35-minute prolongation of time to peak plasma concentration following administration of a single GLUCOPHAGE® tablet containing 850 mg of metformin HCl with food compared to the similar tablet administered under fasting conditions.

A controlled release metformin dosage form is also described in WO 99/47128. This a reference describes a controlled release delivery system for metformin which includes an inner solid particulate phase formed of substantially uniform granules containing metformin and one or more hydrophilic polymers, one or more hydrophobic polymers and one or more hydrophobic materials, and an outer continuous phase in which the above granules are embedded and dispersed throughout. The outer continuous phase includes one or more hydrophilic polymers, one or more hydrophobic polymers and one or more hydrophobic materials.

Our own WO 99/47125 discloses controlled release metformin formulations providing a Tmax from 8 to 12 hours.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of the present invention to provide a controlled or sustained release of an antihyperglycemic drug which provides effective control of blood glucose levels in humans.

It is a further object of the present invention to provide a method of treating human patients with non-insulin-dependent diabetes mellitus (NIDDM) on a once-a-day basis with an antihyperglycemic drug which provides effective control of blood glucose levels in humans.

It is a further object of the present invention to provide formulations for treating human patients with non-insulin-dependent diabetes mellitus (NIDDM) which provides advantages over the state-of-the-art, and which may be administered on a once-a-day basis by itself or together with other antidiabetic agents, and methods thereof.

It is a further object of the present invention to provide a controlled or sustained release formulation of an antihyper-

glycernic drug wherein the bioavailability of the drug is not decreased by the presence of food.

It is a further object of the present invention to provide a controlled or sustained release formulation of an antihyperglycemic drug that does not employ an expanding polymer.

It is also a further object of the present invention to provide a controlled or sustained release formulation of an antihyperglycemic drug that can provide continuous and non-pulsating therapeutic levels of the drug to an animal or human in need of such treatment over a twelve hour to twenty-four hour period.

It is an additional object of other embodiments of the present invention to provide a controlled or sustained release formulation for an antihyperglycemic drug that obtains peak plasma levels from 5.5 to 7.5 hours after administration under various conditions. Alternatively, the time to peak plasma levels are from 6.0 to 7.0, from 5.5 to 7.0 or from 6.0 to 7.5.

It is also an object of this invention to provide a controlled or sustained release pharmaceutical formulation having a homogeneous core wherein the core component may be made using ordinary tablet compression techniques.

In accordance with the above-mentioned objects and others, the present invention provides a controlled release oral dosage form comprising an antihyperglycemic drug, preferably a biguanide (e.g., metformin or a pharmaceutically acceptable salt thereof) that is suitable for providing once-a-day administration of the drug, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the drug from 5.5 to 7.5 hours after administration. The dosage form comprises the drug and a membrane. In certain preferred embodiments, the dosage form comprises a tablet.

In preferred embodiments, the controlled release oral dosage form of the present invention is a tablet comprising:

(a) a core comprising:

(i) the antihyperglycemic drug;

(ii) optionally a binding agent; and

(iii) optionally an absorption enhancer;

(b) a membrane coating surrounding the core; and

(c) at least one passageway in the membrane.

When the drug is metformin or a pharmaceutically acceptable salt thereof and is administered on a once-a-day basis, the daily dose may vary, e.g., from about 500 mg to about 2500 mg. Such daily dose may be contained in one controlled-release dosage form of the invention, or may be contained in more than one such dosage form. For example, a controlled-release metformin dosage form may be formulated to contain about 1000 mg of the drug, and two of said dosage form may be administered together to provide once-a-day metformin therapy. The daily dose of the drug (i.e. metformin or pharmaceutically acceptable salt thereof) may range from about 500 mg to about 2500 mg, from about 1000 mg to about 2500 mg, or from about 2000 mg to about 2500 mg, depending on the clinical needs of the patient.

In certain preferred embodiments, the controlled release solid oral dosage form of the present invention provides a width at 50% of the height of a mean plasma concentration/time curve of the drug (e.g., of metformin) from about 4.5 to about 13 hours, more preferably from about 5.5 to about 10 hours, more preferably from about 6 to about 8 hours.

In certain embodiments, the controlled release oral dosage form of the present invention provides a mean maximum plasma concentration (C_{max}) of the antihyperglycemic drug which is more than about seven times the mean plasma level of said drug at about 24 hours after administration. In preferred embodiments, the controlled release oral dosage form of the present invention provides a mean maximum plasma concentration (C_{max}) of the drug which is from about 7 times to about 14 times the plasma level of the drug at about 24 hours after the administration, more preferably from about 8 times to about 12 times the plasma level of the drug at about 24 hours after administration.

In certain embodiments of the present invention, when the drug is metformin or a pharmaceutically acceptable salt thereof, the controlled release oral dosage form provides a mean maximum plasma concentration (C_{max}) of the drug that is about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin, more preferably about 1700 ng/ml to about 2000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

In certain embodiments of the present invention, when the drug is metformin or a pharmaceutically acceptable salt thereof, the controlled release dosage form provides a mean $AUC_{0\text{-}24hr}$ that is about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin; preferably about 17200 ng.hr/ml to about 26500 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin; more preferably about 19800 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

In certain embodiments of the invention, the administration of the antihyperglycemic drug, e.g., at least one metformin dosage form provides a mean $AUC_{0\text{-}24hr}$ from at least 80%, preferably at least 90% of the mean $AUC_{0\text{-}24}$ provided by administration of the reference standard (GLUCOPHAGE) twice a day, wherein the daily dose of the reference standard is equal to the once-a day dose of metformin administered in the controlled release oral dosage form of the present invention.

In certain embodiments of the present invention, the controlled release dosage form exhibits the following dissolution profiles of the antihyperglycemic drug (e.g., metformin) when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal gastric fluid (pH 7.5 phosphate buffer) at 37° C.: 0–30% of the drug released after 2 hours; 10–45% of the drug released after 4 hours; 30–90% of the drug released after 8 hours; not less than 50% of the drug released after 12 hours; not less than 60% of the drug released after 16 hours; and not less than 70% of the drug released after 20 hours.

In certain preferred embodiments, the controlled release solid oral dosage form exhibits the following dissolution profiles when tested in USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal gastric fluid (pH 7.5 phosphate buffer) at 37° C.: 0–25% of the drug (e.g., metformin or a pharmaceutically acceptable salt thereof) released after 2 hours; 20–40% of the drug released after 4 hours; 45–90% of the drug released after 8 hours; not less than 60% of the drug released after 12 hours; not less than 70% of the drug released after 16 hours; and not less than 80% of the drug released after 20 hours.

With respect to embodiments of the present invention where the antihyperglycemic drug is metformin, it has been found that drugs such as metformin provide substantially linear pharmacokinetics up to a level of about 2 grams per day. Therefore, it is contemplated for purposes of the present invention that a given plasma level (e.g., C_{max}) of metformin per specified dose will be directly proportional to other doses of metformin. Such proportional doses and plasma levels are contemplated to be within the scope of the invention and to be within the scope of the appended claims.

The dosage form of the present invention can provide therapeutic levels of the antihyperglycemic drug for twelve to twenty-four hour periods and does not exhibit a decrease in bioavailability if taken with food. In fact, a slight increase in the bioavailability of the antihyperglycemic drug is observed when the controlled release dosage form of the present invention is administered with food. In a preferred embodiment, the dosage form can be administered once-a-day, ideally with or after a meal, preferably with or after the evening meal, and provides therapeutic levels of the drug throughout the day with peak plasma levels being obtained between 5.5 to 7.5 hours after administration.

The present invention is also directed to a method of lowering blood glucose levels in human patients needing treatment for non-insulin-dependent diabetes mellitus (NIDDM), comprising orally administering to human patients on a once-a-day basis a dose of a drug comprising a biguanide (e.g., metformin or a pharmaceutically acceptable salt thereof), said drug being contained in at least one solid oral controlled release dosage form of the present invention. When the drug is metformin, the daily dose of the drug may be from about 500 mg to about 2500 mg, from about 1000 mg to about 2500 mg, or from about 2000 mg to about 2500 mg, depending on the clinical needs of the patient.

The controlled release dosage form of the present invention provides a delayed T_{max}, as compared to the T_{max} provided by GLUCOPHAGE. The delayed T_{max} occurs from 5.5 to 7.5 hours after administration. If the drug (e.g., metformin) is administered at dinner time, the T_{max} would occur during the time when gluconeogenesis is usually at its highest (e.g., around 2 a.m.).

The present invention also includes a method of treating patients with NIDDM comprising orally administering to human patients on a once-a-day basis a dose of a drug comprising a biguanide (e.g., metformin or a pharmaceutically acceptable salt thereof), contained in at least one oral controlled release dosage form of the present invention. When the drug is metformin, the daily dose of the drug maybe from about 500 mg to about 2500 mg, from about 1000 mg to about 2500 mg, or from about 2000 mg to about 2500 mg, depending on the clinical needs of the patient. In certain embodiments, the method of treatment according to the present invention involves once-per-day metformin monotherapy as an adjunct to diet to lower blood glucose in patients with NIDDM whose hyperglycemia may not be satisfactorily managed on diet alone. In certain other embodiments, the once-a-day metformin therapy of the present invention may be used concomitantly with a sulfonylurea, e.g., when diet and monotherapy with a sulfonylurea alone do not result in adequate glycemic control. In certain other embodiments, the once-a-day metformin therapy of the present invention may be used concomitantly with a glitazone, e.g., when diet and monotherapy with a glitazone alone do not result in adequate glycemic control.

The present invention is further directed to a method of controlling the serum glucose concentration in human patients with NIDDM, comprising administering to patients having NIDDM on a once-a-day basis, preferably at dinner time, an effective dose of a biguanide (e.g., metformin) contained in at least one oral controlled release dosage form of the present invention.

The present invention further includes a controlled-release dosage form of a drug comprising a biguanide (e.g., metformin) suitable for once-a-day administration to human patients with NIDDM, the dosage form comprising an effective amount of the drug to control blood glucose levels for up to about 24 hours and an effective amount of a controlled-release carrier to provide controlled release of the drug with a mean time to maximum plasma concentration (T_{max}) of the drug from 5.5 to 7.5 hours after administration and a width at 50% of the height of a mean plasma concentration/time curve of the drug from about 6 to about 13 hours. In preferred embodiments, the administration of the controlled-release dosage form occurs at fed state, more preferably at dinner time.

In certain preferred embodiments, the controlled-release dose of the drug (e.g., metformin or a pharmaceutically acceptable salt thereof) according to the present invention is provided by one or more of a controlled-release tablet comprising

(a) a core comprising:
  (i) the antihyperglycemic drug (e.g., metformin or a pharmaceutically acceptable salt thereof);
  (ii) optionally a binding agent; and
  (iii) optionally an absorption enhancer;
(b) a membrane coating surrounding the core; and
(c) at least one passageway in the membrane.

In certain preferred embodiments, the mean time to maximum plasma concentration of the drug is reached from 6.5 to 7.5 hours after administration at dinner time.

In certain embodiments of the invention when the drug is a biguanide (e.g. metformin or a pharmaceutically acceptable salt thereof), the controlled release dosage form provides upon single administration, a higher mean fluctuation index in the plasma than an equivalent dose of an immediate release composition administered as two equal divided doses, one divided dose at the start of the dosing interval and the other divided dose administered 12 hours later, preferably maintaining bioavailability from at least 80% preferably from at least 90% of the immediate release composition.

In certain embodiments of the present invention, the mean fluctuation index of the dosage form is from about 1 to about 4, preferably about 2 to about 3, more preferably about 2.5.

In certain embodiments of the invention which exhibit a higher mean fluctuation index in the plasma than an equivalent dose of an immediate release composition administered as two equal divided doses, the ratio of the mean fluctuation index between the dosage form and the immediate release composition is about 3:1, preferably about 2:1, more preferably 1.5:1.

When the drug is metformin or a pharmaceutically acceptable salt thereof, the doses of drug which exhibit the above disclosed mean fluctuation indexes can be any effective dose administered to a patient with NIDDM for the reduction of serum glucose levels. For example, the dose can from about 500 mg to about 2500 mg, from about 1000 mg to about 2000 mg or from about 850 mg to about 1700 mg metformin or pharmaceutically acceptable salt thereof.

The drugs which may used in conjunction with the present invention include those drugs which are useful for the treatment of non-insulin-dependent diabetes mellitus (NIDDM), including but not limited to biguinides such as metformin or buformin or pharmaceutically acceptable salts thereof. When the drug used in the present invention is metformin, it is preferred that the metformin be present in a salt form, preferably as metformin hydrochloride.

The term "metformin" as it is used herein means metformin base or any pharmaceutically acceptable salt e.g., metformin hydrochloride.

The term "dosage form" as it is used herein means at least one unit dosage form of the present invention (e.g. the daily dose of the antihyperglycemic agent can be contained in 2

unit dosage forms of the present invention for single once-a-day administration).

The term "morning" as it is used herein with respect to the dosing of the controlled release formulations of the invention means that the controlled release formulation is orally administered early in the day after the patient has awakened from overnight sleep, generally between about 6 a.m. and 11 a.m. (regardless of whether breakfast is eaten at that time, unless so specified herein).

The term "dinnertime" or "at dinner" as it is used herein with respect to the dosing of the controlled release formulations of the invention means that the controlled release formulation is orally administered at a time when dinner is normally eaten (regardless of whether a meal is actually eaten at that time, unless so specified herein), generally between about 4 p.m. and 8 p.m.

The term "bedtime" as it is used herein with respect to the dosing of the controlled release formulations of the invention means that the controlled release formulation is orally administered before the patient goes to bed in the evening, generally between about 8 p.m. and 12 p.m.

The term "therapeutically effective reduction" when used herein is meant to signify that blood glucose levels are reduced by approximately the same amount as an immediate release reference standard (e.g., GLUCOPHAGE®) or more, when the controlled release dosage form is orally administered to a human patient on a once-a-day basis.

The term "sustained release" and "controlled release" are used interchangeably in this application and are defined for purposes of the present invention as the release of the drug from the dosage form at such a rate that when a once-a-day dose of the drug is administered in the sustained release or controlled-release form, blood (e.g., plasma) concentrations (levels) of the drug are maintained within the therapeutic range but below toxic levels over a period of time from about 12 to about 24 hours. When the drug used in the present invention is metformin (preferably metformin hydrochloride) the controlled release solid oral dosage form containing such drug is also referred to as "Metformin XT."

The term "C_{max}" is the highest plasma concentration of the drug attained within the dosing interval, i.e., about 24 hours.

The term "C_{min}" is the minimum plasma concentration of the drug attained within the dosing interval, i.e. about 24 hours.

The term "C_{avg}" as used herein, means the plasma concentration of the drug within the dosing interval, i.e. about 24-hours, and is calculated as AUC/dosing interval.

The term "T_{max}" is the time period which elapses after administration of the dosage form at which the plasma concentration of the drug attains the highest plasma concentration of drug attained within the dosing interval (i.e., about 24 hours).

The term "AUC" as used herein, means area under the plasma concentration-time curve, as calculated by the trapezoidal rule over the complete 24-hour interval.

The term "steady state" means that the blood plasma concentration curve for a given drug does not substantially fluctuate after repeated doses to dose of the formulation.

The term "single dose" means that the human patient has received a single dose of the drug formulation and the drug plasma concentration has not achieved steady state.

The term "multiple dose" means that the human patient has received at least two doses of the drug formulation in accordance with the dosing interval for that formulation (e.g., on a once-a-day basis). Patients who have received multiple doses of the controlled release formulations of the invention may or may not have attained steady state drug plasma levels, as the term multiple dose is defined herein.

The term "a patient" means that the discussion (or claim) is directed to the pharmacokinetic parameters of an individual patient and/or the mean pharmacokinetic values obtained from a population of patients, unless further specified.

The term "mean", when preceding a pharmacokinetic value (e.g. mean T_{max}) represents the arithmetic mean value of the pharmacokinetic value taken from a population of patients unless otherwise specified (e.g. geometric mean).

The term "Degree of Fluctuation" is expressed as $(C_{max}-C_{min})/C_{avg}$.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a graph showing the relative bioavailability of the metformin XT formulation of Example 2 to GLUCOPHAGE® for Clinical Study 2.

FIG. **2** is a graph showing the relative bioavailability of the metformin XT formulation of Example 1 (500 mg) to GLUCOPHAGE® for Clinical Study 3.

FIG. **3** is a graph showing the difference in plasma concentration-time profiles of metformin in eight healthy volunteers between Day **1** and Day **14** dosing following oral administration of the metformin XT formulation of Example 1, 4×500 mg q.d. for 14 days for Clinical Study 4.

FIG. **4** is a graph showing the mean plasma profiles and values of pharmacokinetic parameters of the metformin XT formulation of Example 3 for Clinical Study 5.

FIG. **5** is a graph showing the mean plasma glucose concentration-time profiles after 4 weeks of treatment with the metformin XT formulation of Example 3 and GLUCOPHAGE® for Clinical Study 5.

FIG. **6** is a graph showing the dissolution profile of a 500 mg controlled release metformin formulation of Example 1 of the present invention.

FIG. **7** is a graph showing the dissolution profile of a 850 mg controlled release metformin formulation of Example 2 of the present invention.

FIG. **8** is a graph showing the dissolution profile of a 1000 mg controlled release metformin formulation of Example 3 of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The term antihyperglycemic drugs as used in this specification refers to drugs that are useful in controlling or managing noninsulin-dependent diabetes mellitus (NIDDM). Preferably, the antihyperglycemic drug is a biguanide such as metformin or buformin or a pharmaceutically acceptable salt thereof such as metformin hydrochloride.

It has surprisingly been found that when biguanides such as metformin are administered orally in a controlled release dosage form suitable for once-a-day dosing in the "fed" state, preferably at dinner, the bioavailability is improved as compared to the administration of the controlled release dosage form in the "fasted" state. This is in contrast to GLUCOPHAGE®, which exhibits opposite characteristics. In accordance with the methods and dosage forms of the present invention, it has been determined that the patients suffering from NIDDM achieve improved results (e.g., lowered blood glucose levels) than GLUCOPHAGE® administered according to accepted protocols, e.g., on a twice-a-day basis.

The methods and dosage forms of the invention provide the further advantage in that when dosed at dinnertime, the

controlled release formulations of the invention provide a T_{max} (from 5.5 to 7.5 hours) after oral administration (which T_{max} is delayed relative to the reference standard, GLUCOPHAGE®), such that the level of drug is greatest at the time when human patients are manufacturing glucose at highest levels. Gluconeogenesis is well known to those skilled in the art to be greatest at night. Thus, in accordance with the invention, the T_{max} of the drug occurs for example between 11:30 p.m. and 1:30 a.m., based on a dose administered at 6:00 p.m. Likewise, such administration of the dosage form provides lower drug levels during the day (e.g. the afternoon) when gluconeogenesis is lower than at night. Also, the invention preferably provides the added benefit of lowering insulin levels. Insulin is considered a risk factor in NIDDM, in and of itself, for cardiovascular disease.

In comparison to a twice-daily dose of the reference standard (GLUCOPHAGE®), the plasma levels of metformin are preferably lower in the afternoon. This is an advantage particularly in patients who are under concomitant therapy with one or more additional antidiabetic agents, such as for example, a sulfonylurea. It is known in the art that to date approximately 60% of patients being treated with metformin are also being treated with at least one additional antidiabetic agent (such as a sulfonylurea). Sulfonylureas can possibly cause hypoglycemia, whereas metformin cannot, so there is a benefit to having lower metformin levels in the blood during the afternoon due to the potential for the patient to have hypoglycemia.

Accordingly, the present invention also includes a method of treating human patients with NIDDM comprising administering on a once-a-day basis a therapeutically effective dose of metformin in a controlled-release oral dosage form ("Metformin XT"), in combination with administering an effective amount of a sulfonylurea. In preferred embodiments, metformin is provided by a controlled release dosage form comprising metformin or a pharmaceutically acceptable salt thereof, the dosage form being useful for providing a once-a-day oral administration of the drug, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) of metformin from 5.5 to 7.5 hours after administration.

In certain embodiments, the combination therapy may be provided as follows. If patients do not respond to four weeks of the maximum dose of Metformin XT (2500 mg/day) monotherapy, a sulfonylurea may be gradually added while maintaining the maximum dose of Metformin XT, even if prior primary or secondary failure to a sulfonylurea has occurred. Examples of the sulfonylurea include glyburide (glibenclamid), chloropropamide, tolbutamide, glipizide, acetohexamide and tolazamide. Although Metformin XT is preferably administered on once-a-day basis, the sulfonylurea may be administered in a different dosage form and at a different frequency.

With concomitant Metformin XT and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug.

In certain embodiments, the foregoing objectives are met by a controlled release dosage form comprising:

(a) a core comprising:
  (i) an antihyperglycemic drug;
  (ii) optionally a binding agent; and
  (iii) optionally an absorption enhancer;
(b) a membrane coating surrounding the core; and
(c) at least one passageway in the membrane.

The binding agent may be any conventionally known pharmaceutically acceptable binder such as polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxyethyl cellulose, ethylcellulose, polymethacrylate, waxes and the like. Mixtures of the aforementioned binding agents may also be used. The preferred binding agents are water soluble such as polyvinyl pyrrolidone having a weight average molecular weight of 25,000 to 3,000,000. The binding agent comprises approximately about 0 to about 40% of the total weight of the core and preferably about 3% to about 15% of the total weight of the core.

The core may optionally comprise an absorption enhancer. The absorption enhancer can be any type of absorption enhancer commonly known in the art such as a fatty acid, a surfactant, a chelating agent, a bile salt or mixtures thereof. Examples of some preferred absorption enhancers are fatty acids such as capric acid, oleic acid and their monoglycerides, surfactants such as sodium lauryl sulfate, sodium taurocholate and polysorbate 80, chelating agents such as citric acid, phytic acid, ethylenediamine tetraacetic acid (EDTA) and ethylene glycol-big (B-aminoethyl ether —N,N,N,N-tetraacetic acid (EGTA). The core comprises approximately 0 to about 20% of the absorption enhancer based on the total weight of the core and most preferably about 2% to about 10% of the total weight of the core.

In this embodiment, the core which comprises the antihyperglycemic drug, the binder which preferably is a pharmaceutically acceptable water soluble polymer and the absorption enhancer is preferably formed by wet granulating the core ingredients and compressing the granules with the addition of a lubricant into a tablet on a rotary press. The core may also be formed by dry granulating the core ingredients and compressing the granules with the addition of a lubricant into tablets or by direct compression.

Other commonly known excipients may also be included into the core such as lubricants, pigments or dyes.

The homogeneous core is coated with a membrane, preferably a polymeric membrane to form the controlled release tablet of the invention. The membrane can be a semipermeable membrane by being permeable to the passage of external fluid such as water and biological fluids and being impermeable to the passage of the antihyperglycemic drug in the core. Materials that are useful in forming the membrane are cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate, and cellulose acetate butyrate. Other suitable polymers are described in U.S. Pat. Nos. 3 ,845,770, 3,916,899, 4,008,719, 4,036,228 and 4,11210 which are incorporated herein by reference. The most preferred membrane material is cellulose acetate comprising an acetyl content of 39.3 to 40.3%, commercially available from Eastman Fine Chemicals.

In an alternative embodiment, the membrane can be formed from the above-described polymers and a flux enhancing agent. The flux enhancing agent increases the volume of fluid imbibed into the core to enable the dosage form to dispense substantially all of the antihyperglycemic drug through the passageway and/or the porous membrane. The flux enhancing agent can be a water soluble material or an enteric material. Some examples of the preferred materials that are useful as flux enhancers are sodium chloride, potassium chloride, sucrose, sorbitol, mannitol, polyethylene glycol (PEG), propylene glycol, hydroxypropyl cellulose, hydroxypropyl methycellulose, hydroxyprophy methycellulose phthalate, cellulose acetate phthalate, polyvinyl alcohols, methacrylic acid copolymers and mixtures thereof. The preferred flux enhancer is PEG 400.

The flux enhancer may also be a drug that is water soluble such as metformin or its pharmaceutically acceptable salts or a drug that is soluble under intestinal conditions. If the flux enhancer is a drug, the present dosage form has the added advantage of providing an immediate release of the drug which is selected as the flux enhancer.

The flux enhancing agent comprises approximately 0 to about 40% of the total weight of the coating, most preferably about 2% to about 20% of the total weight of the coating. The flux enhancing agent dissolves or leaches from the membrane to form paths in the membrane for the fluid to enter the core and dissolve the active ingredient.

In alternate embodiments, the membrane may also be formed with commonly known excipients such as a plasticizer. Some commonly known plasticizers include adipate, azelate, enzoate, citrate, stearate, isoebucate, sebacate, triethyl citrate, tri-n-butyl citrate, acetyl tri-n-butyl citrate, citric acid esters, and those described in the Encyclopedia of Polymer Science and Technology, Vol. 10 (1969), published by John Wiley & Sons. The preferred plasticizers are triacetin, acetylated monoglyceride, grape seed oil, olive oil, sesame oil, acetyltributylcitrate, acetyltriethylcitrate, glycerin sorbitol, diethyloxalate, diethylmalate, diethylfumarate, dibutylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacate, triethylcitrate, tributylcitrate, glyceroltributyrate, and the like. Depending on the particular plasticizer, amounts of from 0 to about 25%, and preferably about 2% to about 15% of the plasticizer can be used based upon the total weight of the coating.

As used herein the term passageway includes an aperture, orifice, bore, hole, weakened area or an erodible element such as a gelatin plug that erodes to form an osmotic passageway for the release of the antihyperglycemic drug from the dosage form. A detailed description of the passageway can be found in U.S. Pat. Nos. such as 3,845,770, 3,916,899, 4,034,758, 4,063,064, 4,077,407, 4,088,864, 4,783,337 and 5,071,607 (the disclosures of which are hereby incorporated by reference).

In certain embodiments, the passageway is formed by laser drilling. In other embodiments, the passageway is formed by making an indentation onto the core prior to the membrane coating to form a weakened area of the membrane at the point of the indentation. In preferred embodiments of the invention, the dosage form contains two passageways in order provide the desired pharmacokinetic parameters of the formulation.

Generally, the membrane coating around the core will comprise from about 1% to about 7%, preferably about 1.5% to about 3%, based on the total weight of the core and coating.

The term "membrane" means a membrane that is permeable to both aqueous solutions or bodily fluids and to the active drug or pharmaceutical ingredient (e.g. the formulations of Examples 1–3). Thus, the membrane is porous to drug and, in a preferred embodiment, drug is released through the hole or passageway and through the porous membrane in solution or in vivo. The term "membrane" also generically encompasses the term "semipermeable membrane" as heretofore defined.

In an alternative embodiment, the dosage form of the present invention may also comprise an effective amount of the antihyperglycemic drug that is available for immediate release. The effective amount of antihyperglycemic drug for immediate release may be coated onto the membrane of the dosage form or it may be incorporated into the membrane.

In certain preferred embodiments of the invention where the dosage form is prepared in accordance with the above, the dosage form will have the following composition:

INGREDIENT	Preferred	Most Preferred
CORE:		
Drug	50–98%	75–95%
Binder	0–40%	3–15%
Absorption Enhancer	0–20%	2–10%
COATING:		
Membrane Polymer	50–99%	75–95%
Flux Enhancer	0–40%	2–20%
Plasticizer	0–25% or 0–30%	2–15%

The dosage forms prepared according to certain embodiments of the present invention preferably exhibit the following dissolution profile when tested in a USP type 2 k apparatus at 75 rpms in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37° C.:

Time (Hours)	Preferred	Most Preferred
2	0–30%	0–15% or 0–25%
4	10–45%	20–40%
8	30–90%	45–90%
12	NTL 50%	NTL 60%
16	NTL 60%	NTL 70%
20	NTL 70%	NTL 80%

NTL = Not less than

In the preparation of the tablets of the invention, various conventional well known solvents may be used to prepare the granules and apply the external coating to the tablets of the invention. In addition, various diluents, excipients, lubricants, dyes, pigments, dispersants, etc. which are disclosed in Remington's Pharmaceutical Sciences, 1995 Edition may be used to optimize the formulations of the invention.

Other controlled release technologies known to those skilled in the art can be used in order to achieve the controlled release formulations of the present invention, i.e., formulations which provide a mean T_{max} of the drug and/or other pharmacokinetic parameters described herein when orally administered to human patients. Such formulations can be manufactured as a controlled oral formulation in a suitable tablet or multiparticulate formulation known to those skilled in the art. In either case, the controlled release dosage form may optionally include a controlled release carrier which is incorporated into a matrix along with the drug, or which is applied as a controlled release coating.

An oral dosage form according to the invention may be provided as, for example, granules, spheroids, beads, pellets (hereinafter collectively referred to as "multiparticulates") and/or particles. An amount of the multiparticulates which is effective to provide the desired dose of drug over time may be placed in a capsule or may be incorporated in any other suitable oral form.

In certain preferred embodiments, the tablet core or multiparticulates containing the drug are coated with a hydrophobic material selected from (i) an alkylcellulose and (ii) a polymeric glycol. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2 to about 25% of the substrate in order to obtain a desired sustained release profile. The sustained release coatings of the present invention may also include an exit means com-

prising at least one passageway, orifice, or the like as previously disclosed.

Description of Certain Preferred Embodiments

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1

A controlled release tablet containing 500 mg of metformin HCl and having the following formula is prepared as follows:

I. Core

Ingredients	Amount (mg/tab)
Metformin HCl	500.0
Povidone[3], USP	36.0
Sodium Lauryl Sulfate	25.8
Magnesium Stearate	2.8

[3]approximate molecular weight = 1,000,000; dynamic viscosity (10% w/v solution at 20° C.) = 300–700 m Pa s.

(a) Granulation

The metformin HCl and sodium lauryl sulfate are delumped by passing them through a 40 mesh screen and collecting them in a clean, polyethylene-lined container. The povidone, K-90-F is dissolved in purified water. The delumped metformin HCl and sodium lauryl sulfate are then added to a top-spray fluidized bed granulator and granulated by spraying with the binding solution of povidone under the following conditions: inlet air temperature of 50–70° C.; atomization air pressure of 1–3 bars; and spray rate of 10–100 ml/min.

Once the binding solution is depleted, the granules are dried in the granulator until the loss on drying is less than 2%. The dried granules are passed through a Comil equipped with the equivalent of an 18 mesh screen.

(b) Tableting

The magnesium stearate is passed through a 40 mesh stainless steel screen and blended with the metformin HCl granules for approximately five (5) minutes. After blending, the granules are compressed on a rotary press fitted with 15/32" round standard concave punches.

(c) Seal Coating (Optional)

The core tablet is seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably Opadry Clear (YS-1-7006), in purified water. The Opadry solution is then sprayed onto the core tablet using a pan coater under the following conditions: exhaust air temperature of 38–42° C.; atomization pressure of 28–40 psi; and spray rate of 10–15 ml/min. The Opadry Clear of the coating constitutes about 11.5 mg/tablet.

II. Sustained Release Coating

Ingredients	Amount (mg/tablet)
Cellulose Acetate (398-10)[2]	21.5
Triacetin	1.3
PEG 400	2.5

[2]acetyl content 39.3–40.3%

The cellulose acetate is dissolved in acetone while stirring with a homogenizer. The polyethylene glycol 400 and triacetin are added to the cellulose acetate solution and stirred until a clear solution is obtained. The tablet is coated by spraying the clear coating solution onto the seal coated tablets in a fluidized bed coater employing the following conditions: product temperature of 16–22° C.; atomization pressure of approximately three bars; and spray rate of 120–150 ml/min.

(d) Laser Drilling

The coated tablets were laser drilled two holes (one hole on each side of the tablet).

EXAMPLE 2

A controlled release tablet containing 850 mg of metformin HCl and having the following formula is prepared as follows:

I. Core

Ingredients	Amount (mg/tab)
Metformin HCl	850.0
Povidone[3], USP	61.1
Sodium Lauryl Sulfate	43.9
Magnesium Stearate	4.8

3approximate molecular weight = 1,000,000; dynamic viscosity (10% w/v solution at 20° C.) = 300–700 m Pa s.

(a) Granulation

The metformin HCl and sodium lauryl sulfate are delumped by passing them through a 40 mesh screen and collecting them in a clean, polyethylene-lined container. The povidone, K-90-F is dissolved in purified water. The delumped metformin HCl and sodium lauryl sulfate are then added to a top-spray fluidized bed granulator and granulated by spraying with the binding solution of povidone under the following conditions: inlet air temperature of 50–70° C.; atomization air pressure of 1–3 bars; and spray rate of 10–100 ml/min.

Once the binding solution is depleted, the granules are dried in the granulator until the loss on drying is less than 2%. The dried granules are passed through a Comil equipped with the equivalent of an 18 mesh screen.

(b) Tableting

The magnesium stearate is passed through a 40 mesh stainless steel screen and blended with the metformin HCl granules for approximately five (5) minutes. After blending, the granules are compressed on a rotary press fitted with 15/32" round standard concave punches.

(c) Seal Coating (Optional)

The core tablet is seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably Opadry Clear (YS-1-7006), in purified water. The Opadry solution is then sprayed onto the core tablet using a pan coater under the following conditions: exhaust air temperature of 38–42° C.; atomization pressure of 28–40 psi; and spray rate of 10–15 ml/min. The Opadry Clear of the coating constitutes about 11.5 mg/tablet.

II. Sustained Release Coating

Ingredients	Amount (mg/tablet)
Cellulose Acetate (398-10)[2]	24.0
Triacetin	1.4
PEG 400	2.8

[2]acetyl content 39.3–40.3%

The cellulose acetate is dissolved in acetone while stirring with a homogenizer. The polyethylene glycol 400 and triacetin are added to the cellulose acetate solution and stirred

until a clear solution is obtained. The tablet is coated by spraying the clear coating solution onto the seal coated tablets in a fluidized bed coater employing the following conditions: product temperature of 16–22° C.; atomization pressure of approximately three bars; and spray rate of 120–150 ml/min.

(d) Laser Drilling

The coated tablets were laser drilled two holes (one hole on each side of the tablet).

EXAMPLE 3

A controlled release tablet containing 1000 mg of metformin HCl and having the following formula is prepared as follows:

I. Core

Ingredients	Amount (mg/tablet)
Metformin HCl	1000.0
Povidone[3], USP	71.9
Sodium Lauryl Sulfate	51.7
Magnesium Stearate	5.6

[3]approximate molecular weight = 1,000,000; dynamic viscosity (10% w/v solution at 20° C.) = 300–700 m Pa s.

(a) Granulation

The metformin HCl and sodium lauryl sulfate are delumped by passing them through a 40 mesh screen and collecting them in a clean, polyethylene-lined container. The povidone, K-90-F is dissolved in purified water. The delumped metformin HCl and sodium lauryl sulfate are then added to a fluidized bed granulator and granulated by spraying with the binding solution of povidone under the following conditions: inlet air temperature of 50–70° C.; atomization air pressure of 1–3 bars; and spray rate of 10–100 ml/min.

Once the binding solution is depleted, the granules are dried in the granulator until the loss on drying is less than 2%. The dried granules are passed through a Comil equipped with a screen equivalent to 18 mesh.

(b) Tableting

The magnesium stearate is passed through a 40 mesh stainless steel screen and blended with the metformin HCl granules for approximately five (5) minutes. After blending, the granules are compressed on a rotary press fitted with ½" round standard concave punches.

(c) Seal Coating (Optional)

The core tablet is seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably Opadry Clear (YS-1-7003), in purified water. The Opadry solution is then sprayed onto the core tablet using a pan coater under the following conditions: exhaust air temperature of 38–42° C.; atomization pressure of 28–40 psi; and spray rate of 10–15 ml/min. The core tablet is coated with the sealing solution until the tablet is coated with 23.0 mg/tablet of the Opadry material.

II. Sustained Release Coating

Ingredients	Amount (mg/tablet)
Cellulose Acetate (398-10)[2]	19.0
Triacetin	1.1
PEG 400	2.2

[2]acetyl content 39.3–40.3%

The cellulose acetate is dissolved in acetone while stirring with a homogenizer. The polyethylene glycol 400 and triacetin are added to the cellulose acetate solution and stirred until a clear solution is obtained. The tablet is coated by spraying the clear coating solution onto the seal coated tablets in a fluidized bed coater employing the following conditions: product temperature of 16–22° C.; atomization pressure of approximately three bars; and spray rate of 120–150 ml/min.

(d) Laser Drilling

The coated tablets were laser drilled two holes (one hole on each side of the tablet).

(e) Color Coating (Optional)

Subsequent to the sustained release coating, the laser drilled tablet is coated with a color coating using Opadry White (24 mg/tablet) and waxed with Candelilla wax powder (0.4 mg/tablet).

Clinical Studies

Study 1

In study 1, a total of twelve (12) healthy subjects (six males, six females) were randomized to receive either a single oral dose of metformin XT, 850 mg, prepared in accordance with Example 2 or b.i.d. doses of GLUCOPHAGE in assigned study periods which consisted of one of the following groups: Group A—metformin XT (2×850 mg tablets) taken at approximately 8:00 a.m., immediately following breakfast, Group B—metformin XT (2×850 mg tablets) taken at approximately 6:00 p.m., immediately following dinner; and Group C—GLUCOPHAGE (1×850 mg tablet) taken at approximately 8:00 a.m., immediately following breakfast, and at approximately 6:00 p.m., immediately following dinner. Each drug administration was separated by a washout period of seven days. In this study, one male subject was removed from the study prior to Period II due to non-treatment-related mononucleosis. Thus, 11 (five males and six females) subjects completed the study.

For metformin XT, plasma samples were obtained from subjects at 0 (predose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 24 hour(s) after dosing. For GLUCOPHAGE, plasma samples were obtained from subjects at 0 (predose), 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22, and 24 hour(s) after the first dose in the morning. Plasma concentrations of metformin were determined using a validated HPLC method. The lower quantitation limit of this method is 10 ng/ml. Mean plasma concentration-time profiles are shown in FIG. 1 and mean values of pharmacokinetic parameters of metformin obtained from this study are presented in Table 1.

TABLE 1

Mean (±SD, n = 11) values of pharmacokinetic parameters of metformin (Example 2) in 11 healthy subjects (metformin XT, 2 × 850 mg q.d. or GLUCOPHAGE, 1 × 850 mg b.i.d.)

	$AUC_{0-\infty}$	C_{max}	T_{max}	T_{lag}	$t_{1/2}$	Geometric Mean Ratio*	
Treatment	(ng-hr/ml)	(ng/ml)	(hr.)	(hr)	(hr)	$AUC_{0-\infty}$	C_{max}
Metformin XT	18156	2045	6	0.18	4.4	1.00	1.36
after breakfast	(4183)	(567)	(2)	(0.40)	(0.7)		
Metformin XT	18277	1929	7	0.09	3.6	1.02	1.32
after dinner	(2961)	(333)	(2)	(0.30)	(0.8)		
GLUCOPHAGE	18050	1457	5	0	3.5	—	—
	(3502)	(217)	(3)	(0)	(0.9)		

*Ratio = Metformin XT/GLUCOPHAGE

As shown in FIG. 1 and Table 1, when metformin XT was administered immediately after either breakfast or dinner, the relative bioavailability of metformin XT formulation to GLUCOPHAGE is approximately 100%.

The results of study 1 were used to calculate the approximate degree of fluctuation (C_{max}–C_{min}/C_{avg}) of the formulations.

The C_{max} was directly obtained from the study (see Table 1). The C_{avg} was obtained by dividing the AUC value by the dosing interval, i.e. 24 hours. The value for C_{min} was extrapolated from FIG. 1.

The results are set forth in Table 2 below:

TABLE 2

Mean (±SD, n = 12) values of pharmacokinetic parameters of metformin XT in 12 healthy subjects (metformin XT, 2 × 850 mg q.d. and GLUCOPHAGE, 850 mg b.i.d.)

Treatment	$AUC_{0-\infty}$ (ng-hr/ml)	C_{max} (ng/ml)	C_{min} (ng/ml)	C_{avg} (ng/ml)	Degree of Fluctuation
Metformin XT	18156	2045	143	756	2..51
after breakfast	(4183)	(567)			
Metformin XT	18277	1929	107	761	2.39
after dinner	(2961)	(333)			
GLUCOPHAGE	18050	1457	214 (at 24 hours)	752	1.65
	(3502)	(217)	393 (between doses)	752	1.41

As shown in FIG. 1 and Table 2, a single administration of the metformin XT formulation provides a higher mean fluctuation index in the plasma than a substantially equal dose of Glucophage administered as two equal divided doses, one divided dose at the start of the dosing interval and the other divided dose administered 12 hours later.

Study 2

The study design of Study 2 is the same as Study 1 except for the formulation and the dose (4×500 mg q.d., total dose 2000 mg, for metformin XT prepared according to Example 1 and 2×500 mg b.i.d., total dose 2000 mg, for GLUCOPHAGE in the second study). In this study, 12 healthy volunteers (five males and seven females) were randomized to receive treatments and completed the study. Mean plasma concentration-time profiles and mean values of pharmacokinetic parameters of metformin obtained from this study are presented in FIG. 2 and Table 3.

As shown in FIG. 2 and Table 3, when the metformin XT formulation (500 mg) was administered immediately after dinner, the relative bioavailability of this formulation to GLUCOPHAGE is approximately 100%, while the mean C_{max} value is about the same. The relative bioavailability of metformin XT, however, is approximately 80% when administered immediately after breakfast. A prolonged profile, together with later T_{max} and similar C_{max} of metformin following administration of metformin XT immediately after dinner compared to GLUCOPHAGE indicated that metformin was released in vivo in a sustained fashion (FIG. 2).

TABLE 3

Mean (±SD, n = 12) values of pharmacokinetic parameters of metformin of Example 1 in 12 healthy subjects (metformin XT, 4 × 500 mg q.d. or GLUCOPHAGE, 2 × 500 mg b.i.d.)

	$AUC_{0-\infty}$	C_{max}	T_{max}	T_{lag}	$t_{1/2}$	Geometric Mean Ratio*	
Treatment	(ng-hr/ml)	(ng/ml)	(hr)	(hr)	(hr)	$AUC_{0-\infty}$	C_{max}
Metformin XT	17322	2127	5	0	6.1	0.80	1.15
after breakfast	(4984)	(545)	(1)	(0)	(1.8)		
Metformin XT	20335	2053	7	0.08	3.9	0.96	1.12
after dinner	(4360)	(447)	(2)	(0.29)	(0.6)		
GLUCOPHAGE	21181	1815	4	0	3.6	—	—
	(4486)	(302)	(3)	(0)	(0.8)		

*Ratio = Metformin XT/GLUCOPHAGE

The results of study 2 were used to calculate the approximate degree of fluctuation of the formulations in accordance with the calculations used in study 1 (using FIG. 2 to obtain the extrapolated value for C_{min}).

The results are set forth in Table 4 below:

TABLE 4

Mean (±SD, n = 12) values of pharmacokinetic parameters of metformin XT in 12 healthy subjects (metformin XT, 4 × 500 mg q.d. and GLUCOPHAGE, 2 × 500 mg b.i.d.)

Treatment	$AUC_{0-\infty}$ (ng-hr/ml)	C_{max} (ng/ml)	C_{min} (ng/ml)	C_{avg} (ng/ml)	Degree of Fluctuation
Metformin XT after breakfast	17322 (4984)	2127 (545)	143	721	2.9
Metformin XT after dinner	20335 (4360)	2053 (447)	143	847	2.25
GLUCOPHAGE	21181 (4486)	1815 (302)	214 (at 24 hours)	882	1.8
			357 (between doses)	882	1.65

As shown in FIG. 2 and Table 4, a single administration of the metformin XT formulation provides a higher mean fluctuation index in the plasma than an equivalent dose of Glucophage administered as two equal divided doses, one divided dose at the start of the dosing interval and the other divided dose administered 12 hours later.

Study 3

In Study 3, a multiple-dose, open-label, one-period study was conducted to evaluate the short-term tolerability and steady-state pharmacokinetics of the 500 mg metformin XT formulation used in Study 2. In this study, eight healthy volunteers (four males and four females) were randomized to receive 2000 mg of metformin XT (4×500 mg tablets) at approximately 6:00 p.m., immediately following dinner, for 14 days.

Blood samples were obtained from each subject at 0 (predose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16 and 24 hour(s) following the first dose on Day 1 and at 0 (predose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24, 38 and 48 hour(s) following the last dose on Day 14. Blood samples were also drawn from each subject immediately prior to dosing on Days 10–13. Urine samples were collected from each subject at the following time intervals: six hours prior to the first dose; 0–6, 6–12 and 12–24 hours after the first dose; and 0–6, 6–12, 12–24 and 24–48 hours after the last dose.

Mean plasma profiles and values of pharmacokinetic parameters of metformin are presented in Table 5 below:

TABLE 5

Mean Pharmacokinetic Parameters (Example 1)

	C_{max}	T_{max}	$AUC_{0-24\ hr}$ (ng · hr/ml)
		Day 1	
Mean	2435	6.9	22590
SD	630	1.9	3626
		Day 14	
Mean	2288	6.9	24136
SD	736	2.5	7996

Following oral administration of metformin XT, 4×500 mg q.d., for 14 days, there was little or no difference in plasma concentration-time profiles of metformin in eight healthy volunteers between Day 1 and Day 14 dosing (FIG. 3). On average, trough plasma concentrations of metformin were nearly constant, ranging from 188.8 to 205.1 ng/ml on Days 10–14, indicating that the steady state of metformin was attained rapidly. The mean accumulation ratio was 1.01, indicating that the once-daily dose regimen of metformin XT results in no accumulation.

Following oral administration of a single dose (4×500 mg) of metformin XT, approximately 31% of the dose was excreted in the urine within the first 24 hours. On average, the renal clearance of metformin was 366 ml/min. A slightly higher renal clearance (454 ml/min) was found after multiple-dose administration of 4×500 mg q.d. of metformin XT.

Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence and anorexia) are the most common adverse reactions to GLUCOPHAGE. In controlled trials, GLUCOPHAGE was started at low, nontherapeutic doses and gradually titrated to higher doses. In spite of this gradual titration, GLUCOPHAGE was discontinued due to gastrointestinal reactions in approximately 4% of patients. In contrast, in the multiple-dose study, metformin XT begun at a therapeutic initial dose of 2000 mg once daily with dinner was well tolerated by all healthy volunteers. Diarrhea and nausea were the most common gastrointestinal reactions probably or possibly related to metformin XT. These reactions, however, were either mild or moderate. This suggests that it may be possible to initiate metformin XT treatment with effective doses rather than using the slow titration from non-therapeutic doses required for GLUCOPHAGE.

Study 4

Study 4 was a study designed to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of metformin XT compared to GLUCOPHAGE after multiple-dose treatment in patients with NIDDM. Metformin XT tablets prepared according to Example 3 were used in this study. This study had a single-center, randomized, two-way crossover design. A total of 24 NIDDM patients who were on a stable dose of GLUCOPHAGE, between 1000 and 2550 mg/day, for at least 12 weeks were selected for the study. A Pretreatment Period of at least 3 weeks preceded randomization to study treatment. At the start of the Pretreatment Period, all patients stopped taking any other hypoglycemic agents besides GLUCOPHAGE, and the GLUCOPHAGE dose was adjusted to 1000 mg b.i.d. (with breakfast and with dinner). Following the pretreatment period, patients began Treatment Period I, which lasted 4 weeks. During Period I, a total of 12 patients were randomized to receive two 1000-mg metformin XT tablets q.d. (immediately after dinner), at approximately 6:00 p.m., and 12 were randomized to receive one 1000-mg GLUCOPHAGE tablet b.i.d. (immediately after breakfast and immediately after dinner). Imediately following Period I, each patient was switched to the alternate medication for 4 weeks in Period II. There was no washout between treatment periods.

Plasma metformin concentrations were determined over a 24-hour period at the end of Treatment Periods I and II as follows: immediately prior to dosing and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 15, 16, 17, 18, 19, 20, 22, and 24 hours after the evening dose. One subject withdrew from the study for personal reasons after two weeks of treatment in Treatment Period I, thus pharmacokinetic data were obtained from 23 patients.

Mean plasma profiles and values of pharmacokinetic parameters of metformin are presented in FIG. 4 and Table 6. As shown in FIG. 4 and Table 6, when metformin XT was administered immediately after dinner, the bioavailability of metformin XT relative to GLUCOPHAGE at steady state is close to 100%. Although the dose of metformin XT was twice as large as the dose of GLUCOPHAGE at dinner, the mean C_{max} value was only 32% higher.

TABLE 6

Mean (±SD) values of pharmacokinetic parameters of metformin of Example 3 in 23 NIDDM patients (metformin XT, 2 × 1000 mg q.d. with dinner or GLUCOPHAGE, 1 × 1000 mg b.i.d.)

	AUC_{0-24hr}	C_{max}	T_{max}	T_{lag}	$t_{½}$	Geometric Mean Ratio*	
Treatment	(ng*hr/ml)	(ng/ml)	(hr)	(hr)	(hr)	AUC_{0-24hr}	C_{max}
Metformin XT after dinner	26818 (7052)	2849 (797)	6 (2)	0 (0)	5.4	0.96	1.32
GLUCOPHAGE	27367 (5759)	2131 (489)	14 (6)	0 (0)	4.4	—	—

*Ratio = Metformin XT/GLUCOPHAGE

When the metformin XT was administered immediately after dinner, the bioavailability of metformin XT relative to GLUCOPHAGE at steady state was close to 100%. However, when metformin XT was administered immediately after breakfast, the corresponding relative bioavailability of metformin XT was approximately 80%. The safety profile of metformin XT, 2000 mg given once daily either after dinner or after breakfast was comparable to that of an equal dose of GLUCOPHAGE given b.i.d. The efficacy profile of metformin XT, 2000 mg given once daily after dinner was similar to that of an equal dose of GLUCOPHAGE given b.i.d. The efficacy of metformin XT, 2000 mg given once daily after breakfast, however, appeared to be comparable to or slightly less than that of GLUCOPHAGE given b.i.d.

While certain preferred and alternative embodiments of the invention have been set forth for purposes of disclosing the invention, modifications to the disclosed embodiments may occur to those who are skilled in the art. Accordingly, the appended claims are intended to cover all embodiments of the invention and modifications thereof which do not depart from the spirit and scope of the invention.

What is claimed is:

1. A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising an effective dose of metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier to control the release of said metformin or pharmaceutically acceptable salt thereof from said dosage form, said dosage form being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof, wherein following oral administration of a single dose, the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the metformin from 5.5 to 7.5 hours after administration following dinner.

2. The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 6.0 to 7.0 hours after the administration of the dose.

3. The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 5.5 to 7.0 hours after the administration of the dose.

4. The controlled release oral dosage form of claim 1, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:

0–30% of the metformin or salt thereof is released after 2 hours;

10–45% of the metformin or salt thereof is released after 4 hours;

30–90% of metformin or salt thereof is released after 8 hours;

not less than 50% of the metformin or salt thereof is released after 12 hours;

not less than 60% of the metformin or salt thereof is released after 16 hours; and

not less than 70% of the metformin or salt thereof is released after 20 hours.

5. The controlled release oral dosage form of claim 1, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:

0–25% of the metformin or salt thereof is released after 2 hours;

20–40% of the metformin or salt thereof is released after 4 hours;

45–90% of the metformin or salt thereof is released after 8 hours;

not less than 60% of the metformin or salt thereof is released after 12 hours;

not less than 70% of the metformin or salt thereof is released after 16 hours; and

not less than 80% of the metformin or salt thereof is released after 20 hours.

6. The controlled release oral dosage form of claim 1, which provides a width at 50% of the height of a mean plasma concentration/time curve of the metformin from about 4.5 to about 13 hours.

7. The controlled release oral dosage form of claim 1, which provides a width at 50% of the height of a mean plasma concentration/time curve of the metformin from about 5.5 to about 10 hours.

8. The controlled release oral dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of metformin which is more than about 7 times the mean plasma level of said metformin at about 24 hours after the administration.

9. The controlled release oral dosage form of claim 1, which provides a mean maximum plasma concentration

(C_{max}) of metformin which is from about 7 times to about 14 times the plasma level of said metformin at about 24 hours after administration.

10. The controlled release oral dosage form of claim **1** which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 8 times to about 12 times the plasma level of said metformin at about 24 hours after administration.

11. The controlled release oral dosage form of claim **1** which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

12. The controlled release oral dosage form of claim **1**, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1700 ng/ml to about 2000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

13. The controlled release oral dosage form of claim **1** which provides a mean $AUC_{0\text{-}24hr}$ of at least 80% of the mean $AUC_{0\text{-}24}$ provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

14. The controlled release oral dosage form of claim **1** which provides a mean $AUC_{0\text{-}24hr}$ of at least 90% of the mean $AUC_{0\text{-}24}$ provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

15. The controlled release oral dosage form of claim **1** which provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

16. The controlled release oral dosage form of claim **1** which provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 26500 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

17. The controlled release oral dosage form of claim **1** which provides a mean $AUC_{0\text{-}24hr}$ from about 19800 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

18. The controlled release oral dosage form of claim **1** which provides a mean $AUC_{0\text{-}\infty}$ of 18277±2961 ng.hr/ml and a mean C_{max} of 1929±333 ng/ml, for administration of a 1700 mg once-a-day dose of metformin after an evening meal.

19. The controlled release oral dosage form of claim **1** which provides a mean $AUC_{0\text{-}\infty}$ of 20335±4360 ng.hr/ml and a mean C_{max} of from 2053±447 ng/ml, for administration of a 2000 mg once-a-day dose of metformin after an evening meal.

20. The controlled release oral dosage form of claim **1** which provides a mean $AUC_{0\text{-}24}$ of 26818±7052 ng.hr/ml and a mean C_{max} of 2849±797 ng/ml, for, administration of a 2000 mg once-a-day dose of metformin after an evening meal.

21. The controlled release oral dosage form of claim **1** which provides a mean $AUC_{0\text{-}24}$ of 22590±3626 ng.hr/ml and a mean C_{max} of 2435±630 ng/ml on the first day of administration and a mean $AUC_{0\text{-}24}$ of 24136±7996 ng.hr/ml and a mean C_{max} of 2288±736 ng/ml on the 14^{th} day of administration, for administration of a 2000 mg once-a-day dose of metformin after an evening meal.

22. The controlled release oral dosage form of claim **12** which provides a mean $t_{1/2}$ from 2.8 to 4.4.

23. The controlled release oral dosage form of claim **6**, which provides a mean time to maximum plasma concentration (T_{max}) of metformin from 6.0 to 7.0 hours after the administration.

24. The controlled release oral dosage form of claim **6**, which provides a mean time to maximum plasma concentration (T_{max}) of metformin from 5.5 to 7.0 hours after administration.

25. The controlled release dosage form of claim **1**, wherein the metformin or pharmaceutically acceptable salt thereof is provided by at least one controlled-release tablet, said tablet comprising:

(a) a core comprising:
  (i) the metformin or a pharmaceutically acceptable salt;
  (ii) optionally a binding agent; and
  (iii) optionally an absorption enhancer;
(b) a membrane coating surrounding the core; and
(c) at least one passageway in the membrane.

* * * * *

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UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
300.1012

Total Pages in this Submission
55

09/705620 jc925 U.S. PTO 11/03/00

TO THE ASSISTANT COMMISSIONER FOR PATENTS
Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

CONTROLLED RELEASE METFORMIN COMPOSITIONS

and invented by:

Xiu Xiu CHENG, Chih-Ming CHEN, Steve JAN and Joseph CHOU

If a **CONTINUATION APPLICATION**, *check appropriate box and supply the requisite information:*

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: _____

Which is a:

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: _____

Which is a:

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Enclosed are:

Application Elements

1. ☐ Filing fee as calculated and transmitted as described below

2. ☒ Specification having 42 pages and including the following:

   a. ☒ Descriptive Title of the Invention
   b. ☐ Cross References to Related Applications *(if applicable)*
   c. ☐ Statement Regarding Federally-sponsored Research/Development *(if applicable)*
   d. ☐ Reference to Microfiche Appendix *(if applicable)*
   e. ☒ Background of the Invention
   f. ☒ Brief Summary of the Invention
   g. ☒ Brief Description of the Drawings *(if drawings filed)*
   h. ☒ Detailed Description
   i. ☒ Claim(s) as Classified Below
   j. ☒ Abstract of the Disclosure

UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

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300.1005
Total Pages in this Submission
56

Application Elements (Continued)

3. ☒ Drawing(s) *(when necessary as prescribed by 35 USC 113)*
   a. ☐ Formal Number of Sheets _____
   b. ☒ Informal Number of Sheets 8
4. ☐ Oath or Declaration
   a. ☐ Newly executed *(original or copy)* ☐ Unexecuted
   b. ☐ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*
   c. ☐ With Power of Attorney ☐ Without Power of Attorney
   d. ☐ *DELETION OF INVENTOR(S)*
   Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. 1.63(d)(2) and 1.33(b).
5. ☐ Incorporation By Reference *(usable if Box 4b is checked)*
   The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. ☐ Computer Program in Microfiche *(Appendix)*
7. ☐ Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all must be included)*
   a. ☐ Paper Copy
   b. ☐ Computer Readable Copy *(identical to computer copy)*
   c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

8. ☐ Assignment Papers *(cover sheet & document(s))*
9. ☐ 37 CFR 3.73(B) Statement *(when there is an assignee)*
10. ☐ English Translation Document *(if applicable)*
11. ☐ Information Disclosure Statement/PTO-1449 ☐ Copies of IDS Citations
12. ☐ Preliminary Amendment
13. ☒ Acknowledgment postcard
14. ☒ Certificate of Mailing
    ☐ First Class ☒ Express Mail *(Specify Label No.):* EL 415 728 683 US

UTILITY PATENT APPLICATION TRANSMITTAL
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Total Pages in this Submission
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Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*

16. ☐ Additional Enclosures *(please identify below):*

Request That Application Not Be Published Pursuant To 35 U.S.C. 122(b)(2)

17. ☐ Pursuant to 35 U.S.C. 122(b)(2), Applicant hereby requests that this patent application not be published pursuant to 35 U.S.C. 122(b)(1). Applicant hereby certifies that the invention disclosed in this application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication of applications 18 months after filing of the application.

Warning

An applicant who makes a request not to publish, but who subsequently files in a foreign country or under a multilateral international agreement specified in 35 U.S.C. 122(b)(2)(B)(i), must notify the Director of such filing not later than 45 days after the date of the filing of such foreign or international application. A failure of the applicant to provide such notice within the prescribed period shall result in the application being regarded as abandoned, unless it is shown to the satisfaction of the Director that the delay in submitting the notice was unintentional.

UTILITY PATENT APPLICATION TRANSMITTAL
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300.1005

Total Pages in this Submission

Fee Calculation and Transmittal

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra		Rate	Fee
Total Claims	42	- 20 =	22	x	$18.00	$396.00
Indep. Claims	2	- 3 =	0	x	$80.00	$0.00
Multiple Dependent Claims (check if applicable) ☐						$0.00
					BASIC FEE	$710.00
OTHER FEE *(specify purpose)*						$0.00
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PATENT TRADEMARK OFFICE

CONTROLLED RELEASE METFORMIN COMPOSITIONS

Background of the Invention

The present invention relates to controlled release unit dose formulations containing an antihyperglycemic drug. More specifically, the present invention relates to an oral dosage form comprising a biguanide such as metformin or buformin or a pharmaceutically acceptable salt thereof such as metformin hydrochloride or the metformin salts described in United States Patent Nos. 3,957,853 and 4,080,472 which are incorporated herein by reference.

In the prior art, many techniques have been used to provide controlled and extended-release pharmaceutical dosage forms in order to maintain therapeutic serum levels of medicaments and to minimize the effects of missed doses of drugs caused by a lack of patient compliance.

In the prior art are extended release tablets which have an osmotically active drug core surrounded by a semipermeable membrane. These tablets function by allowing a fluid such as gastric or intestinal fluid to permeate the coating membrane and dissolve the active ingredient so it can be released through a passageway in the coating membrane or if the active ingredient is insoluble in the permeating fluid, pushed through the passageway by an expanding agent such as a hydrogel. Some representative examples of these osmotic tablet systems can be found in United States Patent Nos. 3,845,770, 3,916,899, 4,034,758, 4,077,407 and 4,783,337. United States Patent No. 3,952,741 teaches an osmotic device wherein the active agent is released from a core surrounded by a semipermeable membrane only after sufficient pressure has developed within the membrane to burst or rupture the membrane at a weak portion of the membrane.

The basic osmotic device described in the above cited patents have been refined over time in an effort to provide greater control of the release of the active ingredient. For example United States Patent Nos. 4,777,049 and 4,851,229 describe an osmotic dosage form comprising a semipermeable wall surrounding a core. The core contains an active ingredient and a modulating agent wherein the modulating agent causes the active ingredient to be released through a passageway in the semipermeable membrane in a pulsed manner. Further refinements have

included modifications to the semipermeable membrane surrounding the active core such as varying the proportions of the components that form the membrane; i.e., United States Patent Nos. 5,178,867, 4,587,117 and 4,522,625 or increasing the number of coatings surrounding the active core; i.e., U.S. Patent Nos. 5,650,170 and 4,892,739.

Although vast amounts of research has been performed on controlled or sustained release compositions and in particular on osmotic dosage forms, very little research has been performed in the area of controlled or sustained release compositions that employ antihyperglycemic drugs.

Metformin is an oral antihyperglycemic drug used in the management of non-insulin-dependent diabetes mellitus (NIDDM). It is not chemically or pharmacologically related to oral sulfonylureas. Metformin improves glucose tolerance in NIDDM patients by lowering both basal and postprandial plasma glucose. Metformin hydrochloride is currently marketed as GLUCOPHAGE® tablets by Bristol-Myers Squibb Co. Each GLUCOPHAGE® tablet contains 500, 850 or 1000 mg of metformin hydrochloride. There is no fixed dosage regimen for the management of hyperglycemia in diabetes mellitus with GLUCOPHAGE®. Dosage of GLUCOPHAGE® is individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended dose of 2550 mg per day.

Metformin has been widely prescribed for lowering blood glucose in patients with NIDDM. However, being a short acting drug, metformin requires twice-daily (b.i.d.) or three-times-a-day (t.i.d.) dosing. Adverse events associated with metformin use are often gastrointestinal in nature (e.g., anorexia, nausea, vomiting and occasionally diarrhea, etc.). These adverse events may be partially avoided by either reducing the initial and/or maintenance dose or using an extended-release dosage form. Another clear advantage of an extended release dosage form is a reduction in the frequency of administration. All of these findings suggest that an extended-release dosage form of metformin may improve the quality of therapy in patients with NIDDM and the safety profile relative to a conventional dosage form.

The limited work on controlled or sustained release formulations that employ antihyperglycemic drugs such as metformin hydrochloride includes the combination of the antihyperglycemic drug and an expanding or gelling agent to control the release of the drug from

the dosage form. This research is exemplified by the teachings of WO 96/08243 and by the GLUCOPHAGE® metformin HCl product.

It is reported in the 50th Edition of the Physicians' Desk Reference, copyright 1996, p. 753, that food decreases the extent and slightly delays the absorption of metformin delivered by the GLUCOPHAGE® dosage form. This decrease is shown by approximately a 40% lower peak concentration, a 25% lower bioavailability and a 35-minute prolongation of time to peak plasma concentration following administration of a single GLUCOPHAGE® tablet containing 850 mg of metformin HCl with food compared to the similar tablet administered under fasting conditions.

A controlled release metformin dosage form is also described in WO 99/47128. This reference describes a controlled release delivery system for metformin which includes an inner solid particulate phase formed of substantially uniform granules containing metformin and one or more hydrophilic polymers, one or more hydrophobic polymers and one or more hydrophobic materials, and an outer continuous phase in which the above granules are embedded and dispersed throughout. The outer continuous phase includes one or more hydrophilic polymers, one or more hydrophobic polymers and one or more hydrophobic materials.

Our own WO 99/47125 discloses controlled release metformin formulations providing a Tmax from 8 to 12 hours.

Objects and Summary of the Invention

It is an object of the present invention to provide a controlled or sustained release of an antihyperglycemic drug which provides effective control of blood glucose levels in humans.

It is a further object of the present invention to provide a method of treating human patients with non-insulin-dependent diabetes mellitus (NIDDM) on a once-a-day basis with an antihyperglycemic drug which provides effective control of blood glucose levels in humans.

It is a further object of the present invention to provide formulations for treating human patients with non-insulin-dependent diabetes mellitus (NIDDM) which provides advantages over

the state-of-the-art, and which may be administered on a once-a-day basis by itself or together with other antidiabetic agents, and methods thereof.

It is a further object of the present invention to provide a controlled or sustained release formulation of an antihyperglycemic drug wherein the bioavailability of the drug is not decreased by the presence of food.

It is a further object of the present invention to provide a controlled or sustained release formulation of an antihyperglycemic drug that does not employ an expanding polymer.

It is also a further object of the present invention to provide a controlled or sustained release formulation of an antihyperglycemic drug that can provide continuous and non-pulsating therapeutic levels of the drug to an animal or human in need of such treatment over a twelve hour to twenty-four hour period.

It is an additional object of other embodiments of the present invention to provide a controlled or sustained release formulation for an antihyperglycemic drug that obtains peak plasma levels from 5.5 to 7.5 hours after administration under various conditions. Alternatively, the time to peak plasma levels are from 6.0 to 7.0, from 5.5 to 7.0 or from 6.0 to 7.5.

It is also an object of this invention to provide a controlled or sustained release pharmaceutical formulation having a homogeneous core wherein the core component may be made using ordinary tablet compression techniques.

In accordance with the above-mentioned objects and others, the present invention provides a controlled release oral dosage form comprising an antihyperglycemic drug, preferably a biguanide (e.g., metformin or a pharmaceutically acceptable salt thereof) that is suitable for providing once-a-day administration of the drug, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the drug from 5.5 to 7.5 hours after administration. The dosage form comprises the drug and a membrane. In certain preferred embodiments, the dosage form comprises a tablet.

In preferred embodiments, the controlled release oral dosage form of the present invention is a tablet comprising:

(a) a core comprising:

(i) the antihyperglycemic drug;

(ii) optionally a binding agent; and

(iii) optionally an absorption enhancer;

(b) a membrane coating surrounding the core; and

(c) at least one passageway in the membrane.

When the drug is metformin or a pharmaceutically acceptable salt thereof and is administered on a once-a-day basis, the daily dose may vary, e.g., from about 500 mg to about 2500 mg. Such daily dose may be contained in one controlled-release dosage form of the invention, or may be contained in more than one such dosage form. For example, a controlled-release metformin dosage form may be formulated to contain about 1000 mg of the drug, and two of said dosage form may be administered together to provide once-a-day metformin therapy. The daily dose of the drug (i.e. metformin or pharmaceutically acceptable salt thereof) may range from about 500 mg to about 2500 mg, from about 1000 mg to about 2500 mg, or from about 2000 mg to about 2500 mg, depending on the clinical needs of the patient.

In certain preferred embodiments, the controlled release solid oral dosage form of the present invention provides a width at 50% of the height of a mean plasma concentration/time curve of the drug (e.g., of metformin) from about 4.5 to about 13 hours, more preferably from about 5.5 to about 10 hours, more preferably from about 6 to about 8 hours.

In certain embodiments, the controlled release oral dosage form of the present invention provides a mean maximum plasma concentration (C_{max}) of the antihyperglycemic drug which is more than about seven times the mean plasma level of said drug at about 24 hours after administration. In preferred embodiments, the controlled release oral dosage form of the present invention provides a mean maximum plasma concentration (C_{max}) of the drug which is from about 7 times to about 14 times the plasma level of the drug at about 24 hours after the administration, more preferably from about 8 times to about 12 times the plasma level of the drug at about 24 hours after administration.

In certain embodiments of the present invention, when the drug is metformin or a pharmaceutically acceptable salt thereof, the controlled release oral dosage form provides a mean

maximum plasma concentration (C_{max}) of the drug that is about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin, more preferably about 1700 ng/ml to about 2000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

In certain embodiments of the present invention, when the drug is metformin or a pharmaceutically acceptable salt thereof, the controlled release dosage form provides a mean AUC_{0-24hr} that is about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin; preferably about 17200 ng.hr/ml to about 26500 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin; more preferably about19800 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

In certain embodiments of the invention, the administration of the antihyperglycemic drug, e.g., at least one metformin dosage form provides a mean AUC_{0-24hr} from at least 80%, preferably at least 90% of the mean AUC_{0-24} provided by administration of the reference standard (GLUCOPHAGE) twice a day , wherein the daily dose of the reference standard is equal to the once-a day dose of metformin administered in the controlled release oral dosage form of the present invention.

In certain embodiments of the present invention, the controlled release dosage form exhibits the following dissolution profiles of the antihyperglycemic drug (e.g., metformin) when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal gastric fluid (pH 7.5 phosphate buffer) at 37° C: 0-30% of the drug released after 2 hours; 10-45% of the drug released after 4 hours; 30-90% of the drug released after 8 hours; not less than 50% of the drug released after 12 hours; not less than 60% of the drug released after 16 hours; and not less than 70% of the drug released after 20 hours.

In certain preferred embodiments, the controlled release solid oral dosage form exhibits the following dissolution profiles when tested in USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal gastric fluid (pH 7.5 phosphate buffer) at 37° C: 0-25% of the drug (e.g., metformin or a pharmaceutically acceptable salt thereof) released after 2 hours; 20-40% of the

drug released after 4 hours; 45-90% of the drug released after 8 hours; not less than 60% of the drug released after 12 hours; not less than 70% of the drug released after 16 hours; and not less than 80% of the drug released after 20 hours.

With respect to embodiments of the present invention where the antihyperglycemic drug is metformin, it has been found that drugs such as metformin provide substantially linear pharmacokinetics up to a level of about 2 grams per day. Therefore, it is contemplated for purposes of the present invention that a given plasma level (e.g., C_{max}) of metformin per specified dose will be directly proportional to other doses of metformin. Such proportional doses and plasma levels are contemplated to be within the scope of the invention and to be within the scope of the appended claims.

The dosage form of the present invention can provide therapeutic levels of the antihyperglycemic drug for twelve to twenty-four hour periods and does not exhibit a decrease in bioavailability if taken with food. In fact, a slight increase in the bioavailability of the antihyperglycemic drug is observed when the controlled release dosage form of the present invention is administered with food. In a preferred embodiment, the dosage form can be administered once-a-day, ideally with or after a meal, preferably with or after the evening meal, and provides therapeutic levels of the drug throughout the day with peak plasma levels being obtained between 5.5 to 7.5 hours after administration.

The present invention is also directed to a method of lowering blood glucose levels in human patients needing treatment for non-insulin-dependent diabetes mellitus (NIDDM), comprising orally administering to human patients on a once-a-day basis a dose of a drug comprising a biguanide (e.g., metformin or a pharmaceutically acceptable salt thereof), said drug being contained in at least one solid oral controlled release dosage form of the present invention. When the drug is metformin, the daily dose of the drug may be from about 500 mg to about 2500 mg, from about 1000 mg to about 2500 mg, or from about 2000 mg to about 2500 mg, depending on the clinical needs of the patient.

The controlled release dosage form of the present invention provides a delayed T_{max}, as compared to the T_{max} provided by GLUCOPHAGE. The delayed T_{max} occurs from 5.5 to 7.5

hours after administration. If the drug (e.g., metformin) is administered at dinner time, the T_{max} would occur during the time when gluconeogenesis is usually at its highest (e.g., around 2 a.m.).

The present invention also includes a method of treating patients with NIDDM comprising orally administering to human patients on a once-a-day basis a dose of a drug comprising a biguanide (e.g., metformin or a pharmaceutically acceptable salt thereof), contained in at least one oral controlled release dosage form of the present invention. When the drug is metformin, the daily dose of the drug may be from about 500 mg to about 2500 mg, from about 1000 mg to about 2500 mg, or from about 2000 mg to about 2500 mg, depending on the clinical needs of the patient. In certain embodiments, the method of treatment according to the present invention involves once-per-day metformin monotherapy as an adjunct to diet to lower blood glucose in patients with NIDDM whose hyperglycemia may not be satisfactorily managed on diet alone. In certain other embodiments, the once-a-day metformin therapy of the present invention may be used concomitantly with a sulfonylurea, e.g., when diet and monotherapy with a sulfonylurea alone do not result in adequate glycemic control. In certain other embodiments, the once-a-day metformin therapy of the present invention may be used concomitantly with a glitazone, e.g., when diet and monotherapy with a glitazone alone do not result in adequate glycemic control.

The present invention is further directed to a method of controlling the serum glucose concentration in human patients with NIDDM, comprising administering to patients having NIDDM on a once-a-day basis, preferably at dinner time, an effective dose of a biguanide (e.g., metformin) contained in at least one oral controlled release dosage form of the present invention.

The present invention further includes a controlled-release dosage form of a drug comprising a biguanide (e.g., metformin) suitable for once-a-day administration to human patients with NIDDM, the dosage form comprising an effective amount of the drug to control blood glucose levels for up to about 24 hours and an effective amount of a controlled-release carrier to provide controlled release of the drug with a mean time to maximum plasma concentration (T_{max}) of the drug from 5.5 to 7.5 hours after administration and a width at 50% of

the height of a mean plasma concentration/time curve of the drug from about 6 to about 13 hours. In preferred embodiments, the administration of the controlled-release dosage form occurs at fed state, more preferably at dinner time.

In certain preferred embodiments, the controlled-release dose of the drug (e.g., metformin or a pharmaceutically acceptable salt thereof) according to the present invention is provided by one or more of a controlled-release tablet comprising

(a) a core comprising:

(i) the antihyperglycemic drug (e.g., metformin or a pharmaceutically acceptable salt thereof);

(ii) optionally a binding agent; and

(iii) optionally an absorption enhancer;

(b) a membrane coating surrounding the core; and

(c) at least one passageway in the membrane.

In certain preferred embodiments, the mean time to maximum plasma concentration of the drug is reached from 6.5 to 7.5 hours after administration at dinner time.

In certain embodiments of the invention when the drug is a biguanide (e.g. metformin or a pharmaceutically acceptable salt thereof), the controlled release dosage form provides upon single administration, a higher mean fluctuation index in the plasma than an equivalent dose of an immediate release composition administered as two equal divided doses, one divided dose at the start of the dosing interval and the other divided dose administered 12 hours later, preferably maintaining bioavailability from at least 80% preferably from at least 90% of the immediate release composition.

In certain embodiments of the present invention, the mean fluctuation index of the dosage form is from about 1 to about 4, preferably about 2 to about 3, more preferably about 2.5.

In certain embodiments of the invention which exhibit a higher mean fluctuation index in the plasma than an equivalent dose of an immediate release composition administered as two equal divided doses, the ratio of the mean fluctuation index between the dosage form and the immediate release composition is about 3:1, preferably about 2:1, more preferably 1.5:1.

When the drug is metformin or a pharmaceutically acceptable salt thereof, the doses of drug which exhibit the above disclosed mean fluctuation indexes can be any effective dose administered to a patient with NIDDM for the reduction of serum glucose levels. For example, the dose can from about 500mg to about 2500mg, from about 1000mg to about 2000 mg or from about 850mg to about 1700mg metformin or pharmaceutically acceptable salt thereof.

The drugs which may used in conjunction with the present invention include those drugs which are useful for the treatment of non-insulin-dependent diabetes mellitus (NIDDM), including but not limited to biguinides such as metformin or buformin or pharmaceutically acceptable salts thereof. When the drug used in the present invention is metformin, it is preferred that the metformin be present in a salt form, preferably as metformin hydrochloride.

The term "metformin" as it is used herein means metformin base or any pharmaceutically acceptable salt e.g., metformin hydrochloride.

The term "dosage form" as it is used herein means at least one unit dosage form of the present invention (e.g. the daily dose of the antihyperglycemic agent can be contained in 2 unit dosage forms of the present invention for single once-a-day administration).

The term "morning" as it is used herein with respect to the dosing of the controlled release formulations of the invention means that the controlled release formulation is orally administered early in the day after the patient has awakened from overnight sleep, generally between about 6 a.m. and 11 a.m. (regardless of whether breakfast is eaten at that time, unless so specified herein).

The term "dinnertime" or "at dinner" as it is used herein with respect to the dosing of the controlled release formulations of the invention means that the controlled release formulation is orally administered at a time when dinner is normally eaten (regardless of whether a meal is actually eaten at that time, unless so specified herein), generally between about 4 p.m. and 8 p.m.

The term "bedtime" as it is used herein with respect to the dosing of the controlled release formulations of the invention means that the controlled release formulation is orally administered before the patient goes to bed in the evening, generally between about 8 p.m. and 12 p.m.

The term "therapeutically effective reduction" when used herein is meant to signify that blood glucose levels are reduced by approximately the same amount as an immediate release reference standard (e.g., GLUCOPHAGE®) or more, when the controlled release dosage form is orally administered to a human patient on a once-a-day basis.

The term "sustained release" and "controlled release" are used interchangeably in this application and are defined for purposes of the present invention as the release of the drug from the dosage form at such a rate that when a once-a-day dose of the drug is administered in the sustained release or controlled-release form, blood (e.g., plasma) concentrations (levels) of the drug are maintained within the therapeutic range but below toxic levels over a period of time from about 12 to about 24 hours. When the drug used in the present invention is metformin (preferably metformin hydrochloride) the controlled release solid oral dosage form containing such drug is also referred to as "Metformin XT."

The term "C_{max}" is the highest plasma concentration of the drug attained within the dosing interval, i.e., about 24 hours.

The term "C_{min}" is the minimum plasma concentration of the drug attained within the dosing interval, i.e. about 24 hours.

The term "C_{avg}" as used herein, means the plasma concentration of the drug within the dosing interval, i.e. about 24-hours, and is calculated as AUC/dosing interval.

The term "T_{max}" is the time period which elapses after administration of the dosage form at which the plasma concentration of the drug attains the highest plasma concentration of drug attained within the dosing interval (i.e., about 24 hours).

The term "AUC" as used herein, means area under the plasma concentration-time curve, as calculated by the trapezoidal rule over the complete 24-hour interval.

The term "steady state" means that the blood plasma concentration curve for a given drug does not substantially fluctuate after repeated doses to dose of the formulation.

The term "single dose" means that the human patient has received a single dose of the drug formulation and the drug plasma concentration has not achieved steady state.

The term "multiple dose" means that the human patient has received at least two doses of the drug formulation in accordance with the dosing interval for that formulation (e.g., on a once-a-day basis). Patients who have received multiple doses of the controlled release formulations of the invention may or may not have attained steady state drug plasma levels, as the term multiple dose is defined herein.

The term "a patient" means that the discussion (or claim) is directed to the pharmacokinetic parameters of an individual patient and/or the mean pharmacokinetic values obtained from a population of patients, unless further specified.

The term "mean", when preceding a pharmacokinetic value (e.g. mean T_{max}) represents the arithmetic mean value of the pharmacokinetic value taken from a population of patients unless otherwise specified (e.g. geometric mean)..

The term "Degree of Fluctuation" is expressed as $(C_{max} - C_{min})/C_{avg}$.

Brief Description of the Drawings

FIG. 1 is a graph showing the relative bioavailability of the metformin XT formulation of Example 2 to GLUCOPHAGE® for Clinical Study 2.

FIG. 2 is a graph showing the relative bioavailability of the metformin XT formulation of Example 1 (500 mg) to GLUCOPHAGE® for Clinical Study 3.

FIG. 3 is a graph showing the difference in plasma concentration-time profiles of metformin in eight healthy volunteers between Day 1 and Day 14 dosing following oral administration of the metformin XT formulation of Example 1, 4 x 500 mg q.d. for 14 days for Clinical Study 4.

FIG. 4 is a graph showing the mean plasma profiles and values of pharmacokinetic parameters of the metformin XT formulation of Example 3 for Clinical Study 5.

FIG. 5 is a graph showing the mean plasma glucose concentration-time profiles after 4 weeks of treatment with the metformin XT formulation of Example 3 and GLUCOPHAGE® for Clinical Study 5.

FIG. 6 is a graph showing the dissolution profile of a 500 mg controlled release metformin formulation of Example 1 of the present invention.

FIG. 7 is a graph showing the dissolution profile of a 850 mg controlled release metformin formulation of Example 2 of the present invention.

FIG. 8 is a graph showing the dissolution profile of a 1000 mg controlled release metformin formulation of Example 3 of the present invention.

Detailed Description of the Invention

The term antihyperglycemic drugs as used in this specification refers to drugs that are useful in controlling or managing noninsulin-dependent diabetes mellitus (NIDDM). Preferably, the antihyperglycemic drug is a biguanide such as metformin or buformin or a pharmaceutically acceptable salt thereof such as metformin hydrochloride.

It has surprisingly been found that when biguanides such as metformin are administered orally in a controlled release dosage form suitable for once-a-day dosing in the "fed" state, preferably at dinner, the bioavailability is improved as compared to the administration of the controlled release dosage form in the "fasted" state. This is in contrast to GLUCOPHAGE®, which exhibits opposite characteristics. In accordance with the methods and dosage forms of the present invention, it has been determined that the patients suffering from NIDDM achieve improved results (e.g., lowered blood glucose levels) than GLUCOPHAGE® administered according to accepted protocols, e.g., on a twice-a-day basis.

The methods and dosage forms of the invention provide the further advantage in that when dosed at dinnertime, the controlled release formulations of the invention provide a T_{max} (from 5.5 to 7.5 hours) after oral administration (which T_{max} is delayed relative to the reference standard, GLUCOPHAGE®), such that the level of drug is greatest at the time when human patients are manufacturing glucose at highest levels. Gluconeogenesis is well known to those skilled in the art to be greatest at night. Thus, in accordance with the invention, the T_{max} of the drug occurs for example between 11:30 p.m. and 1:30a.m., based on a dose administered at 6:00 p.m. Likewise, such administration of the dosage form provides lower drug levels during the day

(e.g. the afternoon) when gluconeogenesis is lower than at night. Also, the invention preferably provides the added benefit of lowering insulin levels. Insulin is considered a risk factor in NIDDM, in and of itself, for cardiovascular disease.

In comparison to a twice-daily dose of the reference standard (GLUCOPHAGE®), the plasma levels of metformin are preferably lower in the afternoon. This is an advantage particularly in patients who are under concomitant therapy with one or more additional antidiabetic agents, such as for example, a sulfonylurea. It is known in the art that to date approximately 60% of patients being treated with metformin are also being treated with at least one additional antidiabetic agent (such as a sulfonylurea). Sulfonylureas can possibly cause hypoglycemia, whereas metformin cannot, so there is a benefit to having lower metformin levels in the blood during the afternoon due to the potential for the patient to have hypoglycemia.

Accordingly, the present invention also includes a method of treating human patients with NIDDM comprising administering on a once-a-day basis a therapeutically effective dose of metformin in a controlled-release oral dosage form ("Metformin XT"), in combination with administering an effective amount of a sulfonylurea. In preferred embodiments, metformin is provided by a controlled release dosage form comprising metformin or a pharmaceutically acceptable salt thereof, the dosage form being useful for providing a once-a-day oral administration of the drug, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) of metformin from 5.5 to 7.5 hours after administration.

In certain embodiments, the combination therapy may be provided as follows. If patients do not respond to four weeks of the maximum dose of Metformin XT (2500 mg/ day) monotherapy, a sulfonylurea may be gradually added while maintaining the maximum dose of Metformin XT, even if prior primary or secondary failure to a sulfonylurea has occurred. Examples of the sulfonylurea include glyburide (glibenclamid), chloropropamide, tolbutamide, glipizide, acetohexamide and tolazamide. Although Metformin XT is preferably administered on once-a-day basis, the sulfonylurea may be administered in a different dosage form and at a different frequency.

With concomitant Metformin XT and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug.

In certain embodiments, the foregoing objectives are met by a controlled release dosage form comprising:

(a) a core comprising:

(i) an antihyperglycemic drug;

(ii) optionally a binding agent; and

(iii) optionally an absorption enhancer;

(b) a membrane coating surrounding the core; and

(c) at least one passageway in the membrane.

The binding agent may be any conventionally known pharmaceutically acceptable binder such as polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxyethyl cellulose, ethylcellulose, polymethacrylate, waxes and the like. Mixtures of the aforementioned binding agents may also be used. The preferred binding agents are water soluble such as polyvinyl pyrrolidone having a weight average molecular weight of 25,000 to 3,000,000. The binding agent comprises approximately about 0 to about 40% of the total weight of the core and preferably about 3% to about 15% of the total weight of the core.

The core may optionally comprise an absorption enhancer. The absorption enhancer can be any type of absorption enhancer commonly known in the art such as a fatty acid, a surfactant, a chelating agent, a bile salt or mixtures thereof. Examples of some preferred absorption enhancers are fatty acids such as capric acid, oleic acid and their monoglycerides, surfactants such as sodium lauryl sulfate, sodium taurocholate and polysorbate 80, chelating agents such as citric acid, phytic acid, ethylenediamine tetraacetic acid (EDTA) and ethylene glycol-big (B-aminoethyl ether -N,N,N,N-tetraacetic acid (EGTA). The core comprises approximately 0 to about 20% of the absorption enhancer based on the total weight of the core and most preferably about 2% to about 10% of the total weight of the core.

In this embodiment, the core which comprises the antihyperglycemic drug, the binder which preferably is a pharmaceutically acceptable water soluble polymer and the absorption

enhancer is preferably formed by wet granulating the core ingredients and compressing the granules with the addition of a lubricant into a tablet on a rotary press. The core may also be formed by dry granulating the core ingredients and compressing the granules with the addition of a lubricant into tablets or by direct compression.

Other commonly known excipients may also be included into the core such as lubricants, pigments or dyes.

The homogeneous core is coated with a membrane, preferably a polymeric membrane to form the controlled release tablet of the invention. The membrane can be a semipermeable membrane by being permeable to the passage of external fluid such as water and biological fluids and being impermeable to the passage of the antihyperglycemic drug in the core. Materials that are useful in forming the membrane are cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate, and cellulose acetate butyrate. Other suitable polymers are described in United States Patent Nos. 3,845,770, 3,916,899, 4,008,719, 4,036,228 and 4,11210 which are incorporated herein by reference. The most preferred membrane material is cellulose acetate comprising an acetyl content of 39.3 to 40.3%, commercially available from Eastman Fine Chemicals.

In an alternative embodiment, the membrane can be formed from the above-described polymers and a flux enhancing agent. The flux enhancing agent increases the volume of fluid imbibed into the core to enable the dosage form to dispense substantially all of the antihyperglycemic drug through the passageway and/or the porous membrane. The flux enhancing agent can be a water soluble material or an enteric material. Some examples of the preferred materials that are useful as flux enhancers are sodium chloride, potassium chloride, sucrose, sorbitol, mannitol, polyethylene glycol (PEG), propylene glycol, hydroxypropyl cellulose, hydroxypropyl methycellulose, hydroxyprophy methycellulose phthalate, cellulose acetate phthalate, polyvinyl alcohols, methacrylic acid copolymers and mixtures thereof. The preferred flux enhancer is PEG 400.

The flux enhancer may also be a drug that is water soluble such as metformin or its pharmaceutically acceptable salts or a drug that is soluble under intestinal conditions. If the flux enhancer is a drug, the present dosage form has the added advantage of providing an immediate release of the drug which is selected as the flux enhancer.

The flux enhancing agent comprises approximately 0 to about 40% of the total weight of the coating, most preferably about 2% to about 20% of the total weight of the coating. The flux enhancing agent dissolves or leaches from the membrane to form paths in the membrane for the fluid to enter the core and dissolve the active ingredient.

In alternate embodiments, the membrane may also be formed with commonly known excipients such as a plasticizer. Some commonly known plasticizers include adipate, azelate, enzoate, citrate, stearate, isoebucate, sebacate, triethyl citrate, tri-n-butyl citrate, acetyl tri-n-butyl citrate, citric acid esters, and those described in the Encyclopedia of Polymer Science and Technology, Vol. 10 (1969), published by John Wiley & Sons. The preferred plasticizers are triacetin, acetylated monoglyceride, grape seed oil, olive oil, sesame oil, acetyltributylcitrate, acetyltriethylcitrate, glycerin sorbitol, diethyloxalate, diethylmalate, diethylfumarate, dibutylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacate, triethylcitrate, tributylcitrate, glyceroltributyrate, and the like. Depending on the particular plasticizer, amounts of from 0 to about 25%, and preferably about 2% to about 15% of the plasticizer can be used based upon the total weight of the coating.

As used herein the term passageway includes an aperture, orifice, bore, hole, weakened area or an erodible element such as a gelatin plug that erodes to form an osmotic passageway for the release of the antihyperglycemic drug from the dosage form. A detailed description of the passageway can be found in United States Patent Nos. such as 3,845,770, 3,916,899, 4,034,758, 4,063,064, 4,077,407, 4,088,864, 4,783,337 and 5,071,607 (the disclosures of which are hereby incorporated by reference).

In certain embodiments, the passageway is formed by laser drilling. In other embodiments, the passageway is formed by making an indentation onto the core prior to the membrane coating to form a weakened area of the membrane at the point of the indentation. In

preferred embodiments of the invention, the dosage form contains two passageways in order provide the desired pharmacokinetic parameters of the formulation.

Generally, the membrane coating around the core will comprise from about 1% to about 7%, preferably about 1.5% to about 3%, based on the total weight of the core and coating.

The term "membrane" means a membrane that is permeable to both aqueous solutions or bodily fluids and to the active drug or pharmaceutical ingredient (e.g. the formulations of Examples 1-3). Thus, the membrane is porous to drug and, in a preferred embodiment, drug is released through the hole or passageway and through the porous membrane in solution or in vivo. The term "membrane" also generically encompasses the term "semipermeable membrane" as heretofore defined.

In an alternative embodiment, the dosage form of the present invention may also comprise an effective amount of the antihyperglycemic drug that is available for immediate release. The effective amount of antihyperglycemic drug for immediate release may be coated onto the membrane of the dosage form or it may be incorporated into the membrane.

In certain preferred embodiments of the invention where the dosage form is prepared in accordance with the above, the dosage form will have the following composition:

INGREDIENT	Preferred	Most Preferred
CORE:		
Drug	50-98%	75-95%
Binder	0-40%	3-15%
Absorption Enhancer	0-20%	2-10%
COATING:		
Membrane Polymer	50-99%	75-95%
Flux Enhancer	0-40%	2-20%
Plasticizer	0-25% or 0-30%	2-15%

The dosage forms prepared according to certain embodiments of the present invention preferably exhibit the following dissolution profile when tested in a USP type 2 apparatus at 75 rpms in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37°C:

Time (Hours)	Preferred	Most Preferred
2	0-30%	0-15% or 0-25%
4	10-45%	20-40%
8	30-90%	45-90%
12	NTL 50%	NTL 60%
16	NTL 60%	NTL 70%
20	NTL 70%	NTL 80%

NTL = Not less than

In the preparation of the tablets of the invention, various conventional well known solvents may be used to prepare the granules and apply the external coating to the tablets of the invention. In addition, various diluents, excipients, lubricants, dyes, pigments, dispersants, etc. which are disclosed in Remington's Pharmaceutical Sciences, 1995 Edition may be used to optimize the formulations of the invention.

Other controlled release technologies known to those skilled in the art can be used in order to achieve the controlled release formulations of the present invention, i.e., formulations which provide a mean T_{max} of the drug and/or other pharmacokinetic parameters described herein when orally administered to human patients. Such formulations can be manufactured as a controlled oral formulation in a suitable tablet or multiparticulate formulation known to those skilled in the art. In either case, the controlled release dosage form may optionally include a

controlled release carrier which is incorporated into a matrix along with the drug, or which is applied as a controlled release coating.

An oral dosage form according to the invention may be provided as, for example, granules, spheroids, beads, pellets (hereinafter collectively referred to as "multiparticulates") and/or particles. An amount of the multiparticulates which is effective to provide the desired dose of drug over time may be placed in a capsule or may be incorporated in any other suitable oral form.

In certain preferred embodiments, the tablet core or multiparticulates containing the drug are coated with a hydrophobic material selected from (i) an alkylcellulose and (ii) a polymeric glycol. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2 to about 25% of the substrate in order to obtain a desired sustained release profile. The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like as previously disclosed.

Description of Certain Preferred Embodiments

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

Example 1

A controlled release tablet containing 500 mg of metformin HCl and having the following formula is prepared as follows:

I. Core

Ingredients	Amount (mg/tab)
Metformin HCl	500.0
Povidone[3], USP	36.0
Sodium Lauryl Sulfate	25.8
Magnesium Stearate	2.8

[3]approximate molecular weight = 1,000,000; dynamic viscosity (10%w/v solution at 20°C) = 300-700 m Pa s.

(a) Granulation

The metformin HCl and sodium lauryl sulfate are delumped by passing them through a 40 mesh screen and collecting them in a clean, polyethylene-lined container. The povidone, K-90-F is dissolved in purified water. The delumped metformin HCl and sodium lauryl sulfate are then added to a top-spray fluidized bed granulator and granulated by spraying with the binding solution of povidone under the following conditions: inlet air temperature of 50-70°C; atomization air pressure of 1-3 bars; and spray rate of 10-100 ml/min.

Once the binding solution is depleted, the granules are dried in the granulator until the loss on drying is less than 2%. The dried granules are passed through a Comil equipped with the equivalent of an 18 mesh screen.

(b) Tableting

The magnesium stearate is passed through a 40 mesh stainless steel screen and blended with the metformin HCl granules for approximately five (5) minutes. After blending, the granules are compressed on a rotary press fitted with 15/32" round standard concave punches.

(c) Seal Coating (optional)

The core tablet is seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably Opadry Clear (YS-1-7006), in purified water. The Opadry solution is then sprayed onto the core tablet using a pan coater under the following conditions: exhaust air temperature of 38-42°C; atomization pressure of 28-40 psi; and spray rate of 10-15 ml/min. The Opadry Clear of the coating constitutes about 11.5 mg/tablet.

II. Sustained Release Coating

Ingredients	Amount (mg/tablet)
Cellulose Acetate (398-10)[2]	21.5
Triacetin	1.3
PEG 400	2.5

[2]acetyl content 39.3 - 40.3%

The cellulose acetate is dissolved in acetone while stirring with a homogenizer. The polyethylene glycol 400 and triacetin are added to the cellulose acetate solution and stirred until a clear solution is obtained. The tablet is coated by spraying the clear coating solution onto the seal coated tablets in a fluidized bed coater employing the following conditions: product temperature of 16-22°C; atomization pressure of approximately three bars; and spray rate of 120-150 ml/min.

(d) Laser Drilling

The coated tablets were laser drilled two holes (one hole on each side of the tablet).

Example 2

A controlled release tablet containing 850 mg of metformin HCl and having the following formula is prepared as follows:

I. Core

Ingredients	Amount (mg/tab)
Metformin HCl	850.0
Povidone[3], USP	61.1
Sodium Lauryl Sulfate	43.9
Magnesium Stearate	4.8

[3]approximate molecular weight = 1,000,000; cynamic viscosity (10%w/v solution at 20°C) = 300-700 m Pa s.

(a) Granulation

The metformin HCl and sodium lauryl sulfate are delumped by passing them through a 40 mesh screen and collecting them in a clean, polyethylene-lined container. The povidone, K-90-F is dissolved in purified water. The delumped metformin HCl and sodium lauryl sulfate are then added to a top-spray fluidized bed granulator and granulated by spraying with the binding solution of povidone under the following conditions: inlet air temperature of 50-70°C; atomization air pressure of 1-3 bars; and spray rate of 10-100 ml/min.

Once the binding solution is depleted, the granules are dried in the granulator until the loss on drying is less than 2%. The dried granules are passed through a Comil equipped with the equivalent of an 18 mesh screen.

(b) Tableting

The magnesium stearate is passed through a 40 mesh stainless steel screen and blended with the metformin HCl granules for approximately five (5) minutes. After blending, the granules are compressed on a rotary press fitted with 15/32" round standard concave punches.

(c) Seal Coating (optional)

The core tablet is seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably Opadry Clear (YS-1-7006), in purified water. The Opadry solution is then sprayed onto the core tablet using a pan coater under the following conditions: exhaust air temperature of 38-42°C; atomization pressure of 28-40 psi; and spray rate of 10-15 ml/min. The Opadry Clear of the coating constitutes about 11.5 mg/tablet.

II. Sustained Release Coating

Ingredients	Amount (mg/tablet)
Cellulose Acetate (398-10)[2]	24.0
Triacetin	1.4
PEG 400	2.8

[2]acetyl content 39.3 - 40.3%

The cellulose acetate is dissolved in acetone while stirring with a homogenizer. The polyethylene glycol 400 and triacetin are added to the cellulose acetate solution and stirred until a clear solution is obtained. The tablet is coated by spraying the clear coating solution onto the seal coated tablets in a fluidized bed coater employing the following conditions: product temperature of 16-22°C; atomization pressure of approximately three bars; and spray rate of 120-150 ml/min.

(d) Laser Drilling

The coated tablets were laser drilled two holes (one hole on each side of the tablet).

Example 3

A controlled release tablet containing 1000 mg of metformin HCl and having the following formula is prepared as follows:

I. Core

Ingredients	Amount (mg/tablet)
Metformin HCl	1000.0
Povidone[3], USP	71.9
Sodium Lauryl Sulfate	51.7
Magnesium Stearate	5.6

[3]approximate molecular weight = 1,000,000; dynamic viscosity (10%w/v solution at 20°C) = 300-700 m Pa s.

(a) Granulation

The metformin HCl and sodium lauryl sulfate are delumped by passing them through a 40 mesh screen and collecting them in a clean, polyethylene-lined container. The povidone, K-90-F is dissolved in purified water. The delumped metformin HCl and sodium lauryl sulfate are then added to a fluidized bed granulator and granulated by spraying with the binding solution of povidone under the following conditions: inlet air temperature of 50-70°C; atomization air pressure of 1-3 bars; and spray rate of 10-100 ml/min.

Once the binding solution is depleted, the granules are dried in the granulator until the loss on drying is less than 2%. The dried granules are passed through a Comil equipped with a screen equivalent to 18 mesh.

(b) Tableting

The magnesium stearate is passed through a 40 mesh stainless steel screen and blended with the metformin HCl granules for approximately five (5) minutes. After blending, the granules are compressed on a rotary press fitted with ½" round standard concave punches.

(c) Seal Coating (optional)

The core tablet is seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably Opadry Clear (YS-1-7003), in purified water. The Opadry solution is then sprayed onto the core tablet using a pan coater under the following conditions: exhaust air temperature of 38-42°C; atomization pressure of 28-40 psi; and spray rate of 10-15 ml/min. The core tablet is coated with the sealing solution until the tablet is coated with 23.0 mg/tablet of the Opadry material.

II. Sustained Release Coating

Ingredients	Amount (mg/tablet)
Cellulose Acetate (398-10)[2]	19.0
Triacetin	1.1
PEG 400	2.2

[2]acetyl content 39.3 - 40.3%

The cellulose acetate is dissolved in acetone while stirring with a homogenizer. The polyethylene glycol 400 and triacetin are added to the cellulose acetate solution and stirred until a clear solution is obtained. The tablet is coated by spraying the clear coating solution onto the seal coated tablets in a fluidized bed coater employing the following conditions: product temperature of 16-22°C; atomization pressure of approximately three bars; and spray rate of 120-150 ml/min.

(d) Laser Drilling

The coated tablets were laser drilled two holes (one hole on each side of the tablet).

(e) **Color Coating (optional)**

Subsequent to the sustained release coating, the laser drilled tablet is coated with a color coating using Opadry White (24 mg/tablet) and waxed with Candelilla wax powder (0.4 mg/tablet).

Clinical Studies

Study 1

In study 1, a total of twelve (12) healthy subjects (six males, six females) were randomized to receive either a single oral dose of metformin XT, 850mg, prepared in accordance with Example 2 or b.i.d. doses of GLUCOPHAGE in assigned study periods which consisted of one of the following groups: Group A - metformin XT (2 x 850 mg tablets) taken at approximately 8:00 a.m., immediately following breakfast, Group B - metformin XT (2 x 850 mg tablets) taken at approximately 6:00 p.m., immediately following dinner; and Group C - GLUCOPHAGE (1 x 850 mg tablet) taken at approximately 8:00 a.m., immediately following breakfast, and at approximately 6:00 p.m., immediately following dinner. Each drug administration was separated by a washout period of seven days. In this study, one male subject was removed from the study prior to Period II due to non-treatment-related mononucleosis. Thus, 11 (five males and six females) subjects completed the study.

For metformin XT, plasma samples were obtained from subjects at 0 (predose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 24 hour(s) after dosing. For GLUCOPHAGE, plasma samples were obtained from subjects at 0 (predose), 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22, and 24 hour(s) after the first dose in the morning. Plasma concentrations of metformin were determined using a validated HPLC method. The lower quantitation limit of this method is 10 ng/ml. Mean plasma concentration-time profiles are shown in Fig. 1 and mean values of pharmacokinetic parameters of metformin obtained from this study are presented in Table 1.

Table 1

Mean (±SD, n = 11) values of pharmacokinetic parameters of metformin (Example 2) in 11 healthy subjects (metformin XT, 2 x 850 mg q.d. or GLUCOPHAGE, 1 x 850 mg b.i.d.)

						Geometric Mean Ratio*	
Treatment	**$AUC_{0-\infty}$ (ng-hr/ml)**	**C_{max} (ng/ml)**	**T_{max} (hr.)**	**T_{lag} (hr)**	**$t_{1/2}$ (hr)**	$AUC_{0-\infty}$	C_{max}
Metformin XT after breakfast	18156 (4183)	2045 (567)	6 (2)	0.18 (0.40)	4.4 (0.7)	1.00	1.36
Metformin XT after dinner	18277 (2961)	1929 (333)	7 (2)	0.09 (0.30)	3.6 (0.8)	1.02	1.32
GLUCOPHAGE	18050 (3502)	1457 (217)	5 (3)	0 (0)	3.5 (0.9)	–	–

*Ratio = Metformin XT/GLUCOPHAGE

As shown in Figure 1 and Table 1, when metformin XT was administered immediately after either breakfast or dinner, the relative bioavailability of metformin XT formulation to GLUCOPHAGE is approximately 100%.

The results of study 1 were used to calculate the approximate degree of fluctuation (C_{max} - C_{min}/C_{avg}) of the formulations.

The C_{max} was directly obtained from the study (see Table 1). The C_{avg} was obtained by dividing the AUC value by the dosing interval, i.e. 24 hours. The value for C_{min} was extrapolated from Figure 1.

The results are set forth in Table 2 below:

Table 2

Mean (±SD, n = 12) values of pharmacokinetic parameters of metformin XT in 12 healthy subjects (metformin XT, 2 x 850 mg q.d. and GLUCOPHAGE, 850 mg b.i.d.)

Treatment	$AUC_{0-\infty}$ (ng-hr/ml)	C_{max} (ng/ml)	C_{min} (ng/ml)	C_{avg} (ng/ml)	Degree of Fluctuation
Metformin XT after breakfast	18156 (4183)	2045 (567)	143	756	2..51
Metformin XT after dinner	18277 (2961)	1929 (333)	107	761	2.39
GLUCOPHAGE	18050 (3502)	1457 (217)	214 (at 24 hours)	752	1.65
			393 (between doses)	752	1.41

As shown in Figure 1 and Table 2, a single administration of the metformin XT formulation provides a higher mean fluctuation index in the plasma than a substantially equal dose of Glucophage administered as two equal divided doses, one divided dose at the start of the dosing interval and the other divided dose administered 12 hours later.

Study 2

The study design of Study 2 is the same as Study 1 except for the formulation and the dose (4 x 500 mg q.d., total dose 2000mg, for metformin XT prepared according to Example 1 and 2 x 500 mg b.i.d., total dose 2000mg, for GLUCOPHAGE in the second study). In this study, 12 healthy volunteers (five males and seven females) were randomized to receive treatments and completed the study. Mean plasma concentration-time profiles and mean values

of pharmacokinetic parameters of metformin obtained from this study are presented in Figure 2 and Table 3.

As shown in Figure 2 and Table 3, when the metformin XT formulation (500 mg) was administered immediately after dinner, the relative bioavailability of this formulation to GLUCOPHAGE is approximately 100%, while the mean C_{max} value is about the same. The relative bioavailability of metformin XT, however, is approximately 80% when administered immediately after breakfast. A prolonged profile, together with later T_{max} and similar C_{max} of metformin following administration of metformin XT immediately after dinner compared to GLUCOPHAGE indicated that metformin was released *in vivo* in a sustained fashion (Figure 2).

Table 3

Mean (±SD, n = 12) values of pharmacokinetic parameters of metformin of Example 1 in 12 healthy subjects (metformin XT, 4 x 500 mg q.d. or GLUCOPHAGE, 2 x 500 mg b.i.d.)

						Geometric Mean Ratio*	
Treatment	**$AUC_{0-\infty}$ (ng-hr/ml)**	**C_{max} (ng/ml)**	**T_{max} (hr)**	**T_{lag} (hr)**	**$t_{1/2}$ (hr)**	**$AUC_{0-\infty}$**	**C_{max}**
Metformin XT after breakfast	17322 (4984)	2127 (545)	5 (1)	0 (0)	6.1 (1.8)	0.80	1.15
Metformin XT after dinner	20335 (4360)	2053 (447)	7 (2)	0.08 (0.29)	3.9 (0.6)	0.96	1.12
GLUCOPHAGE	21181 (4486)	1815 (302)	4 (3)	0 (0)	3.6 (0.8)	--	--

*Ratio = Metformin XT/GLUCOPHAGE

The results of study 2 were used to calculate the approximate degree of fluctuation of the formulations in accordance with the calculations used in study 1 (using Figure 2 to obtain the extrapolated value for C_{min}).

The results are set forth in Table 4 below:

Table 4

Mean (±SD, n = 12) values of pharmacokinetic parameters of metformin XT in 12 healthy subjects (metformin XT, 4 x 500 mg q.d. and GLUCOPHAGE, 2 x 500 mg b.i.d.)

Treatment	$AUC_{0-\infty}$ (ng-hr/ml)	C_{max} (ng/ml)	C_{min} (ng/ml)	C_{avg} (ng/ml)	Degree of Fluctuation
Metformin XT after breakfast	17322 (4984)	2127 (545)	143	721	2.9
Metformin XT after dinner	20335 (4360)	2053 (447)	143	847	2.25
GLUCOPHAGE	21181 (4486)	1815 (302)	214 (at 24 hours)	882	1.8
			357 (between doses)	882	1.65

As shown in Figure 2 and Table 4, a single administration of the metformin XT formulation provides a higher mean fluctuation index in the plasma than an equivalent dose of Glucophage administered as two equal divided doses, one divided dose at the start of the dosing interval and the other divided dose administered 12 hours later.

Study 3

In Study 3, a multiple-dose, open-label, one-period study was conducted to evaluate the short-term tolerability and steady-state pharmacokinetics of the 500 mg metformin XT formulation used in Study 2. In this study, eight healthy volunteers (four males and four females) were randomized to receive 2000 mg of metformin XT (4 x 500 mg tablets) at approximately 6:00 p.m., immediately following dinner, for 14 days.

Blood samples were obtained from each subject at 0 (predose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16 and 24 hour(s) following the first dose on Day 1 and at 0 (predose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24, 38 and 48 hour(s) following the last dose on Day 14. Blood samples were also drawn from each subject immediately prior to dosing on Days 10-13. Urine samples were collected from each subject at the following time intervals: six hours prior to the first dose; 0-6, 6-12 and 12-24 hours after the first dose; and 0-6, 6-12, 12-24 and 24-48 hours after the last dose.

Mean plasma profiles and values of pharmacokinetic parameters of metformin are presented in Table 5 below:

Table 5

Mean Pharmacokinetic Parameters (Example 1)

Day 1

	C_{max}	T_{max}	$AUC_{0-24hr\ (ng.hr/ml)}$
Mean	2435	6.9	22590
SD	630	1.9	3626

Day 14

	C_{max}	T_{max}	$AUC_{0-24hr\ (ng.hr/ml)}$
Mean	2288	6.9	24136
SD	736	2.5	7996

Following oral administration of metformin XT, 4 x 500 mg q.d., for 14 days, there was little or no difference in plasma concentration-time profiles of metformin in eight healthy volunteers between Day 1 and Day 14 dosing (Figure 3). On average, trough plasma concentrations of metformin were nearly constant, ranging from 188.8 to 205.1 ng/ml on Days 10-14, indicating that the steady state of metformin was attained rapidly. The mean

accumulation ratio was 1.01, indicating that the once-daily dose regimen of metformin XT results in no accumulation.

Following oral administration of a single dose (4 x 500 mg) of metformin XT, approximately 31% of the dose was excreted in the urine within the first 24 hours. On average, the renal clearance of metformin was 366 ml/min. A slightly higher renal clearance (454 ml/min) was found after multiple-dose administration of 4 x 500 mg q.d. of metformin XT.

Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence and anorexia) are the most common adverse reactions to GLUCOPHAGE. In controlled trials, GLUCOPHAGE was started at low, nontherapeutic doses and gradually titrated to higher doses. In spite of this gradual titration, GLUCOPHAGE was discontinued due to gastrointestinal reactions in approximately 4% of patients. In contrast, in the multiple-dose study, metformin XT begun at a therapeutic initial dose of 2000 mg once daily with dinner was well tolerated by all healthy volunteers. Diarrhea and nausea were the most common gastrointestinal reactions probably or possibly related to metformin XT. These reactions, however, were either mild or moderate. This suggests that it may be possible to initiate metformin XT treatment with effective doses rather than using the slow titration from non-therapeutic doses required for GLUCOPHAGE.

Study 4

Study 4 was a study designed to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of metformin XT compared to GLUCOPHAGE after multiple-dose treatment in patients with NIDDM. Metformin XT tablets prepared according to Example 3 were used in this study. This study had a single-center, randomized, two-way crossover design. A total of 24 NIDDM patients who were on a stable dose of GLUCOPHAGE, between 1000 and 2550 mg/day, for at least 12 weeks were selected for the study. A Pretreatment Period of at least 3 weeks preceded randomization to study treatment. At the start of the Pretreatment Period, all patients stopped taking any other hypoglycemic agents besides GLUCOPHAGE, and the GLUCOPHAGE dose was adjusted to 1000 mg b.i.d. (with breakfast and with dinner).

Following the pretreatment period, patients began Treatment Period I, which lasted 4 weeks. During Period I, a total of 12 patients were randomized to receive two 1000-mg metformin XT tablets q.d. (immediately after dinner), at approximately 6:00 p.m., and 12 were randomized to receive one 1000-mg GLUCOPHAGE tablet b.i.d. (immediately after breakfast and immediately after dinner). Immediately following Period I, each patient was switched to the alternate medication for 4 weeks in Period II. There was no washout between treatment periods.

Plasma metformin concentrations were determined over a 24-hour period at the end of Treatment Periods I and II as follows: immediately prior to dosing and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 15, 16, 17, 18, 19, 20, 22, and 24 hours after the evening dose. One subject withdrew from the study for personal reasons after two weeks of treatment in Treatment Period I, thus pharmacokinetic data were obtained from 23 patients.

Mean plasma profiles and values of pharmacokinetic parameters of metformin are presented in Figure 4 and Table 6. As shown in Figure 4 and Table 6, when metformin XT was administered immediately after dinner, the bioavailability of metformin XT relative to GLUCOPHAGE at steady state is close to 100%. Although the dose of metformin XT was twice as large as the dose of GLUCOPHAGE at dinner, the mean C_{max} value was only 32% higher.

Table 6

Mean (± SD) values of pharmacokinetic parameters of metformin of Example 3 in 23 NIDDM patients (metformin XT, 2 x 1000 mg q.d. with dinner or GLUCOPHAGE, 1 x 1000 mg b.i.d.)

						Geometric Mean Ratio*	
Treatment	AUC_{0-24hr} (ng•hr/ml)	C_{max} (ng/ml)	T_{max} (hr)	T_{lag} (hr)	$t_{½}$ (hr)	AUC_{0-24hr}	C_{max}
Metformin XT after dinner	26818 (7052)	2849 (797)	6 (2)	0 (0)	5.4	0.96	1.32
GLUCOPHAGE	27367 (5759)	2131 (489)	14 (6)	0 (0)	4.4	--	--

* Ratio = Metformin XT/GLUCOPHAGE

When the metformin XT was administered immediately after dinner, the bioavailability of metformin XT relative to GLUCOPHAGE at steady state was close to 100%. However, when metformin XT was administered immediately after breakfast, the corresponding relative bioavailability of metformin XT was approximately 80%. The safety profile of metformin XT, 2000 mg given once daily either after dinner or after breakfast was comparable to that of an equal dose of GLUCOPHAGE given b.i.d. The efficacy profile of metformin XT, 2000 mg given once daily after dinner was similar to that of an equal dose of GLUCOPHAGE given b.i.d. The efficacy of metformin XT, 2000 mg given once daily after breakfast, however, appeared to be comparable to or slightly less than that of GLUCOPHAGE given b.i.d.

While certain preferred and alternative embodiments of the invention have been set forth for purposes of disclosing the invention, modifications to the disclosed embodiments may occur to those who are skilled in the art. Accordingly, the appended claims are intended to cover all embodiments of the invention and modifications thereof which do not depart from the spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising an effective dose of at least one suitable antihyperglycemic drug or a pharmaceutically acceptable salt thereof and a controlled-release carrier, said dosage form being suitable for providing once-a-day oral administration of the agent or pharmaceutically acceptable salt thereof, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the agent from 5.5 to 7.5 hours after the administration.

2. The controlled release dosage form of claim 1 wherein said at least one antihyperglycemic drug is a biguanide.

3. The controlled release dosage form of claim 2 wherein said biguanide is metformin or a pharmaceutically acceptable salt thereof.

4. The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of the drug from 6.0 to 7.0 hours after the administration of the dose.

5. The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of the drug from 5.5 to 7.0 hours after the administration of the dose, when the dose is administered at dinner time.

6. The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of the drug from about 6.0 to 7.5 hours after the administration of the dose, when the dose is administered at breakfast.

7. The controlled release oral dosage form of claim 1, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:
0-30% of the drug is released after 2 hours;
10-45% of the drug is released after 4 hours;
30-90% of drug is released after 8 hours;
not less than 50% of the drug is released after 12 hours;
not less than 60% of the drug is released after 16 hours; and
not less than 70% of the drug is released after 20 hours.

Sub B3

8. The controlled release oral dosage form of claim 1, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:
0-25% of the drug is released after 2 hours;
20-40% of the drug is released after 4 hours;
45-90% of the drug is released after 8 hours;
not less than 60% of the drug is released after 12 hours;
not less than 70% of the drug is released after 16 hours; and
not less than 80% of the drug is released after 20 hours.

9. The controlled release oral dosage form of claim 1, which provides a width at 50% of the height of a mean plasma concentration/time curve of the drug from about 4.5 to about 13 hours.

10. The controlled release oral dosage form of claim 1, which provides a width at 50% of the height of a mean plasma concentration/time curve of the drug from about 5.5 to about 10 hours.

11. The controlled release oral dosage form of claim 3, which provides a mean maximum plasma concentration (C_{max}) of metformin which is more than about 7 times the mean plasma level of said metformin at about 24 hours after the administration.

12. The controlled release oral dosage form of claim 3, which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 7 times to about 14 times the plasma level of said metformin at about 24 hours after administration.

13. The controlled release oral dosage form of claim 3 which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 8 times to about 12 times the plasma level of said metformin at about 24 hours after administration.

14. The controlled release oral dosage form of claim 3 which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

15. The controlled release oral dosage form of claim 3, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1700 ng/ml to about 2000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

16. The controlled release oral dosage form of claim 3 which provides a mean AUC_{0-24hr} of at least 80% of the mean AUC_{0-24} provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

17. The controlled release oral dosage form of claim 3 which provides a mean AUC_{0-24hr} of at least 90% of the mean AUC_{0-24} provided by administration of an immediate release

reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

18. The controlled release oral dosage form of claim 3 which provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

19. The controlled release oral dosage form of claim 3 which provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 26500 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

20. The controlled release oral dosage form of claim 3 which provides a mean $AUC_{0\text{-}24hr}$ from about19800 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

21. The controlled release oral dosage form of claim 3 which provides a mean plasma concentration-time profiles of metformin substantially as set forth in FIG. 1, based on administration of a 1700 mg once-a-day dose of metformin.

22. The controlled release oral dosage form of claim 3 which provides a mean plasma concentration-time profiles of metformin substantially as set forth in FIG. 2, based on administration of a 2000 mg once-a-day dose of metformin.

23. The controlled release oral dosage form of claim 3 which provides a mean plasma concentration-time profiles of metformin substantially as set forth in FIG. 4, based on administration of a 2000 mg once-a-day dose of metformin at dinner.

24. The controlled release oral dosage form of claim 3 which provides a mean plasma concentration-time profiles of metformin substantially as set forth in FIG. 6, based on administration of a 2000 mg once-a-day dose of metformin at breakfast.

25. The controlled release oral dosage form of claim 3 which provides a mean plasma glucose concentration-time profiles substantially as set forth in FIG. 5, based on administration of a 2000 mg once-a-day dose of metformin at dinner.

26. The controlled release oral dosage form of claim 9, which provides a mean time to maximum plasma concentration (T_{max}) of metformin from 6.0 to 7.0 hours after the administration.

27. The controlled release oral dosage form of claim 9, which provides a mean time to maximum plasma concentration (T_{max}) of metformin from 5.5 to 7.0 hours after administration at dinner time.

28. The controlled release oral dosage form of claim 9, which provides a mean time to maximum plasma concentration (T_{max}) of metformin from 6.0 to 7.5 hours after administration at breakfast.

29. The controlled release dosage form of claim 1, wherein the metformin is provided by at least one controlled-release tablet, said tablet comprising:

(a) a core comprising:

(i) the metformin or a pharmaceutically acceptable salt;

(ii) optionally a binding agent; and

(iii) optionally an absorption enhancer;

(b) a membrane coating surrounding the core; and

(c) at least one passageway in the membrane.

30. The controlled release oral dosage form of claim 29, wherein said membrane is a semipermeable membrane.

31. A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising at least one biguanide or pharmaceutically acceptable salt thereof and a controlled release carrier wherein a single administration of said dosage form provides a higher mean fluctuation index in the plasma than a substantially equal dose of an immediate release composition administered as two equal divided doses, one divided dose at the start of the dosing interval and the other divided dose administered 12 hours later.

32. The controlled release oral dosage form of claim 31 wherein the mean fluctuation index of the dosage form is from about 1 to about 4.

33. The controlled release oral dosage form of claim 32 wherein the mean fluctuation index of the dosage form is from about 2 to about 3.

34. The controlled release oral dosage form of claim 33 wherein the mean fluctuation index of the dosage form is about 2.5.

35. The controlled release oral dosage form of claim 31 wherein the ratio of the mean fluctuation index between the dosage form and the immediate release composition is about 3:1.

36. The controlled release oral dosage form of claim 35 wherein the ratio of the mean fluctuation index between the dosage form and the immediate release composition is about 2:1.

37. The controlled release oral dosage form of claim 36 wherein the ratio of the mean fluctuation index between the dosage form and the immediate release composition is about 1.5:1.

38. The controlled release oral dosage form of claim 31 wherein said dosage form comprises metformin or a pharmaceutically acceptable salt thereof.

39. The controlled release oral dosage form of claim 31 wherein said dosage form maintains bioavailability from at least about 80% of the immediate release composition.

40. The controlled release oral dosage form of claim 31 wherein the substantially equal dose of the dosage form and the immediate release composition comprises from about 500mg to about 2500 mg metformin or pharmaceutically acceptable salt thereof.

41. The controlled release oral dosage form of claim 40 wherein the substantially equal dose of the dosage form and the immediate release composition comprises from about 1000mg to about 2000 mg metformin or pharmaceutically acceptable salt thereof.

42. The controlled release oral dosage form of claim 40 wherein the substantially equal dose of the dosage form and the immediate release composition comprises from about 850mg to about 1700mg metformin or pharmaceutically acceptable salt thereof.

ABSTRACT

A composition for treating patients having non-insulin-dependent diabetes mellitus (NIDDM) by administering a controlled release oral solid dosage form containing preferably a biguanide drug such as metformin, on a once-a-day basis. The dosage form provides a mean time to maximum plasma concentration (T_{max}) of the drug which occurs at 5.5 to 7.5 hours after oral administration on a once-a-day basis to human patients. Preferably, the dose of drug is administered at dinnertime to a patient in the fed state.

PRINT OF DRAWINGS
AS ORIGINALLY FILE

FIGURE 1

Mean plasma concentration-time profiles of metformin in eleven subjects after an oral administration of metformin XT (2 x 500 mg q.d.) or GLUCOPHAGE (850 mg b

PRINT OF DRAWINGS
AS ORIGINALLY FILED

FIGURE 2

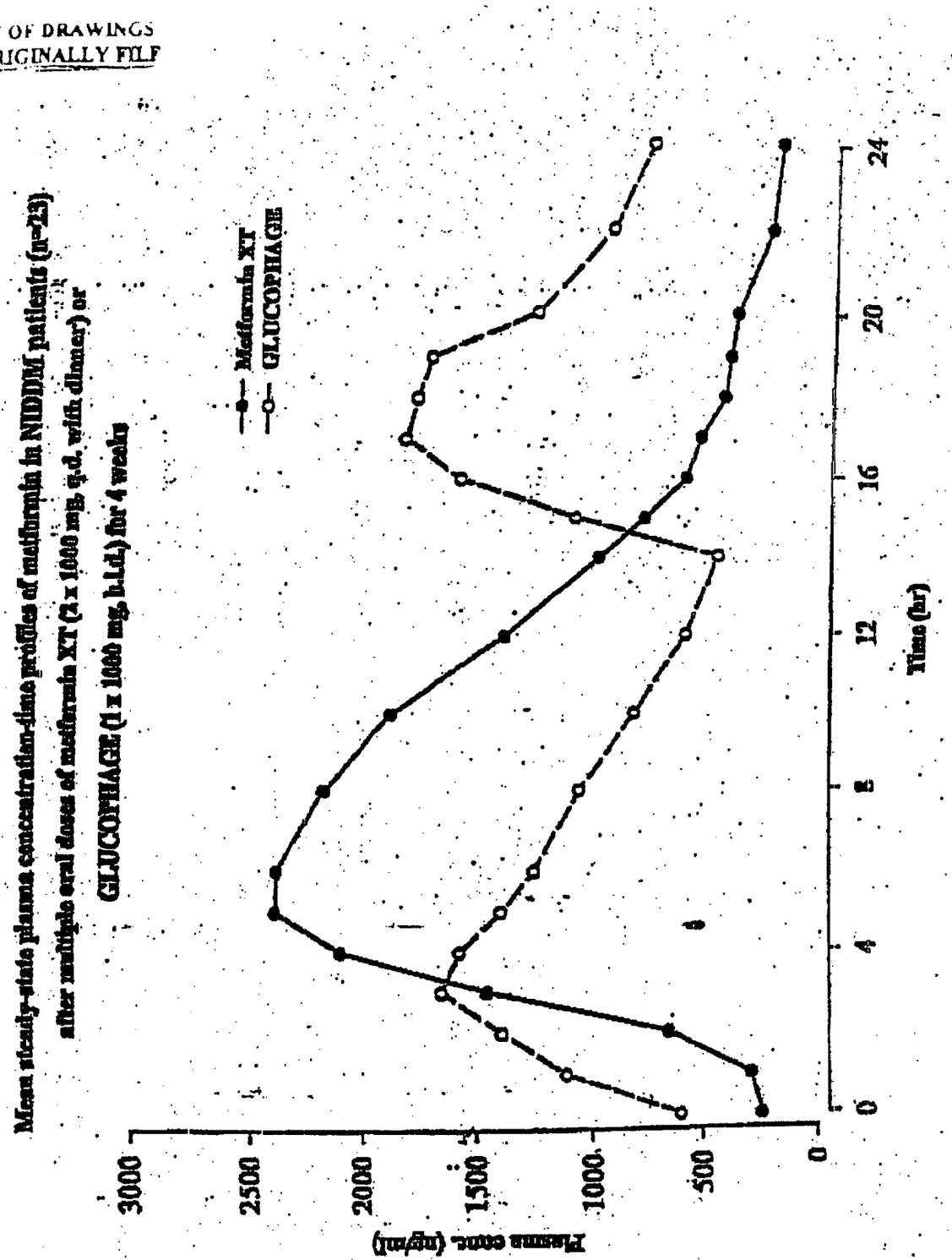
PRINT OF DRAWINGS
AS ORIGINALLY FILF

FIGURE 3

Mean plasma concentration-time profiles of metformin in eight healthy subjects after multiple oral doses of metformin XT (4 x 500 mg q.d.)

PRINT OF DRAWINGS
AS ORIGINALLY FILF

FIGURE 4



PRINT OF DRAWINGS
AS ORIGINALLY FILF

FIGURE 5

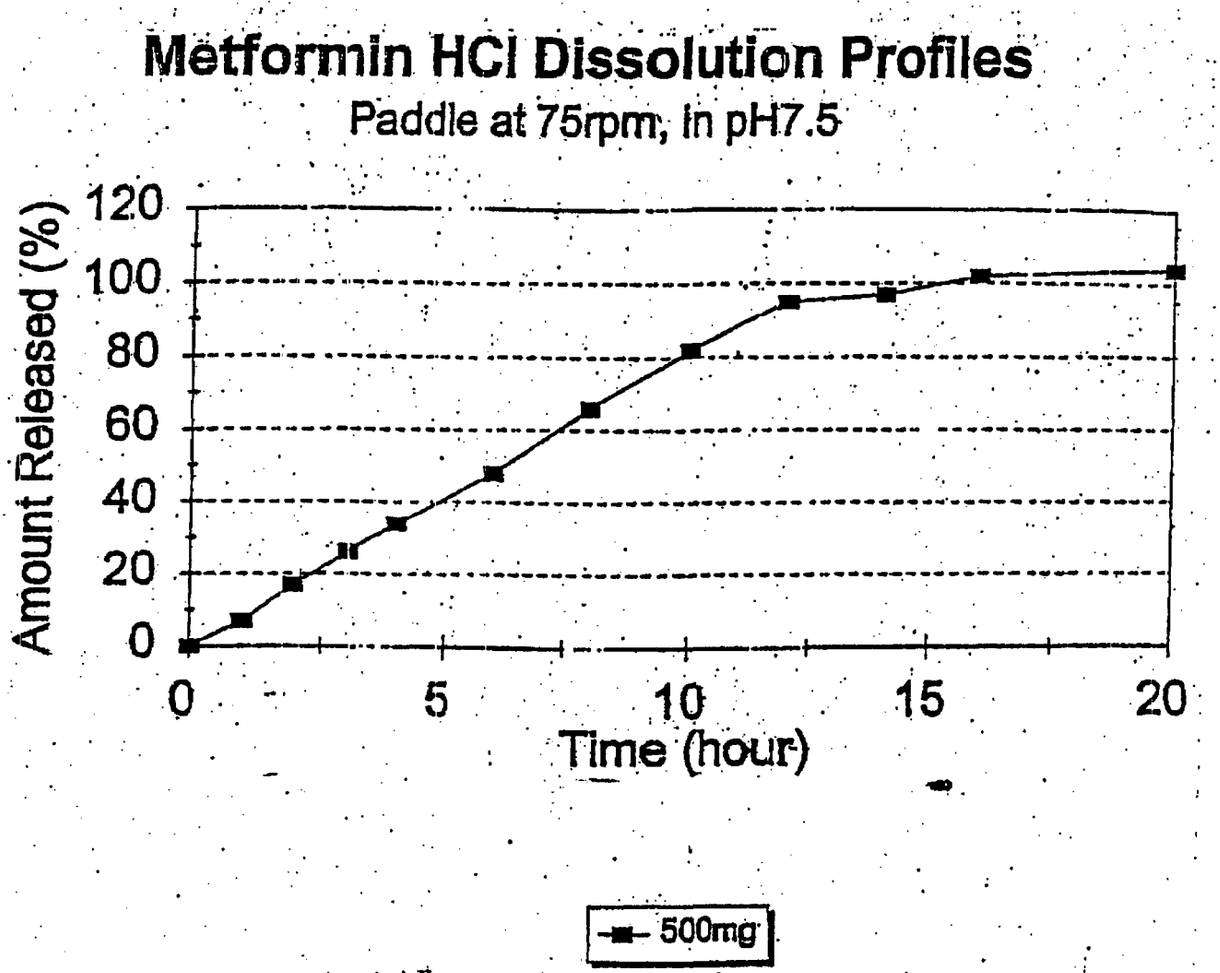


FIGURE 6

PRINT OF DRAWINGS
AS ORIGINALLY FILF

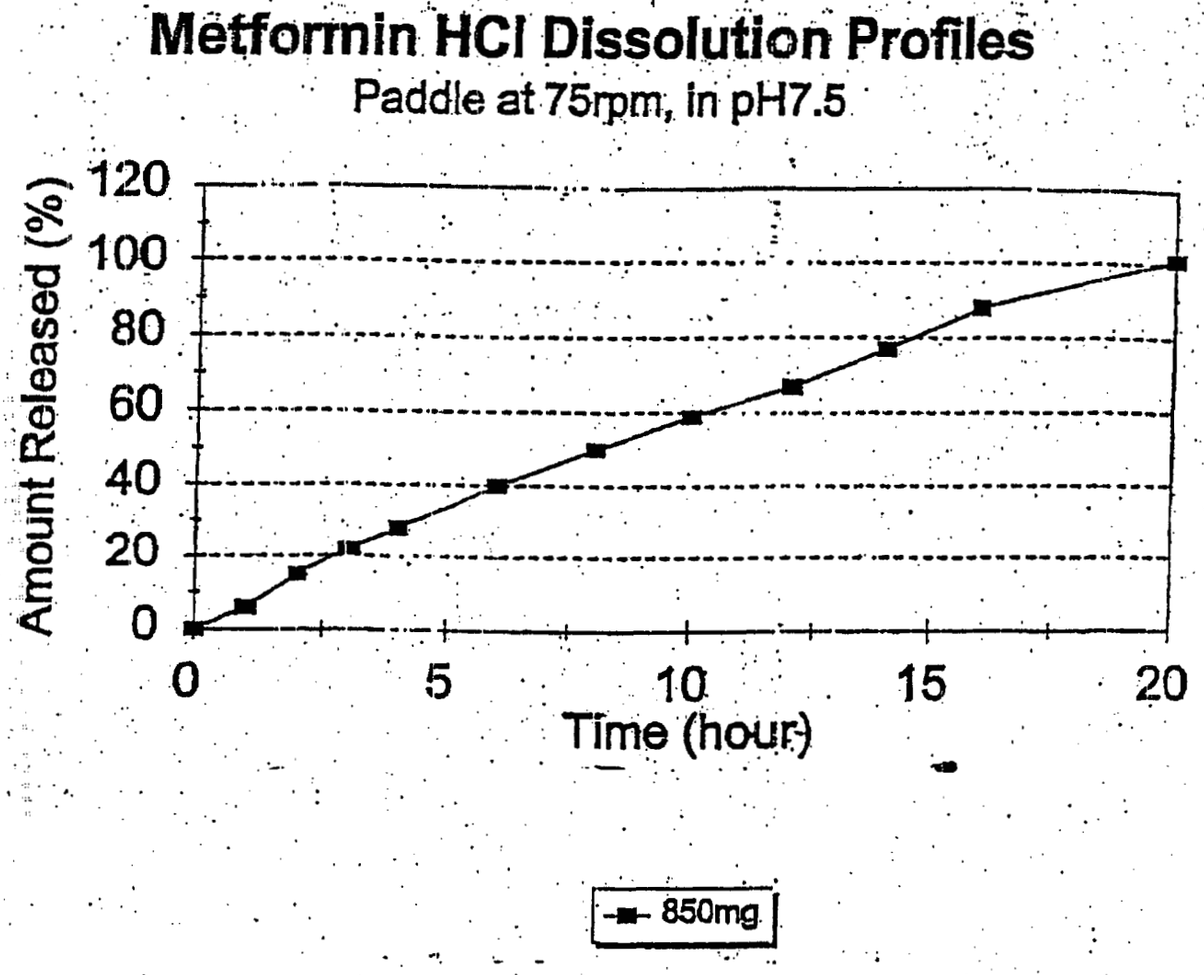


FIGURE 7

PRINT OF DRAWINGS
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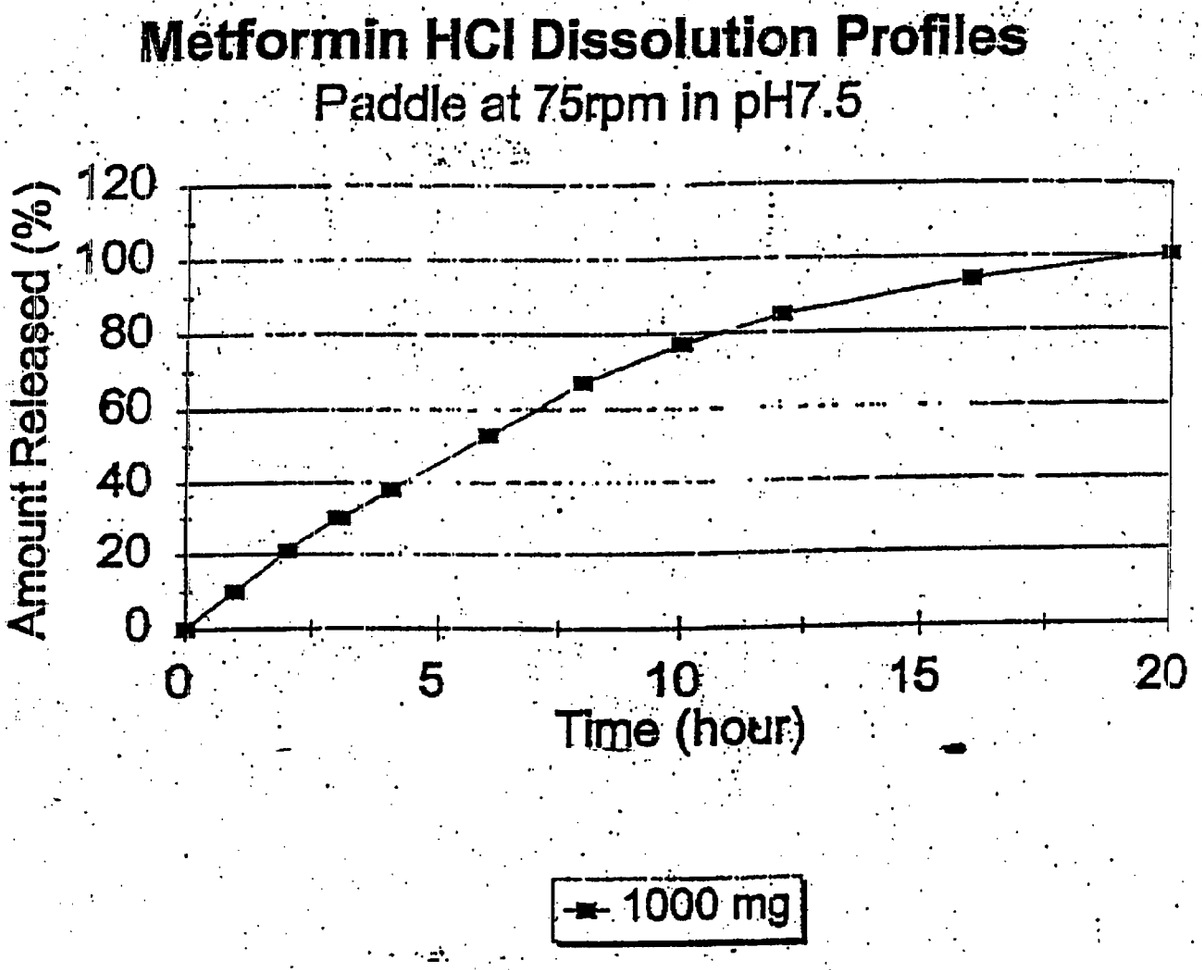

FIGURE 8

#2

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
09/705,630	11/03/2000	Xiu Xiu Cheng	300.1012

23280
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

FORMALITIES LETTER

OC000000005728415

Date Mailed: 02/02/2001

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given TWO MONTHS from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit **$ 710** *to complete the basic filing fee and/or file a small entity statement claiming such status (37 CFR 1.27).*
- Total additional claim fee(s) for this application is $396.
  - **$396** for **22** total claims over 20.
- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(e) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.

- **The balance due by applicant is $ 1236.**

A copy of this notice MUST be returned with the reply.

B Monroe

Customer Service Center
Initial Patent Examination Division (703) 308-1202
PART 3 - OFFICE COPY

Docket No.: 300.1005

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled: CONTROLLED RELEASE METFORMIN COMPOSITIONS, the specification of which

X — is attached hereto
was filed on November 3, 2000 as Application Serial No. 09/705,630 and was amended on _____ (if applicable).
I hereby authorize and request our attorney, Davidson, Davidson & Kappel, LLC. of 485 Seventh Avenue, 14th Floor, New York, New York 10018 to insert here in parentheses (Application number _____, filed _____) the filing date and application number of said application when known.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information which is known to me to be material to the patentability of this application as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign and/or provisional application(s) for patent or inventor's certificate listed below and have also identified below any foreign and/or provisional application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

PRIOR APPLICATION(S)			Priority claimed	
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial Number)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial Number)	(Filing Date)	(Status) (patented, pending, abandoned)

And I hereby appoint Clifford M. Davidson, Registration No. 32,728, Leslye B. Davidson, Registration No. 38,854, Cary S. Kappel, Registration No. 36,561, William C. Gehris, Registration No. 38,156, Morey B. Wildes, Registration No. 36,968, Robert J. Paradiso, Registration No. 41,240, Erik R. Swenson, Registration No. 40,833, Scott L. Appelbaum, Registration No. 41,587, Cynthia R. Moore, Registration No. 46,086, David Knasiak, Registration No. 45,091, Salvatore J. Maiorino, Registration No. 42,830, my attorneys, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith; correspondence address: DAVIDSON, DAVIDSON & KAPPEL, LLC, 485 Seventh Avenue, 14th Floor, New York, New York 10018; Telephone: (212) 736-1940; Fax: (212) 736-2427.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first Inventor Chih-Ming Chen	Full name of joint Inventor, if any Xiu-Xiu Cheng
Inventor's signature	Second Inventor's signature
Date 3/14/01	Date 3/22/01
Residence (city) , (state or country)	Residence (city) , (state or country)
Citizenship UNITED STATES	Citizenship UNITED STATES
Post Office Address:	Post Office Address:

Full name of joint Inventor, if any Steve Jan

Third Inventor's signature

Date 3/23/01

Residence (city) (state or country)

Citizenship UNITED STATES

Post Office Address:

Full name of joint Inventor, if any Joseph Chou

Fourth Inventor's signature

Date 3/1/01

Residence (city) (state or country)

Citizenship UNITED STATES

Post Office Address:

300.1005

UNITED STATES PATENT & TRADEMARK OFFICE

#3

Re: Application of: Chih-Ming Chen, et al.

Serial No.: 09/705,630

Filed: November 3, 2000

For: **Controlled Release Metformin Compositions**

BOX: MISSING PARTS
Assistant Commissioner for Patents
Washington, D.C. 20231

April 2, 2001

RESPONSE TO NOTICE TO FILE MISSING PARTS

Sir:

In response to the Notification of Missing Requirements dated February 2, 2001, a copy of which is enclosed, please find an executed Declaration/Power of Attorney form signed by the inventors, and a check in the amount of $1236.00 covering the basic filing fee, additional claims fee, and surcharge.

If any additional fees are deemed to be due at this time, the Assistant Commissioner is authorized to charge payment of the same to Deposit Account No. 50-0552.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By_____
Robert J. Paradiso
Reg. No. 41,240

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

I hereby certify that this correspondence and/or documents referred to as attached therein and/or fee are being deposited with the United States Postal Service as "first class mail" in an envelope addressed to "Assistant Commissioner for Patents, Washington, DC 20231" on April 2, 2001.
DAVIDSON, DAVIDSON & KAPPEL, LLC

BY: _____

FORM PTO-1083

ASSISTANT COMMISSIONER FOR PATENTS
Washington DC 20231

Docket No.: 300.1005
Date: April 2, 2001

Sector
#

In re application of: **Chih-Ming Chen, et al.**
Serial No.: **09/705,630**
Filed: **November 3, 2000**
For: **Controlled Release Metformin Compostions**

Sir:

Transmitted herewith is a **Response to Notice to File Missing Parts** in the above-identified application.

[ ] Small entity status under 37 C.F.R. 1.9 and 1.27 has been previously established.
[ ] Applicants assert small entity status under 37 C.F.R. 1.9 and 1.27.
[X] No fee for additional claims is required.
[ ] A filing fee for additional claims calculated as shown below, is required:

	(Col. 1)	(Col. 2)		SMALL ENTITY			LARGE ENTITY	
FOR:	REMAINING AFTER AMENDMENT	HIGHEST PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	FEE	OR	RATE	FEE
TOTAL CLAIMS	* Minus**	=	0	x $ 9	$		x $ 18	$
INDEP. CLAIMS	* Minus***	=	0	x $ 40	$		x $ 80	$
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM				+ $135	$		+ $270	$
				TOTAL:	$	OR	TOTAL:	$

[X] Also transmitted herewith are:
[ ] Petition for extension under 37 C.F.R. 1.136 (in duplicate)
[X] Other: **Copy of Notice to File Missing Parts of Nonprovisional Application**
Declaration and Power of Attorney
Application Data Sheet

[X] Check(s) in the amount of **$1236.00** is/are attached to cover:
[X] Filing fee for additional claims under 37 C.F.R. 1.16
[ ] Petition fee for extension under 37 C.F.R. 1.136
[X] Other: **Basic Filing Fee**
Late Filing Fee Surcharge

[X] The Assistant Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 50-0552.

[X] Any filing fee under 37 C.F.R. 1.16 for the presentation of additional claims which are not paid by check submitted herewith.
[X] Any patent application processing fees under 37 C.F.R. 1.17.
[X] Any petition fees for extension under 37 C.F.R. 1.136 which are not paid by check submitted herewith, and it is hereby requested that this be a petition for an automatic extension of time under 37 CFR 1.136.

Robert J. Paradiso, Reg. No. 41,240
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
Tel: (212) 736-1940
Fax: (212) 736-2427

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Citizenship Country::	United States

Correspondence Information

Correspondence Customer Number::	23280
Telephone::	(212) 736-1940
Fax::	(212) 736-2427
Electronic Mail::	ddk@ddkpatent.com

Application Information

Title Line One::	Controlled Release Metformin
Title Line Two::	Compositions
Total Drawings Sheets::	8
Formal Drawings::	No
Application Type::	Utility
Docket Number::	300.1005

Representative Information

Representative Customer Number::	23280

Assignee Information

Name::	Andrx Corporation
Postal Address Line One::	4001 SW 47th Avenue
City::	Fort Lauderdale
State::	Florida
Country::	United States
Postal or Zip Code::	33314

#3

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
09/705,630	11/03/2000	Xiu Xiu Cheng	300.1012

23280
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

FORMALITIES LETTER

Date Mailed: 02/02/2001

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given TWO MONTHS from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit **$ 710** *to complete the basic filing fee and/or file a small entity statement claiming such status (37 CFR 1.27).*
- Total additional claim fee(s) for this application is $396.
  - **$396** for **22** total claims over 20.
- The oath or declaration is missing
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(e) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.

- **The balance due by applicant is $ 1236.**

A copy of this notice MUST be returned with the reply.

Customer Service Center
Initial Patent Examination Division (703) 308-1202
PART 2 - COPY TO BE RETURNED WITH RESPONSE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/705,620	11/03/2000	Xiu Xiu Cheng	300.1005	6707

23280 7590 12/3 /2001

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

EXAMINER	
WARE, TODD	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 12/31/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)	
	09/705,630	CHENG ET AL.	
	Examiner	Art Unit	
	Todd D Ware	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after S X (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2001* .

2a)☐ This action is **FINAL**.. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt of declaration and fee filed 4-5-01 and IDS filed 9-19-01 is acknowledged. Claims 1-42 are pending.

Information Disclosure Statement

The information disclosure statement filed 9-19-01 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 21-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claims 21-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that they fail to point out what is included or excluded by the claim language. These claims are omnibus type claims.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

5. Claims 1-28, 31-42 are rejected under 35 U.S.C. 102(a) as being anticipated by Lewis et al (WO 00/28989; hereafter '989).

'989 discloses controlled release metformin compositions. '989 does not explicitly disclose the functional limitations of the instant claims, however since the formulations of '989 are substantially the same, it appears that the instant claimed functional limitations are inherent within '989. Therefore, the burden is shifted to

applicants to demonstrate a difference between '989 and the instant claims (*In re Swinehart*, 169 USPQ 226 and *In re Fitzgerald* 205 USPQ 594).

6. Claims 1-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Cheng et al (WO 99/47125; hereafter '125).

'125 discloses controlled release metformin compositions and is relied upon for the same reasons set forth in the previous 35 U.S.C. 102(a) rejections as being anticipated by Lewis et al (WO 00/28989; hereafter '989). In addition, '125 discloses a semi-permeable membrane coating surrounding the core.

7. Claims 1-28, 31-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Moeckel et al (5,955,106; hereafter '106).

'106 discloses controlled release metformin compositions and is relied upon for the same reasons set forth in the previous 35 U.S.C. 102(a) rejections as being anticipated by Lewis et al (WO 00/28989; hereafter '989).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-28, 31-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al (WO 00/28989; hereafter '989) or Moeckel et al (5,955,106; hereafter '106).

'989 and '106 both teach controlled release metformin compositions. They do not explicitly teach the functional limitations of the instant claims, however since the formulations of these references are substantially the same, it appears that the instant claimed functional limitations are inherent. Therefore, the burden is shifted to applicants to demonstrate a difference between the prior art and the instant claims (*In re Swinehart*, 169 USPQ 226 and *in re Fitzgerald* 205 USPQ 594). Varying amounts of ingredients, such as dose, would have been obvious to one skilled in the art at the time of the invention to provide a greater or lesser drug effect.

11. Claims 1-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al (WO 99/47125; hereafter '125) .

'125 teaches controlled release metformin compositions. They do not explicitly teach the functional limitations of the instant claims, however since the formulations of these references are substantially the same, it appears that the instant claimed functional limitations are inherent. Therefore, the burden is shifted to applicants to demonstrate a difference between the prior art and the instant claims (*In re Swinehart*, 169 USPQ 226 and *In re Fitzgerald* 205 USPQ 594).). In addition, '125 discloses a semi-permeable membrane coating surrounding the core. Varying amounts of ingredients, such as dose, woulc have been obvious to one skilled in the art at the time of the invention to provide a greater or lesser drug effect.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 6,099,859. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are directed to limitations that are in a genus-species relationship and the functional limitations of the instant claims would be inherent in '859.

14. Claims 1-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-39 of U.S. Patent No. 6,284,275. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are directed to limitations that are in a genus-species relationship and the functional limitations of the instant claims would be inherent in '275. Also, buformin is an adjacent homolog of metformin and therefore metformin is obvious over buformin.

15. Claims 1-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,099,862. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are directed to limitations that are in a genus-species relationship and the functional limitations of the instant claims would be inherent in '275.

16. Claims 1-42 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-42 of copending Application No. 09/705,605 TW 5-13-03 09/705,630. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method claims disclose the compositions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 1-42 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of copending Application No. 09/726,193. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method claims disclose the compositions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 1-42 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-54 of copending Application No. 09/594,637. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method claims disclose the compositions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Todd D Ware whose telephone number is (703) 305-1700. The examiner can normally be reached on M-F, 8:30 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (703)308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

tw
December 21, 200[illegible]

Notice of References Cited	Application/Control No. 09/705,630	Applicant(s)/Patent Under Reexamination HENG ET AL.	
	Examiner Todd D Ware	Art Unit 1615	Page 1 of

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-6,284,275	09-2001	Chen et al	424/473
	B	US-6,099,862	08-2000	Chen et al	424/473
	C	US-6,099,859	08-2000	Cheng et al	424/464
	D	US-5,955,106	09-1999	Moeckel et al	424/464
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N	WO 00/28989	05-2000	WIPO	Lewis et al	
	O	WO 99/47125	09-1999	WIPO	Cheng et al	
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Sheet 1 of 2

FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. 300.1005	SERIAL NO. 09/705,630
LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	APPLICANTS Chih-Ming CHEN, et al.	
	FILING DATE November 3, 2000	GROUP 1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL										DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
TV	AA	6	0	1	0	7	1	8		1/4/00	Al-Razzak et al.	424	464	
TV	AB	5	8	5	8	3	9	8		1/12/99	Cho	424	450	
TV	AC	5	6	9	1	3	8	6		11/25/97	Inman et al.	514	691	
TV	AD	5	6	8	8	5	1	8		11/18/97	Ayer et al.	424	422	
	AE	5	6	7	4	9	0	0		10/7/97	Ubillas et al.	514	557	
	AF	5	6	6	8	1	1	7		9/16/97	Shaeiro	514	55	
	AG	5	6	6	7	8	0	4		9/16/97	Wong et al.	424	472	
	AH	5	6	5	0	1	7	0		7/22/97	Wright et al.	424	473	
	AI	5	6	3	1	2	2	4		5/20/97	Efendic et al.	514	12	
	AJ	5	6	2	9	3	1	9		5/13/97	Luo et al.	514	284	

FOREIGN PATENT DOCUMENTS

										DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION	
														YES	NO
	AK	9	9	4	7	1	2	8		9/23/99	WO	A61K	9/24		
TV	AL	9	9	4	7	1	2	5		9/23/99	WO	A61K	9/20		
	AM	9	9	2	9	3	1	4		6/17/99	WO	A61K	31/155		
	AN	9	6	0	8	2	4	3		3/21/96	WO	A61K	31/155		

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	AO	*Physicians' Desk Reference* (54th Ed. 2000), pp. 831-835.
	AP	Sheen, Andre J., Clinical Pharmacokinetics of Metformin, *Clinical Pharmacokinetics*, May 30, 1996, 5:359-371.
	AQ	Bailey, Clifford J., et al., Metformin, *The New England Journal of Medicine*, Feb. 29, 1996, 334:574-579.
	AR	Dunn, Christopher J., et al., Metformin: A Review of its Pharmacological Properties and Therapeutic Use in Non-Insulin-Dependent Diabetes Mellitus, *Drugs* (1995), 49:721-747.
	AS	Karttunen, P., et al., The Pharmacokinetics of Metformin: A Comparison of the Properties of a Rapid-Release and a Sustained-Release Preparation, pp. 31-36.

EXAMINER [signature] DATE CONSIDERED 12-21-01

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

H:\300\1005\prosecution\PTO1449 14 Dec 00.wpd

FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. 300.1005	SERIAL NO. 09/705,630
LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	APPLICANTS Chih-Ming CHEN, et al.	
	FILING DATE: November 3, 20000	GROUP 1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL									DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	BA	5	6	1	4	5	7	8	3/25/97	Dong et al.	524	377	
	BB	5	5	9	1	4	5	4	1/7/97	Kuczynski et al.	424	486	
	BC	5	5	4	5	4	1	3	8/13/96	Kuczynski et al.	424	473	
	BD	5	5	4	3	1	5	6	8/6/96	Rourda et al.	424	484	
	BE	5	5	3	2	2	9	3	4/30/96	Lundruu et al.	424	449	
	BF	5	4	1	3	5	7	2	5/9/95	Wong et al.	604	892.1	
	BG	5	3	0	8	3	4	8	5/3/94	Balaban et al.	604	892.1	
	BH	5	1	8	5	1	5	8	2/9/93	Ayer et al.	424	473	
	BI	5	[illegible]	7	8	8	6	7	1/12/93	Guittard et al.	424	473	
	BJ	5	[illegible]	4	1	7	5	2	8/25/92	Ayer et al.	424	473	
	BK	5	1	2	0	5	4	8	6/9/92	McClelland et al.	424	473	
	BL	5	1	1	0	5	9	7	5/5/92	Wong et al.	424	438	
	BM	5	0	9	1	1	9	0	2/25/92	Kuczynski et al.	424	473	
	BN	5	0	7	1	6	0	7	12/10/91	Ayer et al.	264	112	
	BO	5	0	2	4	8	4	3	6/18/91	Kuczynski et al.	514	255.06	
	BP	4	9	6	3	1	4	1	10/16/90	Eckenhoff	604	892.1	
	BQ	4	8	9	2	7	3	9	1/9/90	Shah et al.	424	473	
	BR	4	8	6	5	5	9	8	9/12/89	Eckenhoff	604	892.1	

FOREIGN PATENT DOCUMENTS

									DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION	
													YES	NO
	BS													

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	BT	

EXAMINER	DATE CONSIDERED
[signature]	12-21-01

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

#4

Sheet 4

FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. 300.1005	SERIAL NO. 09/705,630
LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	APPLICANTS: Chih-Ming CHEN, et al.	
	FILING DATE November 3, 2000	GROUP 1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL									DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	CA	4	[illegible]	5	1	2	2	9	7/25/89	Magruder et al.	424	457	
	CB	4	7	8	3	3	3	7	11/8/88	Wong et al.	424	468	
	CC	4	7	7	7	0	4	9	10/11/88	Magruder et al.	424	457	
	CD	4	7	0	4	1	1	8	11/3/87	Eckenhoff	424	438	
	CE	4	6	9	2	3	3	6	9/8/87	Eckenhoff et al.	424	468	
	CF	4	6	2	7	8	5	0	12/9/86	Deters et al.	604	892.1	
	CG	4	6	2	4	8	4	7	11/25/86	Ayer et al.	424	467	
	CH	4	6	1	5	6	9	8	10/7/86	Guittard et al.	604	892.1	
	CI	4	6	1	2	0	0	8	9/16/86	Wong et al.	604	892	
	CJ	4	6	0	9	3	7	4	9/2/86	Ayer	424	473	
	CK	4	5	8	7	1	1	7	5/6/86	Edgren et al.	424	473	
	CL	4	5	2	2	6	2	5	6/11/85	Edgren	424	473	
	CM	4	1	1	1	2	0	1	9/5/78	Theeuwes	424	473	
	CN	4	0	8	8	8	6	4	5/9/78	Theeuwes et al.	219	121.71	
	CO	4	0	8	0	4	7	2	3/21/78	Bohuon	514	555	
	CP	4	0	7	7	4	0	7	3/7/78	Theeuwes et al.	424	427	
	CQ	4	0	6	3	0	6	4	12/13/77	Saunders et al.	219	121.7	

FOREIGN PATENT DOCUMENTS

									DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION	
													YES	NO
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OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	CS	

EXAMINER [signature]	DATE CONSIDERED 12-21-01

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FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

ATTY. DOCKET NO.	SERIAL NO.
300.1005	09/705,630
APPLICANTS: Chih-Ming CHEN, et al.	
FILING DATE November 3, 2000	GROUP 1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL									DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	DA	4	0	3	6	2	2	8	7/19/77	Theeuwes	424	473	
	DB	4	0	3	4	7	5	8	7/12/77	Theeuwes	424	427	
	DC	4	0	0	8	7	1	9	2/22/77	Theeuwes et al.	424	427	
	DD	3	9	5	7	8	6	3	5/18/76	Bohuon	560	143	
	DE	3	9	5	2	7	4	1	4/27/76	Baker	424	405	
	DF	3	9	1	6	8	9	9	11/4/75	Theeuwes et al.	424	424	
	DG	3	8	4	5	7	7	0	11/5/74	Theeuwes et al.	424	427	
	DH												
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	DJ												
	DK												
	DL												
	DM												
	DN												
	DO												
	DP												
	DQ												

FOREIGN PATENT DOCUMENTS

				DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION YES	TRANSLATION NO
	DR								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	DS	

EXAMINER [signature] DATE CONSIDERED 12-21-04

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/705,630	11/03/2000	Xiu Xiu Cheng	300.1005	6707

23280 7590 03/27/2002

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

EXAMINER
WARE, TODD

ART UNIT	PAPER NUMBER
1615	6

DATE MAILED: 03/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKETT NO.
09/705,630	11/03/00	CHENG ET AL	

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

(1) Clifford Davidson (3) Thurman K. Page

(2) Ted Whitlock (4)

Date of Interview 11/20/03

Type: ☐ Telephonic ☒ Personal (copy is given to ☐ applicant ☒ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description:

Agreement ☐ was reached with respect to some or all of the claims in question. ☐ was not reached.

Claims discussed: OF RECORD

Identification of prior art discussed: OF RECORD

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Importance of Tmp presented and the relationship to gluconeogenesis. Closest prior art suggest the general teaching of a Tmp of 8. Applicant to request reconsideration and reconsideration to be given in view of the working examples.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

☒ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph below has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1-7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

☐ 2. Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the substance of the interview unless box 1 above is also checked.

Thurman K. Page
Examiner's Signature

PTOL-413 (REV. 2-93)

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) (Large Entity)	Docket No. 300.1005

In Re Application Of: Chih-Ming CHEN, et al.

Serial No.	Filing Date	Examiner	Group Art Unit
09/705,630	November 3, 2000	T. Ware	1615

Invention: CONTROLLED RELEASE METFORMIN COMPOSITIONS

TO THE ASSISTANT COMMISSIONER FOR PATENTS:

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a response to the Office Action of December 31, 2001 (Date) above-identified application.

The requested extension is as follows (check time period desired):

☐ One month ☐ Two months ☒ Three months ☐ Four months ☐ Five months

from: March 31, 2002 (Date) until: June 30, 2002 (Date)

The fee for the extension of time is $920 and is to be paid as follows:

☒ A check in the amount of the fee is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account No.
A duplicate copy of this sheet is enclosed.

☒ If an additional extension of time is required, please consider this a petition therefor and charge any additional fees which may be required to Deposit Account No.
A duplicate copy of this sheet is enclosed.

Signature

Dated: July 1, 2002

Robert J. Paradiso, Reg. No. 41,240
Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th floor
New York, New York 10018
212-736-1940

I certify that this document and fee is being deposited on with the U.S. Postal Service as first class mail under 37 C.F.R. 1.8 and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Signature of Person Mailing Correspondence

Typed or Printed Name of Person Mailing Correspondence

07/12/2002 HMOHAMM1 00000010 09705630
01 FC:117 920.00 OP

cc:

P12LARGE/REV06

UNITED STATES PATENT & TRADEMARK OFFICE

Re:	Application of:	Chih-Ming Chen, et al.
	Serial No.:	09/705,630
	Filed:	November 3, 2000
	For:	**Controlled Release Metformin Compositions**
	Examiner: T. Ware	Art Unit: 1615

Assistant Commissioner for Patents
Washington, D.C. 20231

July 1, 2002

AMENDMENT UNDER 37 C.F.R. §1.111

Sir:

In response to the Office Action dated December 31, 2001, please enter the following amendments and remarks:

IN THE CLAIMS

Please amend the claims as follows:

21. The controlled release oral dosage form of claim 3 which provides a mean $AUC_{0-\infty}$ of 18277 ± 2961 ng·hr/ml and a mean C_{max} of 1929 ± 333 ng/ml, based on administration of a 1700 mg once-a-day dose of metformin after an evening meal.

22. The controlled release oral dosage form of claim 3 which provides a mean $AUC_{0-\infty}$ of 20335 ± 4360 ng·hr/ml and a mean C_{max} of from 2053 ± 447 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin after an evening meal.

23. The controlled release oral dosage form of claim 3 which provides a mean AUC_{0-24} of 26818 ± 7052 ng·hr/ml and a mean C_{max} of 2849 ± 797 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin after an evening meal.

24. The controlled release oral dosage form of claim 3 which provides a mean AUC_{0-24} of 22590 ± 3626 ng·hr/ml and a mean C_{max} of 2435 ± 630 ng/ml on the first day of administration and a mean AUC_{0-24} of 24136 ± 7996 ng·hr/ml and a mean C_{max} of 2288 ± 736 ng/ml on the 14th day of administration, based on administration of a 2000 mg once-a-day dose of metformin after an evening meal.

A1 cont.

25. The controlled release oral dosage form of claim 21 which provides a mean $T_{1/2}$ from 2.8 to 4.4.

REMARKS

The undersigned attorney gratefully acknowledges the courtesies extended by Examiner Spear and Examiner Ware during the personal interview conducted at the United States Patent and Trademark Office on March 21, 2002.

I. Status of the Claims

Claims 1-42 are pending. Claims 21-25 have been amended. Support for the amendment to claim 21 is found in the original specification as filed, e.g., at page 28, table 1; support for the amendment to claim 22 is found in the original specification as filed, e.g., at page 30, table 3; support for the amendment to claim 23 is found in the original specification as filed, e.g., at page 35, table 6; support for the amendment to claim 24 is found in the original specification as filed, e.g., at page 32, table 5; support for the amendment to claim 25 is found in the original specification as filed, e.g., at page 28, table 1. It is respectfully submitted that no new matter has been added by virtue of this amendment.

II. Information Disclosure Statement

In the Office Action, it was indicated that the Information Disclosure Statement filed on September 19, 2001 did not comply with 37 C.F.R. 1.98(a)(2). As discussed during the interview, it appears that the cited references became disassociated with the file and copies of the references cited in the Information Disclosure Statement will be resubmitted by hand delivery.

III. Rejections Under 35 U.S.C. § 112

In the Office Action, claims 21-25 were rejected as being indefinite on the grounds of that the claims are "omnibus type claims."

In response, claims 21-25 have been amended as not to make reference to the Figures of the application and it is respectfully requested that these rejections be withdrawn.

IV. Rejections Under 35 U.S.C. § 102 and 35 U.S.C. § 103

In the Office Action, claims 1-28 and 31-42 were rejected as being anticipated and obvious over WO 00/28989 ("Lewis et al."), on the grounds that Lewis et al. "discloses controlled release metformin compositions [and] does not explicitly disclose the functional limitations of the instant claims, however since the formulations of [Lewis et al.] are substantially the same, it appears that the instant claimed functional limitations are inherent within [Lewis et al.]"

Claims 1-28 and 31-42 were rejected as being anticipated and obvious over U.S. Patent No. 5,955,106 ("Moeckel et al."), on the grounds that Moeckel et al. "is relied upon for the same reasons set forth in the [Lewis et al.] rejections".

Claims 1-42 were rejected as being anticipated and obvious over WO 99/47125 ("Cheng et al."), on the grounds that Cheng et al. "is relied upon for the same reasons set forth in the [Lewis et al.] rejections ... [and Cheng et al.] discloses a semi-permeable membrane coating surrounding the core "

With respect to rejections under the doctrine of inherency, it is noted that as set forth in the MPEP, 8th edition, section 2122, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be recognized by one of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-

51 (Fed. Cir. 1999).

It is further set forth in the MPEP, 8th edition, section 2122 that "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the alleged inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. And Inter. 1990) (emphasis in original).

Further, as discussed during the interview, the Federal Circuit stated the following in *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268-69, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991):

> *Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.*

In view of the above discussion on the doctrine of inherency, the references cited by the Examiner are discussed below:

THE CHENG REFERENCE

The rejection of claims 1-42 on the grounds of anticipation and obviousness over WO 99/47125 ("Cheng et al.") is respectfully traversed as the Cheng reference has not been fully considered in its entirety.

As stated at page 3, lines 14-17 and at page 4, lines 6-9 of the Cheng reference, the formulations disclosed therein provide a controlled or sustained release formulation for an antihyperglycemic drug that obtain peak plasma levels approximately 8-12 hours after administration. Therefore, the T_{max} of the agent at from 5.5 to 7.5 hours after administration as recited in the present claims cannot be inherent in the formulations disclosed in the Cheng reference. Further, the Cheng reference does not provide motivation to one skilled in the art to modify the formulations therein to obtain a T_{max} of the agent other than that which is specifically taught in the reference, i.e., a T_{max} of 8 to 12 hours.

In view of the arguments presented, the Examiner is respectfully requested to remove the

anticipation and obviousness rejections over the Cheng reference.

THE LEWIS REFERENCE

The rejection of claims 1-28 and 31-42 on the grounds of anticipation and obviousness over WO 00/28989 ("Lewis et al.") is respectfully traversed.

As set forth in the MPEP, 8th edition, section 2112.01, in order to establish a prima facie case of inherency based on either anticipation or obviousness, the prior art composition must be produced by identical or substantially identical processes. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977).

The exemplified formulations of the Lewis reference are Examples 1-7 on pages 10-12. Example 1 describes a single or bilayer tablet comprising 4 or 8 mg of Compound I (an insulin sensitizer) and 1000 to 1500 mg of metformin HCl coated with an enteric coating of Eudragit L30 D-55, triethyl citrate and talc Alphafil 500 in the described percentages; Example 2 describes the single or bilayer tablets of Example 1 coated with a semi-permeable membrane of Eudragit RS30D, triethyl citrate and talc in the described percentages; Example 3 describes a non-disintegrating matrix single layer tablet of Compound I, metformin HCl and the described excipients in the described amounts, and a bilayer tablet to provide sustained release of Compound I and immediate release of metformin HCl with the described excipients in the described amounts; Example 4 describes a single and trilayer tablet of Compound I and metformin HCl with the described excipients in the described amounts; Example 5 describes a single layer tablet of Compound I and metformin HCl with the described excipients in the described amounts; Example 6 describes a single and bilayer tablet of Compound I and metformin HCl with the described excipients in the described amounts; and Example 7 describes a capsule containing multiple pellet cores having Compound I, metformin HCl with the described excipient in the described amounts.

The examples of the present specification teach formulations which comprise a core comprising metformin or a salt thereof, a membrane surrounding the core, and at least one passageway in the membrane, the formulations providing a mean T_{max} from 5.5 to 7.5 hours after administration. Given the benefit of the information provided by the present specification, one skilled in the art would be able to modify other controlled release technologies in order to achieve these pharmacokinetic parameters.

As demonstrated above, the examples of the present application and the examples of the Lewis reference are directed to different controlled release technologies by virtue of their different ingredients, structure and methods of manufacture. Accordingly, a *prima facie* case of anticipation or obviousness based on inherency has not been established as the Examiner has not provided a basis in fact and/or technical reasoning to reasonably support the determination that the alleged inherent characteristic necessarily flows from the teachings of the applied prior art. In fact, the Office Action has contradicted the position that the formulations described in the Lewis reference and the examples of the present invention are substantially the same, as the Office Action has indicated that claim 29[1] is not anticipated or obvious over Lewis.

Further, the Office Action has not taken into account that there is no teaching in the Lewis reference to arrive at the claimed T_{max} as recited in the present claims, nor does Lewis provide any motivation to one skilled in the art to achieve this parameter using the formulations described therein. In fact, it is respectfully submitted that as Lewis is silent as to the T_{max} of their formulations, one skilled in the art would be motivated to achieve a T_{max} from an antihyperglycemic agent controlled release formulation which is known in the art, (e.g., a T_{max} of 8-12 hours as taught in the Cheng reference). It is pointed out that the present claims do not recite an all encompassing range of T_{max}, but rather a particular subset which is not taught or obvious over the prior art.

In view of the arguments presented, the Examiner is respectfully requested to remove the anticipation and obviousness rejections over the Lewis reference.

THE MOECKEL REFERENCE

The rejection of claims 1-28 and 31-42 on the grounds of anticipation and obviousness over U.S. Patent No. 5,955,106 ("Moeckel et al.") is respectfully traversed as the same arguments set forth above with respect to the Lewis reference are applicable to the Moeckel reference.

The exemplified formulations of the Moeckel reference are Examples 1-7 on columns 5-9

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[1]Claim 29 recites "[t]he controlled release dosage form of claim 1, wherein the metformin is provided by at least one controlled-release tablet, said tablet comprising:

(a) a core comprising:
  (i) the metformin or a pharmaceutically acceptable salt;
  (ii) optionally a binding agent; and
  (iii) optionally an absorption enhancer;
(b) a membrane coating surrounding the core; and
(c) at least one passageway in the membrane".

of the patent. Example 1 describes a process of preparing a formulation with a core of metformin hydrochloride, methylhydroxypropylcellulose, polyvidone and magnesium stearate in the specified amounts with a film envelope of methylhydroxypropylcellulose, ethylcellulose, Macrogol and titanium dioxide in the specified amounts; Example 2 describes a process of preparing a formulation with a core of metformin hydrochloride, hydroxyethylcellulose, *polyvidone and magnesium stearate in the specified amounts with a film envelope of* methylhydroxypropyl-cellulose, lactose, ethylcellulose, Macrogol and titanium dioxide in the specified amounts; Example 3 describes a process of preparing a formulation with a core of metformin hydrochloride, sodium carboxy methyl cellulose, polyvidone and magnesium stearate in the specified amounts with a film envelope of methylhydroxypropylcellulose, ethylcellulose, Macrogol and titanium dioxide in the specified amounts; Example 4 describes a process of preparing a formulation with a core of metformin hydrochloride, polyacrylic acid, methylhydroxypropylcellulose, and magnesium stearate in the specified amounts with a film envelope of methylhydroxypropylcellulose, ethylcellulose, Macrogol and titanium dioxide in the specified amounts; Example 5 describes a process of preparing a formulation with a core of metformin hydrochloride, hydroxypropyl-cellulose, polyvidone and magnesium stearate in the specified amounts with a film envelope of poly(ethylacrylate-methylacrylate, talcum and anti-foaming agent in the specified amounts; Example 6 describes a process of preparing a formulation with a core of metformin hydrochloride, methylhydroxypropylcellulose and magnesium stearate in the specified amounts with a film envelope of methylhydroxypropylcellulose, ethylcellulose, Macrogol and titanium dioxide in the specified amounts; and Example 7 describes a process of preparing a formulation with a core of metformin hydrochloride, methylhydroxypropylcellulose, polyvidone and magnesium stearate in the specified amounts with a film envelope of methylhydroxypropylcellulose, ethylcellulose, Macrogol and titanium dioxide in the specified amounts.

As set forth above, the Examples of the present specification teach formulations which comprise a core comprising metformin or a salt thereof, a membrane surrounding the core, and at least one passageway in the membrane, the formulations providing the claimed pharmacokinetic parameter of a mean T_{max} from 5.5 to 7.5 hours after administration.

Accordingly, the examples of the present application and the examples of the Moeckel reference are directed to different controlled release technologies by virtue of their different

ingredients, structure and methods of manufacture. With respect to the Moeckel reference, as well as the Lewis reference, the Office Action has contradicted the position that the formulations described in the Moeckel reference and the examples of the present invention are substantially the same, as the Office Action has indicated that claim 29[2] is not anticipated or obvious over Moeckel.

Therefore a *prima facie* case of anticipation or obviousness based on inherency has not been established as the Office Action has not provided a basis in fact and/or technical reasoning to reasonably support the determination that the alleged inherent characteristic necessarily flows from the teachings of the applied prior art.

Further, the Office Action has not taken into account the fact that that there is no teaching in the Moeckel reference to arrive at the claimed T_{max} as recited in the present claims, nor does Moeckel provide any motivation to one skilled in the art to achieve this parameter using the formulations described therein. In fact, it is respectfully submitted that as Moeckel is silent as to the T_{max} of their formulations, one skilled in the art would be motivated to achieve a T_{max} from a biguanide controlled release formulation which is known in the art, (e.g., a T_{max} of 8-12 hours as taught in the Cheng reference). As stated above with respect to the Lewis reference, it is pointed out that the present claims do not recite an all encompassing range of T_{max}, but rather a particular subset which is not taught or obvious over the prior art.

In view of the arguments presented, the Examiner is respectfully requested to remove the anticipation and obviousness rejections over the Moeckel reference.

V. Double Patenting Rejections

Claims 1-42 were provisionally rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over what is believed to be claims 1-34 of copending application serial number no. 09/705,625, as the Examiner inadvertantly rejected the claims over claims 1-42 of 09/705,630 (the present application).

In response, in order to expedite the issuance of a patent, a terminal disclaimer is submitted herewith over this copending application. Applicants note that the obviation of an obvious-type double patenting rejection by the filing of a terminal disclaimer is not an admission, acquiescence, or estoppel on the merits of an issue of obviousness. *See Quad Environmental*

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[2]Ibid

Technologies Corp. v. Union Sanitary District, 946 F.2d 870, 873-74, 20 U.S.P.Q.2d 1392, 1394-95 (Fed. Cir. 1991).

Claims 1-42 were rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 1-29 of U.S. Patent no. 6,099,859; claims 1-39 of U.S. Patent No. 6,284,275; claims 1-4 of U.S. Patent No. 6,099,862. The Examiner states with respect to each reference that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because the claims are directed to limitations that are in a genus-species relationship and the functional limitations of the instant claims would be inherent in [the reference]." Further, claims 1-42 were provisionally rejected under obviousness type double patenting as being unpatentable over claims 1-54 of copending application no. 09/594,637 and over claims 1-29 of copending application no. 09/726,193 on the grounds that "the method claims disclose the compositions".

These rejections are respectfully traversed. It is submitted that the claimed pharmacokinetic parameter of a mean T_{max} of 5.5 to 7.5 hours after administration as recited in the present claims are not obvious in view of the claims of the cited references. As discussed during the interview, although formulations encompassed by the claims of these references may provide a T_{max} of between 5.5 to 7.5, the claimed pharmacokinetic parameters do not necessarily flow from formulations encompassed by these claims. Therefore, the Examiner is requested to remove these rejections.

VI. Conclusion

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings To Show Changes Made**."

It is now believed that the above-referenced rejections and objections have been obviated and it is respectfully requested that the rejections and objections be withdrawn. It is believed that all claims are now in condition for allowance.

According to currently recommended Patent Office policy the Examiner is specifically authorized to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

An early and favorable action is earnestly solicited.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By:_____
Robert J. Paradiso
Reg. No. 41,240

Davidson, Davidson & Kappel, LLC
Patents, Trademarks and Copyrights
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

Version With Markings To Show Changes Made

IN THE CLAIMS

The following claim has been amended as follows:

21. (Amended) The controlled release oral dosage form of claim 3 which provides a mean $AUC_{0-\infty}$ of 18277 ± 2961 ng·hr/ml and a mean C_{max} of 1929 ± 333 ng/ml [a mean plasma concentration-time profiles of metformin substantially as set forth in FIG. 1], based on administration of a 1700 mg once-a-day dose of metformin after an evening meal.

22. (Amended) The controlled release oral dosage form of claim 3 which provides a mean $AUC_{0-\infty}$ of 20335 ± 4360 ng·hr/ml and a mean C_{max} of from 2053 ± 447 ng/ml [a mean plasma concentration-time profiles of metformin substantially as set forth in FIG. 2], based on administration of a 2000 mg once-a-day dose of metformin after an evening meal.

23. (Amended) The controlled release oral dosage form of claim 3 which provides a mean AUC_{0-24} of 26818 ± 7052 ng·hr/ml and a mean C_{max} of 2849 ± 797 ng/ml [a mean plasma concentration-time profiles of metformin substantially as set forth in FIG. 4], based on administration of a 2000 mg once-a-day dose of metformin after an evening meal [at dinner].

24. (Amended) The controlled release oral dosage form of claim 3 which provides a mean AUC_{0-24} of 22590 ± 3626 ng·hr/ml and a mean C_{max} of 2435 ± 630 ng/ml on the first day of administration and a mean AUC_{0-24} of 24136 ± 7996 ng·hr/ml and a mean C_{max} of 2288 ± 736 ng/ml on the 14th day of administration [a mean plasma concentration-time profiles of metformin substantially as set forth in FIG. 6], based on administration of a 2000 mg once-a-day dose of metformin after an evening meal [at breakfast].

25. (Amended) The controlled release oral dosage form of claim 21 [3] which provides a mean $T_{1/2}$ from 2.8 to 4.4 [about mean plasma glucose concentration-time profiles substantially as set forth in FIG. 5, based on administration of a 2000 mg once-a-day dose of metformin at dinner].

FORM P70-1083

Docket No.: 300.1005
Date: July 1, 2002

RECEIVED
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ASSISTANT COMMISSIONER FOR PATENTS
Washington, DC 20231

In re applicationf: **Chih-Ming Chen, et al.**
Serial No.: **09/705,630**
Filed: **November 3, 2000**
For: **CONTROLLED RELEASE METFORMIN COMPOSTIONS**

OIPE
JUL 0 8 2002
PATENT & TRADEMARK OFFICE

Sir:

Transmitted herewith is an **Amendment** in the above-identified application.

[ ] Small entity status under 37 C.F.R. 1.9 and 1.27 has been previously established.
[ ] Applicants assert small entity status under 37 C.F.R. 1.9 and 1.27.
[X] No fee for additional claims is required.
[ ] A filing fee for additional claims calculated as shown below, is required:

	(Col. 1)	(Col. 2)		SMALL ENTITY		OR	LARGE ENTITY	
FOR:	REMAINING AFTER AMENDMENT	HIGHEST PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	FEE		RATE	FEE
TOTAL CLAIMS	* Minus** =		x0	$ 9	$		x $ 18	$
INDEP. CLAIMS	* Minus*** =		x0	$ 40	$		x $ 80	$
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM					$		+ $270	$
				TOTAL:	$	OR	TOTAL:	$

[X] Also transmitted herewith are:
[X] Petition for extension under 37 C.F.R. 1.136 (in duplicate)
[X] Other: **Version With Markings to Show Changes Made and Terminal Disclaimer to Obviate a Provisional Double Patenting Rejection over a Pending Second Application**

[X] Check(s) in the amount of **$1030.00** is/are attached to cover:
[ ] Filing fee for additional claims under 37 C.F.R. 1.16
[X] Petition fee for extension under 37 C.F.R. 1.136
[X] Other: Terminal Disclaimer Fee

[X] The Assistant Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 50-0552.

[X] Any filing fee under 37 C.F.R. 1.16 for the presentation of additional claims which are not paid by check submitted herewith.
[X] Any patent application processing fees under 37 C.F.R. 1.17.
[X] Any petition fees for extension under 37 C.F.R. 1.136 which are not paid by check submitted herewith, and it is hereby requested that this be a petition for an automatic extension of time under 37 CFR 1.136.

Robert J. Paradiso, Reg. No. 41,240
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
Tel: (212) 736-1940
Fax: (212) 736-2427

I hereby certify that this correspondence and/or documents referred to as attached therein and/or fee are being deposited with the United States Postal Service as "first class mail" in an envelope addressed to "Assistant Commissioner for Patents, Washington, D.C. 20231" on July 1, 2002.

DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____

#9

TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING SECOND APPLICATION

Docket No. 300.1005

JUL 0 8 2002 PATENT AND TRADEMARK OFFICE

TECH CENTER 1600/2900 RECEIVED JUL 0 5 2002

In re Application of: **Chih-Ming Chen, et al.**
Application No. **09/705,630**
Filed: **November 3, 2000**
For: **CONTROLLED RELEASE METFORMIN COMPOSITIONS**

The owner, **Andrx Corporation** of **100.00** percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173 as shortened by any terminal disclaimer filed prior to the grant of any patent granted on pending second Application Number **09/705,625**, filed on **November 3, 2000**. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the second application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of any patent granted on the second application, as shortened by any terminal disclaimer filed prior to the patent grant, in the event that any such granted patent: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims cancelled by a reexamination certificate, is reissued, or in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2, if appropriate.

1. ☐ For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney of record.

3. Owner/applicant is ☐ Small entity ☒ Large entity

The terminal disclaimer fee under 37 CFR 1.20(d) is **$110.00** and is to be paid as follows:

☒ A check in the amount of the fee is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number **50-0552**. A duplicate copy of this sheet is enclosed.

PTO suggested wording for terminal disclaimer was

☒ unchanged. ☐ changed (if changed, an explanation should be supplied.)

Signature

Dated: July 1, 2002

Name and Address of Person Signing

Robert J. Paradiso, Reg. No. 41,240
Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
736-1940

10HAMM1 00000010 09705630
110.00 OP

I certify that this document and fee is being deposited on with the U.S. Postal Service as first class mail under 37 C.F.R. 1.8 and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Signature of Person Mailing Correspondence

Typed or Printed Name of Person Mailing Correspondence

SUBJECT: DECISION ON TERMINAL DISCLAIMERS INFORMAL FORM

DATE: 8-2-02 APPL. S.N.: 09/205,630

TO EXAMINER: J. Ware ART UNIT: 1615

MOSE MONTGOMERY ROOM 11E18 MAILROOM DATE 8-8-02

AFTER FINAL YES ____ NO ✓ NUMBER OF T.D(S). FILED 1

INSTRUCTIONS: I have reviewed the submitted T.D. with the results as set forth below. If you agree, please use the appropriate form paragraphs identified by this informal memo in your next office action to notify applicant about the T.D. If you disagree with my analysis or have questions at all about the acceptability of the T.D., please see me or our Special Program Examiner. THIS MEMO IS AN INFORMAL, INTERNAL MEMO ONLY. IT MUST NOT BE MAILED TO APPLICANT, NOR SHOULD A COPY BE IN LEFT IN FILE.

[ ] The T.D. is PROPER and has been recorded. (See 14.23).

[✓] The T.D. is NOT PROPER and has not been accepted for the reason(s) checked below. (See 14.24).

[ ] The recording fee of $_____ has not been submitted nor is there any pre authorization in the application file to charge to a deposit account. (See 14.26.07)

[ ] Application Examiner has not processed T.D. fee. (See fee authorization).

[ ] The T.D. does not satisfy Rule 321(b)(3) in that the person who has signed the T.D. has not stated his/her interest (and/or the extent of the interest of the business entity represented by the signature) in the application/patent. (See 14.26 and 14.26.01).

[ ] The T.D. lacks the enforceable only during the common owership clause needed to overcome a double patenting rejection, Rule 321(c). (See 14.27, 14.27.01).

[ ] It is directed to a particular claims(s), which is not acceptable since "the disclaimer must be of a terminal portion of the term of the entire patent to be granted". MPEP 1490. (See 14.26, 14.26.02).

[ ] The person who signed the terminal disclaimer:
- [ ] has failed to state his/her capacity to sign for the business entity. (See 14.28).
- [ ] is not recognized as an officer of the assignee. (See 14.29 and possibly 14.29.01).

[ ] No documentary evidence of a chain of title from the original inventor(s) to assignee has been submitted, nor is the reel and frame specified as to where such evidence is recorded in the office. 37 CFR 3.73(b). (See 1140 O.G. 72). *NOTE:* This documentary evidence or the specifying of the reel and frame may be found in the T.D. or in a seperate paper submitted by applicant. (See 14.30).

[ ] No "statement" specifying that the evidentiary documents have been reviewed and that, to the best of the assignee's knowledge and belief the title is in the assignee seeking to take action. 37 CFR 3.73(b). (See 1140 O.G. 72) (See 14.31).

[ ] The T.D. is not signed. (See 14.26, 14.26.3), or 14.26.03 If TD is not signed by all the owners.

[ ] Attorney not of record in oath/decl. or a seperate paper filed appointing a new or associate attorney. (See 14.29.01).

[✓] The serial number of the application (or the number of the patent) which forms the basis for the double patenting is missing or incorrect. (See 14.32).

[ ] The serial number of this application (or the number of the patent in reexam or reissue case(s) being disclaimed is missing or incorrect. (See 14.26, 14.26.04 or 14.26.06).

[ ] The period disclaimed is incorrect or not specified. (See 14.27, 14.27.2 or 14.27.3)(For Samples 14.27.04 and 14.27.05)

[ ] Other: _____

[ ] Suggestion to request refund of $_____. (See 14.35, 14.36).

[ ] EXAMINER NOTE: IF APPLICATION IS IN CONDITION FOR ALLOWANCE ANY OF THE ABOVE INFORMALTIES MAY BE FAXED IN TO THE GROUP

FOR SAMPLE TERMINAL DISCLAIMERS AND CERTIFICATES:

[ ] Sample of a TD over a pending application and assignee Certificate (See 14.37).
[ ] Sample of a TD over a prior patent and assignee Certificate (See 14.38).
[ ] Sample Assignee Certificate under 37 CFR 3.73 (b) (See 14.39)

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/705,630	11/03/2000	Xiu Xiu Cheng	300.1005	6707

23280 7590 10/22/2002

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NEW YORK, NY 10018

EXAMINER
WARE, TODD

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 10/22/2002 #10

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)	
	09/705,630	CHENG ET AL.	
	Examiner	Art Unit	
	Todd D Ware	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *08 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Receipt of request for extension of time (granted), amendment and terminal disclaimer all filed 7-8-02 is acknowledged. Claims 1-42 are pending. Based upon the new grounds for rejection, the instant Office Action is "non-final."

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

3. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Applicant fails to set forth the criteria that defines the dosage form or steps in the production of the composition that results in the dosage form having the instant claimed plasma profile. Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain the plasma profile without undue experimentation. In the instant case, the provided examples set forth dosage forms made according to a process where the dosage forms have the same composition as those of US 6,099,859 ('859). However, '859 discloses that the peak plasma profile is approximately 8-12 hours after administration, whereas the instant specification/claims state that the dosage forms, which appear to have the same composition and process of making as '859, have a peak plasma profile of 5.5-7.5 hours. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The instant claims read on all antihyperglycemic drug compositions where the maximum plasma concentration occurs from 5.5-7.5 hours after administration, necessitating an exhaustive search for the embodiments suitable to practice the claimed

invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 21-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 26-30 recite the limitation where the drug is metformin. There is insufficient antecedent basis for this limitation in the claim (the claims from which these depend do not have metformin in the compositions).

7. Recitation of "based on" in claims 21-25 is indefinite since it is unclear whether Applicant is claiming that the dose of administration for metformin is "X" mg after an evening meal or whether another dose of metformin provides these limitations. In the event the $AUC_{0\text{-infinity}}$ for a particular dose of metformin is claimed, amendment with "for administration" is suggested to overcome the instant rejection.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 31-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Cheng et al (WO 99/47125; hereafter '125).

10. '125 discloses controlled release antihyperglycemic dosage form that has the same composition taught by the specification as providing the instant mean fluctuation indexes.

Response to Arguments

11. Applicant's arguments filed 7-8-02 have been fully considered but they are not persuasive. Applicant argues that the dosage forms of '125 do not disclose the same plasma profiles as in instant claims 1-31, however, the instant claims are not limited to plasma profiles. It is again submitted that the instant dosage forms are the same as those of '125 and that they would have the same mean fluctuation index.

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Todd D Ware whose telephone number is (703) 305-1700. The examiner can normally be reached on M-F, 8:30 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (703)308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are (703)

308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

tw
October 20, 2002

THOMAS K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

#11
3/18/03
1615
$

300.1005

UNITED STATES PATENT AND TRADEMARK OFFICE

Re:	Application of:	Xiu Xiu Cheng, et al.
	Serial No.:	09/705,630
	Filed:	November 3, 2000
	For:	**Controlled Release Metformin Compositions**
	Examiner: T. Ware	Art Unit: 1615

PETITION FOR EXTENSION UNDER 37 CFR 1.136(a)

Assistant Commissioner for Patents
Washington, D.C. 20231

February 24, 2003

Sir:

Applicants petition the Assistant Commissioner for Patents to extend the time for response to the Office Action dated October 22, 2002 for one (1) month from January 22, 2003 to February 24, 2003.

A check in the amount of $110.00 is enclosed to cover the one month extension fee. If it is determined that additional fees are due at this time, the Assistant Commissioner is hereby authorized to charge said fees to Deposit Account No. 50-0552.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Clifford M. Davidson
Reg. No. 32,728

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
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Form PTO-1083

Docket No.: 300.1005
Date: February 24, 2003

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ASSISTANT COMMISSIONER FOR PATENTS
Washington, DC 20231

In re application: **Xiu Xiu Cheng, et al.**
Serial No.: **09/705,630**
Filed: **November 3, 2000**
For: **CONTROLLED RELEASE METFORMIN COMPOSTIONS**

Sir:

Transmitted herewith is an **Amendment** in the above-identified application.

[ ] Small entity status under 37 C.F.R. 1.9 and 1.27 has been previously established.
[ ] Applicants assert small entity status under 37 C.F.R. 1.9 and 1.27.
[X] No fee for additional claims is required.
[ ] A filing fee for additional claims calculated as shown below, is required:

	(Col. 1)	(Col. 2)		SMALL ENTITY		OR	LARGE ENTITY	
FOR:	REMAINING AFTER AMENDMENT	HIGHEST PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	FEE		RATE	FEE
TOTAL CLAIMS	* Minus** =		x0	$ 9	$		x $ 18	$
INDEP. CLAIMS	* Minus*** =		x0	$ 40	$		x $ 80	$
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM				$ 135	$		+ $270	$
				TOTAL:	$	OR	TOTAL:	$

[X] Also transmitted herewith are:
[X] Petition for extension under 37 C.F.R. 1.136
[ ] Other:

[X] Check(s) in the amount of **$110.00** s/are attached to cover:
[ ] Filing fee for additional claims under 37 C.F.R. 1.16
[X] Petition fee for extension under 37 C.F.R. 1.136
[ ] Other: Fee for submission of Information Disclosure Statement

[X] The Assistant Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 50-0552.

[X] Any filing fee under 37 C.F.R. 1.16 for the presentation of additional claims which are not paid by check submitted herewith.
[X] Any patent application processing fees under 37 C.F.R. 1.17.
[X] Any petition fees for extension under 37 C.F.R. 1.136 which are not paid by check submitted herewith, and it is hereby requested that this be a petition for an automatic extension of time under 37 CFR 1.136.

Clifford M. Davidson, Reg. No. 32,728
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485 Seventh Avenue, 14th Floor
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Fax: (212) 736-2427

I hereby certify that this correspondence and/or documents referred to as attached therein and/or fee are being deposited with the United States Postal Service as "first class mail" in an envelope addressed to "Assistant Commissioner for Patents, Washington, D.C. 20231" on February 24, 2003.

DAVIDSON, DAVIDSON & KAPPEL, LLC
By:

#12/B
3/12/03

300.1005

UNITED STATES PATENT & TRADEMARK OFFICE

Re:	Application of:	Xiu Xiu Cheng, et al.
	Serial No.:	09/705,630
	Filed:	November 3, 2000
	For:	**Controlled Release Metformin Compositions**
	Examiner: T. Ware	Art Unit: 1615

Assistant Commissioner for Patents
Washington, D.C. 20231

February 24, 2003

AMENDMENT UNDER 37 C.F.R. § 1.111

Sir:

In response to the Office Action mailed on October 22, 2002, Applicants respectfully reconsideration of the application in view of the following amendments and remarks.

IN THE CLAIMS

Please ***cancel*** claims 2-3, 6, 28, and 31-42 without prejudice.

Please **amend** the claims as follows:

1. (Amended) A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising an effective dose of metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier to control the release of said metformin or pharmaceutically acceptable salt thereof from said dosage form, said dosage form being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof, wherein following oral administration of a single dose, the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the metformin from 5.5 to 7.5 hours after administration following dinner.

4. (Amended) The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 6.0 to 7.0 hours after the administration of the dose.

5. (Amended) The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 5.5 to 7.0 hours after the administration of the dose.

7. (Amended) The controlled release oral dosage form of claim 1, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7 5 phosphate buffer) and at 37 C:

0-30% of the metformin or salt thereof is released after 2 hours;
10-45% of the metformin or salt thereof is released after 4 hours;
30-90% of metformin or salt thereof is released after 8 hours;
not less than 50% of the metformin or salt thereof is released after 12 hours;
not less than 60% of the metformin or salt thereof is released after 16 hours; and
not less than 70% of the metformin or salt thereof is released after 20 hours.

8. (Amended) The controlled release oral dosage form of claim 1, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:

0-25% of the metformin or salt thereof is released after 2 hours;
20-40% of the metformin or salt thereof is released after 4 hours;
45-90% of the metformin or salt thereof is released after 8 hours;
not less than 60% of the metformin or salt thereof is released after 12 hours;
not less than 70% of the metformin or salt thereof is released after 16 hours; and
not less than 80% of the metformin or salt thereof is released after 20 hours.

9. (Amended) The controlled release oral dosage form of claim 1, which provides a width at 50% of the height of a mean plasma concentration/time curve of the metformin from about 4.5 to about 13 hours.

10. (Amended) The controlled release oral dosage form of claim 1, which provides a width at 50% of the height of a mean plasma concentration/time curve of the metformin from about 5.5 to about 10 hours.

11. (Amended) The controlled release oral dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of metformin which is more than about 7 times the mean plasma level of said metformin at about 24 hours after the administration.

12. (Amended) The controlled release oral dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 7 times to about 14 times the plasma level of said metformin at about 24 hours after administration.

13. (Amended) The controlled release oral dosage form of claim 1 which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 8 times to about 12 times the plasma level of said metformin at about 24 hours after administration.

14. (Amended) The controlled release oral dosage form of claim 1 which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

15. (Amended) The controlled release oral dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1700 ng/ml to about 2000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

16. (Amended) The controlled release oral dosage form of claim 1 which provides a mean AUC_{0-24hr} of at least 80% of the mean AUC_{0-24} provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release dosage form.

(Amended) The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24hr}$ of at least 90% of the mean $AUC_{0\text{-}24}$ provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

(Amended) The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

(Amended) The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 26500 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

(Amended) The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24hr}$ from about19800 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

(Amended) The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}\infty}$ of 18277 ± 2961 ng·hr/ml and a mean C_{max} of 1929 ± 333 ng/ml, for administration of a 1700 mg once-a-day dose of metformin after an evening meal.

(Amended) The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}\infty}$ of 20335 ± 4360 ng·hr/ml and a mean C_{max} of from 2053 ± 447 ng/ml, for administration of a 2000 mg once-a-day dose of metformin after an evening meal.

(Amended) The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24}$ of 26818 ± 7052 ng·hr/ml and a mean C_{max} of 2849 ± 797 ng/ml, for administration of a 2000 mg once-a-day dose of metformin after an evening meal.

~~24.~~ (Amended) The controlled release oral dosage form of claim 1 which provides a mean AUC_{0-24} of 22590 ± 3626 ng·hr/ml and a mean C_{max} of 2435 ± 630 ng/ml on the first day of administration and a mean AUC_{0-24} of 24136 ± 7996 ng·hr/ml and a mean C_{max} of 2288 ± 736 ng/ml on the 14th day of administration, for [based on] administration of a 2000 mg once-a-day dose of metformin after an evening meal.

~~25.~~ (Amended) The controlled release oral dosage form of claim ~~24~~ 17 which provides a mean $t_{1/2}$ from 2.8 to 4.4.

~~26.~~ (Amended) The controlled release oral dosage form of claim 9, which provides a mean time to maximum plasma concentration (Tmax) of metformin from 5.5 to 7.0 hours after administration.

~~27.~~ (Amended) The controlled release dosage form of claim 1, wherein the metformin or pharmaceutically acceptable salt thereof is provided by at least one controlled-release tablet, said tablet comprising:

(a) a core comprising:

(i) the metformin or a pharmaceutically acceptable salt;

(ii) optionally a binding agent; and

(iii) optionally an absorption enhancer;

(b) a membrane coating surrounding the core; and

(c) at least one passageway in the membrane.

REMARKS

Reconsideration of the present application is respectfully requested. An early and favorable action on the merits is earnestly solicited.

1. Status of the Claims

Claims 1, 4-5, 7-30 are pending; claims 2-3, 6, and 31-42 have been cancelled without prejudice; and claims 1 and 4-5, 7-25, 27 and 29 have been amended without prejudice. It is respectfully submitted that no new matter has been added by virtue of this amendment.

II. Rejections Under 35 U.S.C. § 112, First Paragraph

In the Office Action, claims 1-30 were rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner states that "[t]he instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation." The Examiner directs the Applicants attention to In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) and the eight factors discussed therein when assessing if a disclosure would have required undue experimentation.

The Examiner notes that "these examples are neither exhaustive, nor define the class of compound required," and that "[t]he pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity." The Examiner further states that "the instant claims read on all antihyperglycemic drug compositions where the maximum plasma concentration occurs from 5.5-7.5 hours after administration, necessitating an exhaustive search for the embodiments suitable to practice the claimed invention."

In response and in order to advance the prosecution of the present application, claim 1 has been amended without prejudice to recite "metformin" in place of "antihyperglycemic drug." As mentioned above, the claims of the present application are clearly enabled for metformin or a pharmaceutically acceptable salt thereof, and as amended, the present claims do not "read on all antihyperglycemic compositions".

In any event, Applicants are not required to exemplify every formulation which would be encompassed by the claim and it would be tremendously costly, inefficient and perhaps unethical to require manufacturing and testing of alternative formulations as apparently deemed necessary by the Examiner in the last Office Action. At the time the present application was filed, there were numerous controlled release technologies in the art, and testing for drug-plasma levels is routine in clinical studies.

Therefore, it is respectfully submitted that once the T_{max} range which provides for a useful dosage form has been established, other controlled release technologies known in the art can be manipulated and tested to achieve this T_{max} range without undue experimentation as discussed below.

A. The Test for Enablement

It is well recognized that "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 8 USPQ2d at 1046 (1989). "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." *In re Wands*, 8 USPQ2d at 1404 (*citations omitted*). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id. (Emphasis added)*. The very nature of pharmaceuticals requires both formulation work and clinical (in-vivo) evaluation, and therefore giving due regard for the nature of the invention, the amount of experimentation needed to prepare a suitable controlled release formulation using a technology other than that exemplified in the specification does not amount to undue experimentation.

B. Dosage Forms and Plasma Profile of the Present Invention

In the Office Action the Examiner states that "Applicant fails to set forth the criteria that defines the dosage form or steps in the production of the composition that results in the dosage form having the instant claimed plasma profile," and that "Applicant fails to provide information allowing the skilled artisan to ascertain the plasma profile without undue experimentation."

The invention as claimed is directed to a controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM wherein a maximum plasma

concentration is obtained at 5.5 to 7.5 hours after administration, irrespective of the particular technology employed in the controlled release dosage form. Certain representative examples of these formulations are provided in the present application, and it is explained in the specification that a number of controlled release technologies are useful in order to obtain the claimed pharmacokinetic parameters of the present invention.

Examples 1-3 of the present application which are directed to a tablet formulation containing metformin HCl, a seal coating, and a sustained release coating. Example 3 of the present application described clinical studies which were conducted to evaluate formulations prepared in accordance with Examples 1-3, which together with the specification enable the claimed the controlled release oral dosage forms of metformin or a pharmaceutically salt thereof which provide the T_{max} values of the present invention. The Examiner's attention is respectfully directed to page 19, line 21 to page 20, line 14 which states the following:

> Other controlled release technologies known to those skilled in the art can be used in order to achieve the controlled release formulations of the present invention, i.e., formulations which provide a mean T_{max} of the drug and/or other pharmacokinetic parameters described herein when orally administered to human patients. Such formulations can be manufactured as a controlled oral formulation in a suitable tablet or multiparticulate formulation known to those skilled in the art . . . .

In addition, at the time the application was filed, numerous controlled release technologies were well within the knowledge of pharmaceutical formulators having ordinary skill in the art. Such pharmaceutical formulators know that controlled release technologies can be manipulated, e.g., by varying the amount of controlled release carrier (among other things), to provide a formulation which upon in-vivo testing will provide the T_{max} range of the present invention. This fact is supported, e.g., by a simple review of patents discussed in the specification concerning formulation technologies, which patents provide ranges of ingredients. These ranges represent the acknowledgement of those skilled in the art that a certain amount of experimentation is considered to be necessary to manipulate a controlled release technology to obtain a desired release pattern of the drug. Such release patterns are demonstrated by the (well-known) use of in-vitro dissolution testing, which is considered by pharmaceutical formulators of

ordinary skill in the art to provide guidance as to which particular formulations might provide the desired in-vivo perfonnance.

Next, it is well known to those of ordinary skill in the art that upon formulating prospective products which might be useful in humans, in-vivo clinical studies must be conducted to determine whether the prospective product actually provides the desired in-vivo performance. Plasma profiles are routinely obtained during clinical trials and in particular during phase I-III studies as indicated in J.T. Cartensen, Pharmaceutical Principles of Solid Dosage Forms, 1993 (attached herewith).

It is respectfully submitted that none of the above steps, either separately or collectively, rise to the level of undue experimentation. Once the goal has been identified and has been attained (as in the present exemplified formulations set forth in the specification), it is respectfully submitted that a pharmaceutical formulator of ordinary skill in the art can manufacture prospective dosage forms for evaluation (to determine if they meet the required in-vivo parameters), a clinician of ordinary skill in the art can administer the dosage forms and draw blood at appropriate time intervals, and a pharmacokineticist of ordinary skill in the art can evaluate the in-vivo blood plasma results.

These steps represent a clear pattern followed by every pharmaceutical company in the world. There is no alternative short-cut known which is considered to be acceptable by government regulatory agencies (such as FDA). Since human experiments with pharmaceuticals are generally considered unethical if being done solely for patent purposes, the Examiner appears to be requiring this Applicant to conduct studies that are unethical, unnecessary and not legally required to support the rightful scope of Applicant's claims. Accordingly, it is earnestly requested that the Examiner remove this basis for rejection.

The Examiner is reminded that Applicants are not required to exemplify every formulation which would be encompassed by the claim. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 34 (CCPA 1970); MPEP 2164.01(b) (8th Edition) ("As long as the specification discloses at least one method for making and using the claimed invention that bears

a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied.").

In *Telectronics*, for example, the court found that "[s]ince one embodiment is admittedly disclosed in the specification, along with the general manner in which its current range was ascertained, we are convinced that other permutations of the invention could be practiced by those skilled in the art without undue experimentation." *Telectronics*, 8 USPQ2d at 1223 (*citing SRI Int'l v. Matsushita Elec. Corp. of America*, 775 F.2d 1107, 1121, 227 USPQ 577, 586 (Fed. Cir. 1985) (the law does not require an applicant to describe in his specification every conceivable embodiment of the invention)).

Therefore, it is respectfully submitted that by virtue of the present application Applicants have disclosed a T_{max} range which provides for a useful dosage form of metformin or pharmaceutically acceptable salt thereof, and other controlled release technologies known in the art can be manipulated by one of ordinary skill in the art to achieve this T_{max} range without undue experimentation.

C. U.S. Patent No. 6,099,859

In the rejection, the Examiner states that "[i]n the instant case, the provided examples set forth dosage forms made according to a process where the dosage forms have the same composition as those of U.S. 6,099,859 ('859)." However, the Examiner notes that " '859 discloses that the peak plasma profile is approximately 8-12 hours after administration, whereas the instant specification/claims state that the dosage forms, which appear to have the same composition and process of making as '859, have a peak plasma profile of 5.5-7.5 hours."

(1) The specification of '859 states in a preferred embodiment, that peak plasma levels are obtained between 8-12 hours after administration (See column 2, lines 50-55).

(2) In actuality however, the exemplified formulations did not provide a T_{max} between 8-12 hours except when the formulation prepared in accordance with Example 3 was administered at dinner. As set forth in an Information Disclosure Statement which will subsequently be hand

delivered to the Examiner, the mean T_{max} values for the Examples of the '859 were as follows: Example 1 (fasting) 4.67 hours; Example 2 (fasting) 4.33 hours; Example 2 (fed a.m.) 6.80 hours; Example 3 (fed a.m.) 6.67 hours; Example 3 (Fed p.m.) 9.67 hours. Therefore, the only instance was Example 3 fed in the P.M. (at dinner).

The claims have now been amended to state the "T_{max} of metformin at from 5.5 to 7.5 hours after single dose administration following dinner." The claims as now written are directed to methods and treatments which were never accomplished in the Examples of the '859 patent.

With respect to the Examiner's position that the provided examples of the present application set forth dosage forms made according to a process where the dosage forms have the same composition as those of U.S. 6,099,859 ('859), the Examiner's attention is respectfully directed to the fact that the formulations exemplified and tested in the present application are indeed different as the formulations of the Examples of the present application differ from those of the '859 by having two laser drilled holes, and the method achieved a different result than that reported in the '859 or achieved by clinical testing of Examples 1-3. However, it is respectfully submitted that one skilled in the art would be able to manipulate the processes and formulations of the '859 by other methods to obtain the claimed pharmacokinetic parameters of the present invention by routine experimentation.

Therefore, in view of the aforementioned, it is respectfully submitted that the formulations of the present invention are different than those of the '859 patent.

D. Conclusion

In the specification, Applicants have provided formulations, methods of making the formulations, and clinical studies of these formulations, that support the limitations (e.g., T_{max} values) recited in the present claims. Further, the prior art is replete with controlled release technology and, as stated in the present application, a number of controlled release technologies can be used to manufacture formulations which provide the results recited in the present claims without undue experimentation. Therefore, the Examiner is respectfully requested to remove the 35 U.S.C. §112 rejection of the pending claims.

III. **Rejections Under 35 U.S.C. § 112, Second Paragraph**

Claims 21-30 were rejected under 35 U.S.C. §112, second paragraph, on the grounds of indefiniteness.

Specifically, the Examiner states that "[c]laims 26-30 recite the limitation where the drug is metformin," and "[t]here is insufficient antecedent basis for this limitation in the claim (the claims from which these depend do not have metformin in the compositions)."

In response, claim 1 has been amended without prejudice to recite metformin or a pharmaceutically acceptable salt thereof. Therefore, there is now antecedent basis for this term in claims 26-30.

The Examiner further states that "[r]ecitation of 'based on' in claims 21-25 is indefinite since it is unclear whether Applicant is claiming that the dose of administration for metformin is 'X' mg after an evening meal or whether another dose of metformin provides these limitations. In the event the $AUC_{0\text{-infinity}}$ for a particular dose of metformin is claimed, amendment with 'for administration' is suggested to overcome the instant rejection."

In response, claims 21-24 have been amended without prejudice to recite the term "for" administration rather than "based on" administration, as suggested by the Examiner.

In view of the actions taken, the Examiner is respectfully requested to remove the rejection of claims 21-30 under 33 U.S.C. §112, second paragraph.

IV. **Rejections Under 35 U.S.C. § 102**

Claims 31-42 were rejected under 35 U.S.C. 102(b) "as being anticipated by Cheng et al (WO 99/47125; hereafter '125)". The Examiner states that "'125 discloses controlled release antihyperglycemic dosage form that has the same composition taught by the specification as providing the instant mean fluctuation indexes."

In view of the present amendment, claims 31-42 of the present application have been canceled without prejudice rendering the Examiner's rejection moot. Therefore, the Examiner is respectfully requested to withdraw the rejection of claims 31-42 under 35 U.S.C. §102(b) for the above-referenced application.

V. Conclusion

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings To Show Changes Made**."

It is now believed that the above-referenced rejections and objections have been obviated and it is respectfully requested that the rejections and objections be withdrawn. It is believed that all claims are now in condition for allowance.

According to currently recommended Patent Office policy the Examiner is requested to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

An early and favorable action is earnestly solicited.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Clifford M. Davidson
Reg. No. 32,728

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New York, New York 10018
(212) 736-1940

Version With Markings To Show Changes Made

IN THE CLAIMS

Claims 2-3,6, 28, and 31-42 have been cancelled without prejudice.

The claims have been amended as follows:

2. (Amended) A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising an effective dose of **[at least one suitable antihyperglycemic drug] metformin** or a pharmaceutically acceptable salt thereof and a controlled-release carrier **to control the release of said metformin or pharmaceutically acceptable salt thereof from said dosage form**, said dosage form being suitable for providing once-a-day oral administration of the **[agent] metformin** or pharmaceutically acceptable salt thereof, wherein **following oral administration of a single dose,** the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the **[agent] metformin** from 5.5 to 7.5 hours after **[the]** administration **following dinner**.

4. (Amended) The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of **[the drug] metformin at** from 6.0 to 7.0 hours after the administration of the dose.

5. (Amended) The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of **[the drug] metformin at** from 5.5 to 7.0 hours after the administration of the dose**[, when the dose is administered at dinner time]**.

6. (Amended) The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of **[the drug] metformin at** from about 6.0 to 7.5 hours after the administration of the dose, when the dose is administered at breakfast.

7. (Amended) The controlled release oral dosage form of claim 1, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:

0-30% of the **[drug] metformin or salt thereof** is released after 2 hours;

10-45% of the **[drug] metformin or salt thereof** is released after 4 hours;

30-90% of **[drug] metformin or salt thereof** is released after 8 hours;

not less than 50% of the **[drug] metformin or salt thereof** is released after 12 hours;

not less than 60% of the **[drug] metformin or salt thereof** is released after 16 hours; and

not less than 70% of the **[drug] metformin or salt thereof** is released after 20 hours.

8. (Amended) The controlled release oral dosage form of claim 1, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:

0-25% of the **[drug] metformin or salt thereof** is released after 2 hours;

20-40% of the **[drug] metformin or salt thereof** is released after 4 hours;

45-90% of the **[drug] metformin or salt thereof** is released after 8 hours;

not less than 60% of the **[drug] metformin or salt thereof** is released after 12 hours;

not less than 70% of the **[drug] metformin or salt thereof** is released after 16 hours; and

not less than 80% of the **[drug] metformin or salt thereof** is released after 20 hours.

9. (Amended) The controlled release oral dosage form of claim 1, which provides a width at 50% of the height of a mean plasma concentration/time curve of the **[drug] metformin** from about 4.5 to about 13 hours.

10. (Amended) The controlled release oral dosage form of claim 1, which provides a width at

50% of the height of a mean plasma concentration/time curve of the [drug] **metformin** from about 5.5 to about 10 hours.

11. (Amended) The controlled release oral dosage form of claim [3] 1, which provides a mean maximum plasma concentration (C_{max}) of metformin which is more than about 7 times the mean plasma level of said metformin at about 24 hours after the administration.

12. (Amended) The controlled release oral dosage form of claim [3] 1, which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 7 times to about 14 times the plasma level of said metformin at about 24 hours after administration.

13. (Amended) The controlled release oral dosage form of claim [3] 1 which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 8 times to about 12 times the plasma level of said metformin at about 24 hours after administration.

14. (Amended) The controlled release oral dosage form of claim [3] 1 which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

15. (Amended) The controlled release oral dosage form of claim [3] 1, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1700 ng/ml to about 2000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

16. (Amended) The controlled release oral dosage form of claim [3] 1 which provides a mean AUC_{0-24hr} of at least 80% of the mean AUC_{0-24} provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

17. (Amended) The controlled release oral dosage form of claim [3] 1 which provides a mean

AUC_{0-24hr} of at least 90% of the mean AUC_{0-24} provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

18. (Amended) The controlled release oral dosage form of claim **[3]** 1 which provides a mean AUC_{0-24hr} from about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

19. (Amended) The controlled release oral dosage form of claim **[3]** 1 which provides a mean AUC_{0-24hr} from about 17200 ng.hr/ml to about 26500 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

20. (Amended) The controlled release oral dosage form of claim **[3]** 1 which provides a mean AUC_{0-24hr} from about19800 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

21. (Amended) The controlled release oral dosage form of claim **[3]** 1 which provides a mean $AUC_{0-\infty}$ of 18277 ± 2961 ng·hr/ml and a mean C_{max} of 1929 ± 333 ng/ml, **for [based on]** administration of a 1700 mg once-a-day dose of metformin **[after an evening meal]**.

22. (Amended) The controlled release oral dosage form of claim **[3]** 1 which provides a mean $AUC_{0-\infty}$ of 20335 ± 4360 ng·hr/ml and a mean C_{max} of from 2053 ± 447 ng/ml, **for [based on]** administration of a 2000 mg once-a-day dose of metformin **[after an evening meal]**.

23. (Amended) The controlled release oral dosage form of claim **[3]** 1 which provides a mean AUC_{0-24} of 26818 ± 7052 ng·hr/ml and a mean C_{max} of 2849 ± 797 ng/ml, **for [based on]** administration of a 2000 mg once-a-day dose of metformin **[after an evening meal]**.

24. (Amended) The controlled release oral dosage form of claim **[3]** **1** which provides a mean AUC_{0-24} of 22590 ± 3626 ng·hr/ml and a mean C_{max} of 2435 ± 630 ng/ml on the first day of administration and a mean AUC_{0-24} of 24136 ± 7996 ng·hr/ml and a mean C_{max} of 2288 ± 736 ng/ml on the 14th day of administration, **for** **[based on]** administration of a 2000 mg once-a-day dose of metformin **[after an evening meal]**.

25. (Amended) The controlled release oral dosage form of claim 21 which provides a mean **[$T_{1/2}$]** **$t_{1/2}$** from 2.8 to 4.4.

27. (Amended) The controlled release oral dosage form of claim 9, which provides a mean time to maximum plasma concentration (Tmax) of metformin from 5.5 to 7.0 hours after administration **[at dinner time]**.

29. (Amended) The controlled release dosage form of claim 1, wherein the metformin **or pharmaceutically acceptable salt thereof** is provided by at least one controlled-release tablet, said tablet comprising:

(a) a core comprising:
  (i) the metformin or a pharmaceutically acceptable salt;
  (ii) optionally a binding agent; and
  (iii) optionally an absorption enhancer;
(b) a membrane coating surrounding the core; and
(c) at least one passageway in the membrane.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/705,630	11/03/2000	Xiu Xiu Cheng	300.1005	6707

23280 7590 05/21/2003

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EXAMINER	
WARE, TODD	

ART UNIT	PAPER NUMBER
1615	13

DATE MAILED: 05/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/705,630	CHENG ET AL.	
	Examiner	Art Unit	
	Todd D Ware	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)[X] Responsive to communication(s) filed on *05 April 2001* .

2a)[ ] This action is **FINAL**. 2b)[X] This action is non-final.

3)[ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)[X] Claim(s) *1,4,5,7-27,29 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)[ ] Claim(s) _____ is/are allowed.

6)[X] Claim(s) *1,4,5,9-27,29 and 30* is/are rejected.

7)[X] Claim(s) *7 and 8* is/are objected to.

8)[ ] Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)[ ] The specification is objected to by the Examiner.

10)[ ] The drawing(s) filed on _____ is/are: a)[ ] accepted or b)[ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)[ ] The proposed drawing correction filed on _____ is: a)[ ] approved b)[ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)[ ] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)[ ] All b)[ ] Some * c)[ ] None of:

1.[ ] Certified copies of the priority documents have been received.

2.[ ] Certified copies of the priority documents have been received in Application No. _____ .

3.[ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) [ ] The translation of the foreign language provisional application has been received.

15)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [X] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) [ ] Interview Summary (PTO-413) Paper No(s). _____ .
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other:

DETAILED ACTION

Receipt of request for extension of time (granted) and amendment/response all filed 3-4-03 is acknowledged. In view of Applicant's comments and the new grounds for rejection, the instant Office Action is non-final. Claims 1, 4-5, 7-27, and 29-30 are pending.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, f the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 4-5, 9-27, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al (WO 00/28989; hereafter '989) in view of Chiao (Remington, 1995) or Moeckel et al (5,955,106; hereafter '106) in view of Chiao (Remington, 1995).

4. '989 and '106 both teach controlled release metformin compositions but do not teach the exact release profile(s) of the instant claims.

5. Chiao is relied upon for teaching manipulation of controlled release formulations in achieving a desired release profile. Such manipulation can occur, for example, by varying the controlled release carrier, amount of controlled release ingredients, or thickness of coating(s) of controlled release ingredients.

6. Accordingly, it would have been obvious to one skilled in the art at the time of the invention to combine '989 and Chiao or '106 and Chiao with the motivation of providing controlled delivery of metformin over a desired period of time. Applicant's comments filed 3-4-03, Paper # 12, stating that numerous controlled release technologies are well within the knowledge of pharmaceutical formulators having ordinary skill in the art and such pharmaceutical formulators know that controlled release technologies can be manipulated, e.g. by varying the amount of controlled release carrier (among other things), to provide a formulation which upon *in* vivo testing will provide the T_{max} range of the present invention (pages 8-9 of response), are also relied upon for supporting the above position.

7. **Claims 1, 4-5, 9-27, and 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al (WO 99/47125; hereafter '125).**

8. '125 teaches controlled release metformin compositions but does teach the exact release profile(s) of the instant claims. In addition, '125 discloses a semi-permeable membrane coating surrounding the core. '125 incorporates by reference US Patent No. 3,845,770 (hereafter '770) to further describe the passageway and therefore drug release from the formulations taught therein. Briefly, '770 teaches adjustment of the release profile through manipulation of the interaction between the semi-permeable membrane and passageway(s) of the device (see '770 at C 6, L 39 - C 7, L 21; C 12, L 57 - C 13, L 67).

9. Accordingly, it would have been obvious to one skilled in the art at the time of the invention to manipulate the release profile of '125 in accordance with the teachings in '770 with the motivation of providing controlled delivery of metformin over a desired period of time.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1, 4-5, 9-27, and 29-30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 6,099,859. '859 teaches a semi-permeable membrane metformin formulation and incorporates US Patent No. 3,845,770 (hereafter '770) by reference to further describe the passageway and therefore drug release from the formulations taught therein. '770 teaches adjustment of the release profile through manipulation of the interaction between the semi-permeable membrane and passageway(s) of the device (see '770 at C 6, L 39 - C 7, L 21; C 12, L 57 - C 13, L 67). Accordingly, it would have been obvious to one skilled in the art at the time of the invention to manipulate the release profile of '125 in accordance with the teachings in '770 with the motivation of providing controlled delivery of metformin over a desired period of time.

12. Claims 1, 4-5, 9-27, and 29-30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-39 of U.S. Patent No. 6,284,275. '275 teaches a semi-permeable membrane metformin formulation and incorporates US Patent No. 3,845,770 (hereafter '770) by reference to further describe the passageway and therefore drug release from the formulations taught therein. '770 teaches adjustment of the release profile through manipulation of the interaction between the semi-permeable membrane and passageway(s) of the device (see '770 at C 6, L 39 - C 7, L 21; C 12, L 57 - C 13, L 67). Accordingly, it would

have been obvious to one skilled in the art at the time of the invention to manipulate the release profile of '125 in accordance with the teachings in '770 with the motivation of providing controlled delivery of metformin over a desired period of time.

13. Claims 1, 4-5, 9-27, and 29-30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,099,862. '862 teaches a semi-permeable membrane metformin formulation and incorporates US Patent No. 3,845,770 (hereafter '770) by reference to further describe the passageway and therefore drug release from the formulations taught therein. '770 teaches adjustment of the release profile through manipulation of the interaction between the semi-permeable membrane and passageway(s) of the device (see '770 at C 6, L 39 - C 7, L 21; C 12, L 57 - C 13, L 67). Accordingly, it would have been obvious to one skilled in the art at the time of the invention to manipulate the release profile of '125 in accordance with the teachings in '770 with the motivation of providing controlled delivery of metformin over a desired period of time.

14. Claims 1, 4-5, 9-27, and 29-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of copending Application No. 09/726,193. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are within the scope (species) of the claims of Application No. 09/726,193 (genus).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Allowable Subject Matter

15. Claims 7-8 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Todd D Ware whose telephone number is (703) 305-1700. The examiner can normally be reached on M-F, 8:30 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (703)308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

tw
May 19, 2003

Notice of References Cited	Application/Control No. 09/705,630	Applicant(s)/Patent Under Reexamination CHENG ET AL.	
	Examiner Todd D Ware	Art Unit 1615	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-3,845,770	11-1974	Theeuwes et al.	424/427
*	B	US-5,955,106	09-1999	Moeckel et al.	424/464
*	C	US-6,099,859	08-2000	Cheng et al.	424/464
*	D	US-6,099,862	08-2000	Chen et al.	424/473
*	E	US-6,284,275	09-2001	Chen et al.	424/473
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
*	N	WO 9947125 A1	09-1999	World Intellect	CHENG et al.	A61K 09/20
*	O	WO 0028989 A1	05-2000	World Intellect	Lewis et al	A61K 31/353
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Chiao, C. Sustained-Release Drug Delivery Systems Remington: the Science and Practice of Pharmacy, 1995, Mack Publishing Company, Easton, PA Pages 1660-1669.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

10/1/Elaine
(3 dra) & C

300.1005

UNITED STATES PATENT & TRADEMARK OFFICE

Re:	Application of:	Xiu Xiu Cheng, et al.
	Serial No.:	09/705,630
	Filed:	November 3, 2000
	For:	**Controlled Release Metformin Compositions**
	Examiner: T. Ware	Art Unit: 1615

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

November 21, 2003

AMENDMENT UNDER 37 CFR §1.111 and
STATEMENT OF SUBSTANCE OF INTERVIEW UNDER 37 CFR §1.133

Sir:

Reconsideration of the present application in view of the following amendments and remarks is respectfully requested.

I. INTRODUCTORY COMMENTS

In response to the Office Action mailed on May 21, 2003 and further to the Interview conducted with Supervisory Examiner Page on November 20, 2003, applicants respectfully request reconsideration of the allowability of the claims. The "REMARKS" section of the present amendment includes the substance of the interview as required under 37 CFR §1.133.

II. AMENDMENTS TO THE CLAIMS

Claim 1. **(Cancelled)**

Claims 2-3. **(Cancelled)**

Claim 4. **(Cancelled)**

Claim ~~3~~ 1. **(Currently Amended)** ~~The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 5.5 to 7.0 hours after the administration of the dose.~~ A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising an effective dose of metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier to control the release of said metformin or pharmaceutically acceptable salt thereof from said dosage form, said dosage form being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof, wherein following oral administration of a single dose, dosage form provides a mean time to maximum plasma concentration (T_{max}) of the metformin from 5.5 to 7 hours after administration following dinner.

Claim 6. **(Cancelled)**

Claim 7. **(Currently Amended)** The controlled release oral dosage form of claim ~~1~~ 5 which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:

0-30% of the metformin or salt thereof ~~is~~ released after 2 hours;

10-45% of the metformin or salt thereof ~~is~~ released after 4 hours;

30-90% of metformin or salt thereof ~~is~~ released after 8 hours;

not less than 50% of the metformin or salt thereof ~~is~~ released after 12 hours;

not less than 60% of the metformin or salt thereof ~~is~~ released after 16 hours; and

not less than 70% of the metformin or salt thereof ~~is~~ released after 20 hours.

Claim 8. (Currently Amended) The controlled release oral dosage form of claim ~~1~~ 5, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:

0-25% of the metformin or salt thereof ~~is~~ released after 2 hours;

20-40% of the metformin or salt thereof ~~is~~ released after 4 hours;

45-90% of the metformin or salt thereof ~~is~~ released after 8 hours;

not less than 60% of the metformin or salt thereof ~~is~~ released after 12 hours;

not less than 70% of the metformin or salt thereof ~~is~~ released after 16 hours; and

not less than 80% of the metformin or salt thereof ~~is~~ released after 20 hours.

Claim 9. (Currently Amended) The controlled release oral dosage form of claim ~~1~~ 5, which provides a width at 50% of the height of a mean plasma concentration/time curve of the metformin from about 4.5 to about 13 hours.

Claim 10. (Currently Amended) The controlled release oral dosage form of claim ~~1~~ 5, which provides a width at 50% of the height of a mean plasma concentration/time curve of the metformin from about 5.5 to about 10 hours.

Claim 11 (Currently Amended) The controlled release oral dosage form of claim ~~1~~ 5, which provides a mean maximum plasma concentration (C_{max}) of metformin which is more than about 7 times the mean plasma level of said metformin at about 24 hours after the administration.

Claim 12. (Currently Amended) The controlled release oral dosage form of claim ~~1~~ 5, which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 7 times to about 14 times the plasma level of said metformin at about 24 hours after administration.

Claim 13. (Currently Amended) The controlled release oral dosage form of claim ~~1~~ 5 which

provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 8 times to about 12 times the plasma level of said metformin at about 24 hours after administration.

Claim 14. (Currently Amended) The controlled release oral dosage form of claim ~~1~~ 5 which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 15. (Currently Amended) The controlled release oral dosage form of claim ~~1~~ 5, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1700 ng/ml to about 2000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 16. (Currently Amended) The controlled release oral dosage form of claim ~~1~~ 5 which provides a mean AUC_{0-24hr} of at least 80% of the mean AUC_{0-24} provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

Claim 17. (Currently Amended) The controlled release oral dosage form of claim ~~1~~ 5 which provides a mean AUC_{0-24hr} of at least 90% of the mean AUC_{0-24} provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

Claim 18. (Currently Amended) The controlled release oral dosage form of claim ~~1~~ 5 which provides a mean AUC_{0-24h} from about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 19. (Currently Amended) The controlled release oral dosage form of claim ~~1~~ 5 which provides a mean AUC_{0-24h} from about 17200 ng.hr/ml to about 26500 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 20. (**Currently Amended**) The controlled release oral dosage form of claim ~~19~~ 1 which provides a mean $AUC_{0\text{-}24hr}$ from about 19800 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 21. (**Currently Amended**) The controlled release oral dosage form of claim ~~19~~ 1 which provides a mean $AUC_{0\text{-}\infty}$ of 18277 ± 2961 ng·hr/ml and a mean C_{max} of 1929 ± 333 ng/ml, for administration of a 1700 mg once-a-day dose of metformin.

Claim 22. (**Currently Amended**) The controlled release oral dosage form of claim ~~19~~ 1 which provides a mean $AUC_{0\text{-}\infty}$ of 20335 ± 4360 ng·hr/ml and a mean C_{max} of from 2053 ± 447 ng/ml, for administration of a 2000 mg once-a-day dose of metformin.

Claim 23. (**Currently Amended**) The controlled release oral dosage form of claim ~~19~~ 1 which provides a mean $AUC_{0\text{-}24}$ of 26818 ± 7052 ng·hr/ml and a mean C_{max} of 2849 ± 797 ng/ml, for administration of a 2000 mg once-a-day dose of metformin.

Claim 24. (**Currently Amended**) The controlled release oral dosage form of claim ~~19~~ 1 which provides a mean $AUC_{0\text{-}24}$ of 22590 ± 3626 ng·hr/ml and a mean C_{max} of 2435 ± 630 ng/ml on the first day of administration and a mean $AUC_{0\text{-}24}$ of 24136 ± 7996 ng·hr/ml and a mean C_{max} of 2288 ± 736 ng/ml on the 14th day of administration, for administration of a 2000 mg once-a-day dose of metformin.

Claim 25. (**Previously Presented**) The controlled release oral dosage form of claim 21 which provides a mean $t_{1/2}$ from 2.8 to 4.4.

Claim 26. (**Original**) The controlled release oral dosage form of claim 4, which provides a mean time to maximum plasma concentration (T_{max}) of metformin from 6.0 to 7.0 hours after the administration.

Claim 27. (**Previously Presented**) The controlled release oral dosage form of claim 4, which provides a mean time to maximum plasma concentration (Tmax) of metformin from 5.5 to 7.0 hours after administration.

Claim 28. (**Cancelled**)

Claim 29. (**Currently Amended**) The controlled release dosage form of claim 1, wherein the metformin or pharmaceutically acceptable salt thereof is provided by at least one controlled-release tablet, said tablet comprising:

(a) a core comprising:
  (i) the metformin or a pharmaceutically acceptable salt;
  (ii) optionally a binding agent; and
  (iii) optionally an absorption enhancer;
(b) a membrane coating surrounding the core; and
(c) at least one passageway in the membrane.

Claim 30. (**Original**) The controlled release oral dosage form of claim 29, wherein said membrane is a semipermeable membrane.

Claims 31-42. (**Cancelled**)

Claim 43. (**New**) The controlled release oral dosage form of claim 5, which provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 6.0 to 7 hours after the administration of the dose.

III. REMARKS

The undersigned gratefully acknowledges the courtesies extended by Supervisory Examiner Page to the undersigned and Ted Whitlock, Esq. during the Interview conducted at the USPTO on November 20, 2003.

A. *Status of the Claims*

Claims 5, 7-27, 29-30 and 43 are pending. Claims 1 and 4 have been cancelled. Claim 5 has been re-written into independent form. The dependencies of the dependent claims have been revised to reflect this change. The subject matter of claim 4 has been re-inserted as new claim 43. The upper limit of the T_{max} in claims 5 and 43 (7 hours) was changed from "7.0" to "7" in order that applicants are not limited to an absolute numerical upper T_{max} limit of 7.0 hours with respect to equivalents. Support for the number "7" is found directly from exemplied formulations and is set forth in Table 1 for Example 2 (mean T_{max} value for Metformin XT administered after dinner; page 28) and in Table 3 for Example 1 (mean T_{max} value for Metformin XT administered after dinner; page 30). Minor grammatical correction has been made to dependent claims 7 and 8, which is not meant in any way to further limit the scope or interpretation of that claim.

It is respectfully submitted that no new matter has been added by virtue of changes to the claims.

B. Rejections Under 35 U.S.C. § 103(a)

During the Interview, the undersigned reviewed applicants' documents filed in response to the previous Office Action dated October 22, 2002 with Supervisory Examiner Page, as well as the current Office Action dated May 21, 2003. Applicants' USSN 09/705,625 was also interviewed at the same time.

(1) Lewis et al. in view of Chiao or Moeckel et al in view of Chiao

In the Office Action dated October 22, 2002, claims 1, 4-5, 9-27, and 29 were rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. (WO 00/28989) in view of Chiao (Remington, 1995) or Moeckel et al. (5,955,106) in view of Chiao (Remington, 1995).

During the interview, it was pointed out to Supervisory Examiner Page that Lewis et al. is directed to a combination product (insulin sensitizer plus another antidiabetes agent, which could be metformin), wherein it is stated that one or both of the active agents could be in modified release form. It was noted that Lewis et al. provide no in-vivo data whatsoever, and in fact do not mention any possible pharmacokinetic parameters which their formulations should meet. As stated in the last Office Action, Lewis et al. "do not teach the exact release profile(s) of the instant claims." It was further argued that Chaio does not overcome the deficiencies of Lewis et al. with respect to the particular T_{max} range set forth in the claims. In response, Supervisory Examiner Page agreed that the claimed T_{max} range was patentable over the combination of Lewis and Chiao.

During the interview, it was pointed out to Supervisory Examiner Page that the Moeckel et al. reference, while directed to retarded tablets containing metformin, does not suggest that the formulations described therein are useful for once-a-day administration. Instead, Moeckel et al. state that the retarded tablets of their invention "release metformin in a controlled manner over a time period of 0.5 -- 10 hours preferably over 4 hours (FIG. 1)." (Column 5, lines 30-32). It was noted that Moeckel et al. provide no in-vivo data whatsoever, and in fact do not mention any possible pharmacokinetic parameters which their formulations should meet. As stated in the last Office Action, Moeckel et al. "do not teach the exact release profile(s) of the instant claims." It was further argued that Chaio does not overcome the deficiencies of Lewis et al. with respect to the particular T_{max} range set forth in the claims. In response, Supervisory Examiner Page agreed that the claimed T_{max} range was patentable over the combination of Lewis and Chiao.

In view of the failure of the combined references to teach the claimed T_{max} parameter, it is respectfully requested that these rejections be removed.

(2) Cheng et al

In the last Office Action, claims 1, 4-5, 9-27 and 29-30 were rejected under 35 U.S.C. § 103(a), as being unpatentable over International Patent Application WO 99/47125 to Cheng, et al.

During the Interview, the T_{max} data presented in the Cheng, et al. reference was discussed in detail, and the Examiner's attention was directed to the discussion provided in applicants' responsive papers of February 2003 with respect to the T_{max} information presented in the '859 patent. It was pointed out to the Examiner that the '859 patent was the U.S. priority application to the Cheng, et al. reference. The relationship of the claimed T_{max} range of claim 1 (5.5 – 7.5 hours) when the dosage forms of the invention are administered after dinner was discussed with respect to providing the highest level of the drug in the blood at night (when gluconeogenesis is greatest; see the specification at pages 13-14). The Examiner considered the closest prior art to teach a T_{max} of 8 hours (the Cheng, et al. reference). The Examiner agreed that claim 5, which had an upper T_{max} of 7.0 hours and which value is directly supported by the working examples, is patentably distinct over the Cheng, et al. reference. The Examiner further agreed to consider the patentability of the broader range to 7.5 hours if applicants were to provide a working example of that value, as well.

In view of the deadline for filing this response and in order to expedite the prosecution of this application to issuance, claim 1 has been cancelled by virtue of this amendment and claim 5 has been modified into independent form. This is done without prejudice to applicants' ability to pursue the subject matter of claim 1 in a continuation application. This is also done without the intention that there be no range of equivalents beyond the numerical number of "7" with respect to the upper limit of the T_{max} range specified in the claims.

In view of the above, it is respectfully submitted that the rejection in view of Cheng, et al. should be removed.

C. Obviousness-Type Double Patenting

In the last Office Action, the Examiner made obviousness-type double patenting rejections of the claims as follows: claims 1, 4-5, 9-27 and 29-30 under the judicially created doctrine of as being unpatentable over claims 1-29 of U.S. Patent No. 6,099,859 (equivalent to WO 99/47125, cited above); claims 1, 4-5, 9-27 and 29-30 under the judicially created doctrine of as being unpatentable over claims 1-39 of U.S. Patent No. 6,284,275); and claims 1, 4-5, 9-27 and 29-30 under the judicially created doctrine of as being unpatentable over claims 1-4 of U.S. Patent No. 6,099,862. The Examiner also provisionally rejected claims 1, 4-5, 9-27 and 29-30 under the judicially created doctrine of as being unpatentable over claims 1-29 of copending U.S. Application Serial No. 09/726,193.

During the interview, the Examiner indicated that the above-mentioned obviousness-type double patenting rejections would not be maintained as per the policy of the USPTO and *In re Schneller*, 158 USPQ 210 (CCPA 1968).

Accordingly, it is respectfully requested that the obviousness-type double patenting rejections be withdrawn.

IV. Conclusion

It is now believed that the above-referenced rejections and objections have been obviated and it is respectfully requested that the rejections and objections be withdrawn. It is believed that all claims are now in condition for allowance.

According to currently recommended Patent Office policy the Examiner is requested to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

Upon review of the prosecution history of the present application during the preparation of this response, it was noted that complete copies of the PTO-1449 forms submitted with the Information Disclosure Statements of September 17, 2001 and February 28, 2003 were not initialed and returned to the undersigned. As certain references were disassociated from the file, Applicants again include herewith the Information Disclosure Statements of September 17, 2001 and February 28, 2003, along with the PTO-1449 forms and the references cited therein. The Examiner is requested to consider all of the references herein and return the initialed PTO-1449 forms to the undersigned.

An early and favorable action is earnestly solicited.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
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ok to enter MPM 7/9/04 18

FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. 300.1003	SERIAL NO. 09/705,630
LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	APPLICANTS Chih-Ming CHEN, et al.	
	FILING DATE November 3, 2000	GROUP 1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL									DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
MPM	AA	6	0	1.	0	7	1	8	1/4/00	Al-Razak et al.	424	464	
	AB	5	8	5	8	3	9	8	1/12/99	Cho	426	450	
	AC	5	6	9	1	3	8	6	11/25/97	Inman et al.	514	691	
	AD	5	6	8	8	5	1	8	11/18/97	Avar et al.	424	472	
	AE	5	6	7	4	9	0	0	10/7/97	Ubillas et al.	514	557	
	AF	5	6	6	8	1	1	7	9/16/97	Shapiro	514	55	
	AG	5	6	6	7	8	0	4	9/16/97	Wong et al.	424	472	
	AH	5	6	5	0	1	7	0	7/22/97	Wright et al.	424	473	
	AI	5	6	3	1	2	2	4	5/20/97	Efendic et al.	514	12	
D	AJ	5	6	2	9	3	1	9	5/13/97	Luo et al.	514	284	

FOREIGN PATENT DOCUMENTS

									DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION YES	TRANSLATION NO
MPM	AK	9	9	4	7	1	2	8	9/23/99	WO	A61K	9/24		
	AL	9	9	4	7	1	2	5	9/23/99	WO	A61K	9/20		
	AM	9	9	2	9	3	1	4	6/17/99	WO	A61K	31/155		
D	AN	9	6	0	8	2	4	3	3/21/96	WO	A61K	31/155		

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

MPM	AO	*Physicians' Desk Reference* (54th Ed 2000), pg. 831-835.
	AP	Sheen, Andre J., Clinical Pharmacokinetics of Metformin, *Clinical Pharmacokinetics*, May 30, 1996, 5:359-371
	AQ	Bailey, Clifford J., et al., Metformin, *The New England Journal of Medicine*, Feb. 29, 1996, 334:574-579.
	AR	Duna, Christopher F., et al., Metformin: A Review of its Pharmacological Properties and Therapeutic Use in Non-Insulin-Dependent Diabetes Mellitus, *Drugs* (1995), 49:721-747.
X	AS	Kantawan, P., et al., The Pharmacokinetics of Metformin: A Comparison of the Properties of a Rapid-Release and a Sustained-Release Preparation, pp. 31-36.

EXAMINER MPM DATE CONSIDERED 7/9/04

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY DOCKET NO. 300.1005	SERIAL NO. 09/705,630
LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	APPLICANTS Chih-Ming CHEN, et al.	
	FILING DATE November 3, 20000	GROUP 1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL									DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
MBP	AA	5	8	1	4	5	7	8	2/25/97	Dong et al.	524	377	
	AB	5	5	9	1	4	3	4	1/7/97	Kuczynski et al.	424	486	
	AC	5	5	4	5	4	1	3	8/12/96	Kuczynski et al.	424	473	
	AD	5	5	4	3	1	5	6	6/6/96	Rporda et al.	424	486	
	AE	5	5	1	2	2	9	3	4/30/96	Landrau et al.	424	449	
	AF	5	4	1	3	5	7	2	5/9/95*	Wong et al.	604	892.1	
	AG	5	2	0	8	3	4	5	5/3/94	Balaban et al.	604	892.1	
	AH	5	1	8	5	1	5	3	2/9/93	Ayer et al.	424	473	
	AI	5	1	7	8	8	6	7	1/12/93	Guiltard et al.	424	473	
	AJ	5	1	6	1	7	5	2	8/25/92	Ayer et al.	424	473	
	AK	5	1	2	0	5	4	8	6/9/92	McClelland et al.	424	473	
	AL	5		1	0	5	9	7	5/5/92	Wong et al.	424	638	
	AM	5	0	9	1	1	9	0	2/25/92	Kuczynski et al.	424	473	
	AN	5	0	7	1	6	0	7	12/10/91	Ayer et al.	264	112	
	AO	5	0	2	4	8	4	3	6/18/91	Kuczynski et al.	514	235.06	
	AP	4	9	6	3	1	4	1	10/16/90	Eckenhoff	604	892.1	
	AQ	4	8	9	2	7	3	9	1/9/90	Shah et al.	424	473	
	AR	4	8	6	3	5	9	8	9/12/89	Eckenhoff	604	892.1	

FOREIGN PATENT DOCUMENTS

									DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION YES	TRANSLATION NO
	AS													

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	AT	

EXAMINER Thurman Page DATE CONSIDERED 7/9/04

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. 300.1005	SERIAL NO. 09/703,630
LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	APPLICANTS: Chih-Ming CHEN, et al.	
	FILING DATE November 3, 2000	GROUP 1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL										DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
FMM	CA	4	8	5	1	2	1	9		7/25/89	Magruder et al.	424	457	
	CB	4	7	8	3	1	1	7		11/8/88	Wong et al.	424	468	
	CC	4	7	7	7	0	4	9		10/11/88	Magruder et al.	424	457	
	CD	4	7	0	4	1	1	8		11/3/87	Eckenhoff	424	438	
	CE	4	6	9	2	1	1	6		9/8/87	Eckenhoff et al.	424	468	
	CF	4	6	2	7	8	5	0		12/9/86	Deters et al.	604	892.1	
	CG	4	6	2	4	8	4	7		11/25/86	Ayer et al.	424	467	
	CH	4	6	1	5	6	9	8		10/7/86	Guittard et al.	604	892.1	
	CI	4	6	1	2	0	0	8		9/16/86	Wong et al.	604	892.1	
	CJ	4	6	0	9	1	7	4		9/2/86	Ayer	424	473	
	CK	4	5	8	7	1	1	7		5/6/86	Edgren et al.	424	473	
	CL	4	5	2	2	6	2	5		6/11/85	Edgren	424	493	
	CM	4	1	1	1	2	0	1		9/5/78	Theeuwes	424	473	
	CN	4	0	5	8	5	6	4		5/9/78	Theeuwes et al	219	121.71	
	CO	4	0	8	0	4	7	2		3/21/78	Hohson	514	533	
	CP	4	0	7	7	4	0	7		3/7/78	Theeuwes et al.	424	427	
	CQ	4	0	6	3	0	6	4		12/13/77	Saunders et al.	219	121.7	

FOREIGN PATENT DOCUMENTS

										DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION YES	TRANSLATION NO
	CR														

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	CS	

EXAMINER Thomas Luecy	DATE CONSIDERED 7/9/04

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. 300.1005	SERIAL NO. 09/705,630
LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	APPLICANTS: Chih-Ming CHEN, et al.	
	FILING DATE November 3, 2000	GROUP 1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL									DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
YIBY	DA	4	0	3	6	2	2	6	7/19/77	Theeuwes	424	473	
	DB	4	0	3	4	7	5	8	7/12/77	Theeuwes	424	427	
	DC	4	0	0	8	2	1	9	2/22/77	Theeuwes et al.	424	427	
	DD	3	9	5	7	1	5	3	5/18/76	Bohuon	360	143	
	DE	3	9	5	2	7	4	1	4/27/76	Baker	424	405	
	DF	3	8	1	6	3	9	9	11/4/75	Theeuwes et al.	424	424	
	DG	3	8	4	5	7	7	0	11/3/74	Theeuwes et al.	424	427	
	DH												
	DI												
	DJ												
	DK												
	DL												
	DM												
	DN												
	DO												
	DP												
	DQ												

FOREIGN PATENT DOCUMENTS

									DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION YES	TRANSLATION NO
	DR													

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	DS	
EXAMINER	Mia Ostrup	DATE CONSIDERED 7/6/01

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Our Ref. 300.1005 November 21, 2003 CMD/DGK/dm

Re: Patent Application: Xiu Xiu Cheng, et a.,
Serial No.: 09/705,630
Filed: November 3, 2000
For: CONTROLLED RELEASE METFORMIN COMPOSITIONS

Enclosed are:
- PTO-Form 1083 with Certificate of Mailing (1 page);
- Petition for Three (3) Month Extension of Time (1 page);
- Amendment and Statement of Substance of Interview (11 pages);
- Copies of Information Disclosure Statements submitted on September 17, 2001 and February 28, 2003 including PTO-1449 Forms and references cited therein; and
- Check in the amount of $950.00

WITH FIRST CLASS MAIL CERTIFICATION

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Approved for use through xx/xx/xxxx. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Applicant Initiated Interview Request Form

Application No.: 09/705,630 First Named Applicant: Xiu Xiu CHENG
Examiner: WARE, Todd Art Unit: 1615 Status of Application: Office Action Pending

Tentative Participants:
(1) Clifford M. Davidson (2) Ted Whitlock
(3) Thurman Page (4)

Proposed Date of Interview: 11/20/2003 Proposed Time: 2:00 (AM/PM)

Type of Interview Requested:
(1) [ ] Telephonic (2) [X] Personal (3) [ ] Video Conference

Exhibit To Be Shown or Demonstrated: [ ] YES [X] NO
If yes, provide brief description:

Issues To Be Discussed

Issues (Rej., Obj., etc)	Claims/ Fig. #s	Prior Art	Discussed	Agreed	Not Agreed
(1) 103 rejections			[ ]	[ ]	[ ]
(2) double patenting rejections			[ ]	[ ]	[ ]
(3) allowable subject matter			[ ]	[ ]	[ ]
(4)			[ ]	[ ]	[ ]

[ ] Continuation Sheet Attached

Brief Description of Arguments to be Presented:
Discussion of cited references and claims

An interview was conducted on the above-identified application on _____.

NOTE:
This form should be completed by applicant and submitted to the examiner in advance of the interview (see MPEP § 713.01).
This application will not be delayed from issue because of applicant's failure to submit a written record of this interview. Therefore, applicant is advised to file a statement of the substance of this interview (37 CFR 1.133(b)) as soon as possible.

(Applicant/Applicant's Representative Signature) (Examiner/SPE Signature)

FORM PTO-1083

Docket No.: 300.1005
Date: November 21, 2003

COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, VA 22313-1450

In re application: Xiu Xiu Cheng, et al.
Serial No.: 09/705,630
Filed: November 3, 2000
For: **CONTROLLED RELEASE METFORMIN COMPOSTIONS**

Sir:

Transmitted herewith is an **Amendment and Statement of Substance of Interview** in the above-identified application.

[ ] Small entity status under 37 C.F.R. 1.9 and 1.27 has been previously established.
[ ] Applicants assert small entity status under 37 C.F.R. 1.9 and 1.27.
[X] No fee for additional claims is required.
[ ] A filing fee for additional claims calculated as shown below, is required:

	(Col. 1)	(Col. 2)		SMALL ENTITY			LARGE ENTITY	
FOR:	REMAINING AFTER AMENDMENT	HIGHEST PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	FEE	OR	RATE	FEE
TOTAL CLAIMS	* Minus** =	0		x $ 9	$		x $ 18	$
INDEP. CLAIMS	* Minus*** =	0		x $ 42	$		x $ 84	$
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM				+ $140	$		+ $280	$
				TOTAL:	$	OR	TOTAL:	$

* If the entry in Co. 1 is less than the entry in Col. 2, write "0" in Col. 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

[X] Also transmitted herewith are:
[X] Petition for extension under 37 C.F.R. 1.136
[X] Other: Copies of previously submitted Information Disclosure Statements of September 17, 2001 and February 28, 2003 including PTO-1449 forms, and References Cited therein.

[X] Check(s) in the amount of $950.00 is/are attached to cover:
[ ] Filing fee for additional claims under 37 C.F.R. 1.16
[X] Petition fee for extension under 37 C.F.R. 1.136
[ ] Other:

[X] The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 50-0552.

[X] Any filing fee under 37 C.F.R. 1.16 for the presentation of additional claims which are not paid by check submitted herewith.
[X] Any patent application processing fees under 37 C.F.R. 1.17.
[X] Any petition fees for extension under 37 C.F.R. 1.136 which are not paid by check submitted herewith, and it is hereby requested that this be a petition for an automatic extension of time under 37 CFR 1.136.

Clifford M. Davidson, Reg. No. 32,726
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
Tel: (212) 736-1940
Fax: (212) 736-2427

I hereby certify that this correspondence and/or documents referred to as attached therein and/or fee are being deposited with sufficient postage to the United States Postal Service as "first class mail" in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" on
November 21, 2003
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BY: David M. Grasscak

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*ADMITTED IN NEW JERSEY ONLY
**DDK EUROPE

FACSIMILE TRANSMITTAL

FROM: David G. Knasiak

PAGES: 14 (including cover sheet)

DATE: September 3, 2004

Attorney Docket Nos.: 300.1005

Re: Application of:Xiu Xiu Cheng, et al.
Application Serial No. : 09/705,630
Filed: November 3, 2000
Examiner: Micah Paul Young

PLEASE DELIVER THE FOLLOWING TO:

Recipients(s): **Micah Paul Young** ***Fax Number: 1-703-872-9306***

MESSAGE: As requested by Examiner Micah Paul Young transmitted herewith is a duplicate copy of the amendment filed on November 21, 2003 in the above-identified case and the postcard stamped by the USPTO.

This transmission was sent from fax number (212) 736-2427. If you have any problems with your reception, please telephone the sender at (212) 736-1940 Ext. 231.

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper with enclosures are being facsimile transmitted to the Patent and Trademark Office on the date shown below.

David G. Knasiak — 9/3/04

David G. Knasiak Date

IF THERE ARE ANY PROBLEMS WITH RECEPTION OF THIS FAX, PLEASE CALL OR FAX SENDER TO ADVISE. THANK YOU.

Notice of Allowability	Application No.	Applicant(s)
	09/705,630	CHENG ET AL.
	Examiner	Art Unit
	Micah-Paul Young	1615

-- ***The MAILING DATE of this communication appears on the cover sheet with the correspondence address***--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *interview conducted 11/20/03*.
2. ☒ The allowed claim(s) is/are *1,4,5,7-27 and 29*.
3. ☒ The drawings filed on *03 November 2000* are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.
5. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
   (a) ☐ The translation of the foreign language provisional application has been received.
6. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

7 ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

8 ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No. _____.
   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the Examiner.
   (c) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No. _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the margin according to 37 CFR 1.121(d).

9. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1☐ Notice of References Cited (PTO-892)
2☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No. _____
4☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5☐ Notice of Informal Patent Application (PTO-152)
6☒ Interview Summary (PTO-413), Paper No._____ .
7☐ Examiner's Amendment/Comment
8☐ Examiner's Statement of Reasons for Allowance
9☐ Other

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

#14

Sheet 1 of 1

FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.: 300.1005	SERIAL NO.: 09/705,630
LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)		APPLICANT(S): Xiu Xiu CHENG, et al.	
		FILING DATE: November 3, 2000	GROUP: 1615

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
MT	AA	6 4 7 5 5 2	11/05/2002	Timmins et al.	424	469	Sep. 16, 1999
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AH							
	AI							
	AJ							
	AK							
	AL							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	AM	Andrx Pilot Biostudy Data (20 pages)
	AN	
	AO	
	AP	
	AQ	
	AR	
	AS	

EXAMINER	DATE CONSIDERED
Michael Pacher	12/12/03

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

23280 7590 12/19/2003

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

EXAMINER	
YOUNG, MICAH PAUL	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 12/19/2003

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/705,630	11/03/2000	Xiu Xiu Cheng	300.1005	6707

TITLE OF INVENTION: CONTROLLED RELEASE METFORMIN COMPOSITIONS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1530	$0	$1330	03/19/2004

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status is changed, pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above and notify the United States Patent and Trademark Office of the change in status, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check the box below and enclose the PUBLICATION FEE and 1/2 the ISSUE FEE shown above.

☐ Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 11/03) Approved for use through 04/30/2004.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (703) 746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

23280 7590 12/19/2003

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/705,630	11/03/2000	Xiu Xiu Cheng	300.1005	6707

TITLE OF INVENTION: CONTROLLED RELEASE METFORMIN COMPOSITIONS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$0	$1330	03/19/2004

EXAMINER	ART UNIT	CLASS-SUBCLASS
YOUNG, MICAH PAUL	1615	424-468000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent); ☐ individual ☐ corporation or other private group entity ☐ government

4a. The following fee(s) are enclosed:

☐ Issue Fee
☐ Publication Fee
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s):

☐ A check in the amount of the fee(s) is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☐ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

Director for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) (Date)

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

TRANSMIT THIS FORM WITH FEE(S)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/705,630	11/03/2000	Xiu Xiu Cheng	300.1005	6707

23280 7590 12/19/2003

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

EXAMINER	
YOUNG, MICAH PAUL	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 12/19/2003

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) system (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (703) 305-1383. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

PTOL-85 (Rev. 11/03) Approved for use through 04/30/2004.

PA IDC p#17

QUERY CONTROL FORM			RTIS USE ONLY	
Application No.	09/705,630	Prepared by	Tracking Number	09880889
Examiner-GAU	Page-Wells	Date	Week Date	10-29-03
		No. of queries		

JACKET			
a. Serial No.	f. Foreign Pricrity	k. Print Claim(s)	p. PTO-1449
b. Applicant(s)	g. Disclaimer	l. Print Fig.	q. PTOL-85b
c. Continuing Data	h. Microfiche Appendix	m. Searched Column	r. Abstract
d. PCT	i. Title	n. PTO-270/328	s. Sheets/Figs
e. Domestic Priority	j. Claims Allowed	o. PTO-892	t. Other

SPECIFICATION

a. Page Missing
b. Text Continuity
c. Holes through Data
d. Other Missing Text
e. Illegible Text
f. Duplicate Text
g. Brief Description
h. Sequence Listing
i. Appendix
j. Amendments
k. Other

CLAIMS

a. Claim(s) Missing
b. Improper Dependency
c. Duplicate Numbers
d. Incorrect Numbering
e. Index Disagrees
f. Punctuation
g. Amendments
h. Bracketing
i Missing Text
j Duplicate Text
k. Other

MESSAGE

(1) Claim #2 is missing from text and index.

(2) Sole inventor on oath is the second inventor on Bib.

RECEIVED
JAN 21 2004
Technology Division
13

Please Advise

initials LAG

RESPONSE (1) corrected

(2) order on the bib sheet is correct order of inventorship

initials LH

E-5 (Rev. 10/01/02)

18 / Reg Corrected / Notice

300.1005

Ref 3-19-04

UNITED STATES PATENT & TRADEMARK OFFICE

Re:	Application of:	Xiu Xiu Cheng, et al.
	Serial No.:	09/705,630
	Filed:	November 3, 2000
	For:	***Controlled Release Metformin Compositions***
	Examiner: M. Young	Art Unit: 1615

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

January 8, 2004

Attention: Examiner Micah Paul Young

COMMUNICATION

Sir:

This communication is being submitted in accordance with the telephone message on January 7, 2004, that Examiner Micah Paul Young left with Mr. David G. Knasiak, Associate Attorney for the undersigned.

A Notice of Allowance for the above-referenced application was mailed on December 19, 2003. Upon review of the Notice of Allowability and accompanying documents, Applicants' Attorney determined that certain claims that were indicated as allowable were cancelled (e.g., claims 1 and 4) and certain claims which were pending (claims 30 and 43) were not acknowledged in the Notice of Allowance. In addition, the four (4) pages of Form PTO-1449, which were submitted on September 17, 2001 together with the Information Disclosure Statement of the same date, and resubmitted with the amendment of November 21, 2003 to the United States Patent Office, have not been returned to Applicant initialed by the Examiner.

As requested by the Examiner a listing of the pending claims is provided below and the (4) pages of the above-mentioned Form PTO-1449 are included herewith.

LISTING OF CLAIMS

Claim 5. A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising an effective dose of metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier to control the release of said metformin or pharmaceutically acceptable salt thereof from said dosage form, said dosage form being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof, wherein following oral administration of a single dose, dosage form provides a mean time to maximum plasma concentration (T_{max}) of the metformin from 5.5 to 7 hours after administration following dinner.

Claim 7. The controlled release oral dosage form of claim 5, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:

0-30% of the metformin or salt thereof released after 2 hours;
10-45% of the metformin or salt thereof released after 4 hours;
30-90% of metformin or salt thereof released after 8 hours;
not less than 50% of the metformin or salt thereof released after 12 hours;
not less than 60% of the metformin or salt thereof released after 16 hours; and
not less than 70% of the metformin or salt thereof released after 20 hours.

Claim 8. The controlled release oral dosage form of claim 5, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:

0-25% of the metformin or salt thereof released after 2 hours;
20-40% of the metformin or salt thereof released after 4 hours;
45-90% of the metformin or salt thereof released after 8 hours;
not less than 60% of the metformin or salt thereof released after 12 hours;
not less than 70% of the metformin or salt thereof released after 16 hours; and
not less than 80% of the metformin or salt thereof released after 20 hours.

Claim 9. The controlled release oral dosage form of claim 5, which provides a width at 50% of the height of a mean plasma concentration/time curve of the metformin from about 4.5 to about 13 hours.

Claim 10. The controlled release oral dosage form of claim 5, which provides a width at 50% of the height of a mean plasma concentration/time curve of the metformin from about 5.5 to about 10 hours.

Claim 11. The controlled release oral dosage form of claim 5, which provides a mean maximum plasma concentration (C_{max}) of metformin which is more than about 7 times the mean plasma level of said metformin at about 24 hours after the administration.

Claim 12. The controlled release oral dosage form of claim 5, which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 7 times to about 14 times the plasma level of said metformin at about 24 hours after administration.

Claim 13. The controlled release oral dosage form of claim 5 which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 8 times to about 12 times the plasma level of said metformin at about 24 hours after administration.

Claim 14. The controlled release oral dosage form of claim 5 which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 15. The controlled release oral dosage form of claim 5, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1700 ng/ml to about 2000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 16. The controlled release oral dosage form of claim 5 which provides a mean AUC_{0-24hr} of at least 80% of the mean AUC_{0-24} provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

Claim 17. The controlled release oral dosage form of claim 5 which provides a mean AUC_{0-24hr} of at least 90% of the mean AUC_{0-24} provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

Claim 18. The controlled release oral dosage form of claim 5 which provides a mean AUC_{0-24hr} from about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 19. The controlled release oral dosage form of claim 5 which provides a mean AUC_{0-24hr} from about 17200 ng.hr/ml to about 26500 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 20. The controlled release oral dosage form of claim 5 which provides a mean AUC_{0-24hr} from about19800 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 21. The controlled release oral dosage form of claim 5 which provides a mean $AUC_{0-\infty}$ of 18277 ± 2961 ng·hr/ml and a mean C_{max} of 1929 ± 333 ng/ml, for administration of a 1700 mg once-a-day dose of metformin.

Claim 22. The controlled release oral dosage form of claim 5 which provides a mean $AUC_{0-\infty}$ of 2033.5 ± 4360 ng·hr/ml and a mean C_{max} of from 2053 ± 447 ng/ml, for administration of a 2000 mg once-a-day dose of metformin.

Claim 23. The controlled release oral dosage form of claim 5 which provides a mean AUC_{0-24} of 26818 ± 7052 ng·hr/ml and a mean C_{max} of 2849 ± 797 ng/ml, for administration of a 2000 mg once-a-day dose of metformin.

Claim 24. The controlled release oral dosage form of claim 5 which provides a mean AUC_{0-24} of 22590 ± 3626 ng·hr/ml and a mean C_{max} of 2435 ± 630 ng/ml on the first day of administration and a mean AUC_{0-24} of 24136 ± 7996 ng·hr/ml and a mean C_{max} of 2288 ± 736 ng/ml on the 14th day of administration, for administration of a 2000 mg once-a-day dose of metformin.

Claim 25. The controlled release oral dosage form of claim 21 which provides a mean $t_{1/2}$ from 2.8 to 4.4.

Claim 26. The controlled release oral dosage form of claim 9, which provides a mean time to maximum plasma concentration (T_{max}) of metformin from 6.0 to 7.0 hours after the administration.

Claim 27. The controlled release oral dosage form of claim 9, which provides a mean time to maximum plasma concentration (Tmax) of metformin from 5.5 to 7.0 hours after administration.

Claim 29. The controlled release dosage form of claim 5 , wherein the metformin or pharmaceutically acceptable salt thereof is provided by at least one controlled-release tablet, said tablet comprising:

(a) a core comprising:
  (i) the metformin or a pharmaceutically acceptable salt;
  (ii) optionally a binding agent; and
  (iii) optionally an absorption enhancer;
(b) a membrane coating surrounding the core; and
(c) at least one passageway in the membrane.

Claim 30. The controlled release oral dosage form of claim 29, wherein said membrane is a semipermeable membrane.

Claim 43. The controlled release oral dosage form of claim 5, which provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 6.0 to 7 hours after the administration of the dose.

Conclusion

Applicants respectfully request that the Examiner provide a supplemental notice of allowance indicating the properly allowed claims and the initialed four (4) pages of Form PTO-1449 to the undersigned.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
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FACSIMILE TRANSMITTAL

FROM: David G. Knasiak

PAGES: 12 (including cover sheet)

DATE: January 8, 2004

Attorney Docket Nos.: 300.1005

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300.1005

UNITED STATES PATENT & TRADEMARK OFFICE

Re:	Application of:	Xiu Xiu Cheng, et al.
	Serial No.:	09/705,630
	Filed:	November 3, 2000
	For:	**Controlled Release Metformin Compositions**
	Examiner: M. Young	Art Unit: 1615

AMENDMENT UNDER 37 C.F.R. § 1.312

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

January 9, 2004

I. INTRODUCTORY COMMENTS

Sir:

In response to the Notice of Allowance dated December 19, 2003, Applicants respectfully request that the following clean claim set be published in the printed patent. Applicants also request that the initialed copies of the PTO 1449 Forms previously submitted on September 17, 2001 together with the Information Disclosure Statement of the same date, and resubmitted with the amendment of November 21, 2003 be returned to the Applicant, as described in more detail in the "Remarks" section below.

II. CLEAN SET OF CLAIMS

Claim 5. A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising an effective dose of metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier to control the release of said metformin or pharmaceutically acceptable salt thereof from said dosage form, said dosage form being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof, wherein following oral administration of a single dose, dosage form provides a mean time to maximum plasma concentration (T_{max}) of the metformin from 5.5 to 7 hours after administration following dinner.

Claim 7. The controlled release oral dosage form of claim 5, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:

0-30% of the metformin or salt thereof released after 2 hours;
10-45% of the metformin or salt thereof released after 4 hours;
30-90% of metformin or salt thereof released after 8 hours;
not less than 50% of the metformin or salt thereof released after 12 hours;
not less than 60% of the metformin or salt thereof released after 16 hours; and
not less than 70% of the metformin or salt thereof released after 20 hours.

Claim 8. The controlled release oral dosage form of claim 5, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:

0-25% of the metformin or salt thereof released after 2 hours;
20-40% of the metformin or salt thereof released after 4 hours;
45-90% of the metformin or salt thereof released after 8 hours;
not less than 60% of the metformin or salt thereof released after 12 hours;
not less than 70% of the metformin or salt thereof released after 16 hours; and
not less than 80% of the metformin or salt thereof released after 20 hours.

Claim 9. The controlled release oral dosage form of claim 5, which provides a width at 50% of the height of a mean plasma concentration/time curve of the metformin from about 4.5 to about 13 hours.

Claim 10. The controlled release oral dosage form of claim 5, which provides a width at 50% of the height of a mean plasma concentration/time curve of the metformin from about 5.5 to about 10 hours.

Claim 11. The controlled release oral dosage form of claim 5, which provides a mean maximum plasma concentration (C_{max}) of metformin which is more than about 7 times the mean plasma level of said metformin at about 24 hours after the administration.

Claim 12. The controlled release oral dosage form of claim 5, which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 7 times to about 14 times the plasma level of said metformin at about 24 hours after administration.

Claim 13. The controlled release oral dosage form of claim 5 which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 8 times to about 12 times the plasma level of said metformin at about 24 hours after administration.

Claim 14. The controlled release oral dosage form of claim 5 which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 15. The controlled release oral dosage form of claim 5, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1700 ng/ml to about 2000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 16. The controlled release oral dosage form of claim 5 which provides a mean $AUC_{0\text{-}24hr}$ of at least 80% of the mean $AUC_{0\text{-}24}$ provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

Claim 17. The controlled release oral dosage form of claim 5 which provides a mean $AUC_{0\text{-}24hr}$ of at least 90% of the mean $AUC_{0\text{-}24}$ provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

Claim 18. The controlled release oral dosage form of claim 5 which provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 19. The controlled release oral dosage form of claim 5 which provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 26500 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 20. The controlled release oral dosage form of claim 5 which provides a mean $AUC_{0\text{-}24hr}$ from about19800 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

Claim 21. The controlled release oral dosage form of claim 5 which provides a mean $AUC_{0\text{-}\infty}$ of 18277 ± 2961 ng·hr/ml and a mean C_{max} of 1929 ± 333 ng/ml, for administration of a 1700 mg once-a-day dose of metformin.

Claim 22. The controlled release oral dosage form of claim 5 which provides a mean $AUC_{0\text{-}\infty}$ of 20335 ± 4360 ng·hr/ml and a mean C_{max} of from 2053 ± 447 ng/ml, for administration of a 2000 mg once-a-day dose of metformin.

Claim 23. The controlled release oral dosage form of claim 5 which provides a mean AUC_{0-24} of 26818 ± 7052 ng·hr/ml and a mean C_{max} of 2849 ± 797 ng/ml, for administration of a 2000 mg once-a-day dose of metformin.

Claim 24. The controlled release oral dosage form of claim 5 which provides a mean AUC_{0-24} of 22590 ± 3626 ng·hr/ml and a mean C_{max} of 2435 ± 630 ng/ml on the first day of administration and a mean AUC_{0-24} of 24136 ± 7996 ng·hr/ml and a mean C_{max} of 2288 ± 736 ng/ml on the 14th day of administration, for administration of a 2000 mg once-a-day dose of metformin.

Claim 25. The controlled release oral dosage form of claim 21 which provides a mean $t_{1/2}$ from 2.8 to 4.4.

Claim 26. The controlled release oral dosage form of claim 9, which provides a mean time to maximum plasma concentration (T_{max}) of metformin from 6.0 to 7.0 hours after the administration.

Claim 27. The controlled release oral dosage form of claim 9, which provides a mean time to maximum plasma concentration (Tmax) of metformin from 5.5 to 7.0 hours after administration.

Claim 29. The controlled release dosage form of claim 5, wherein the metformin or pharmaceutically acceptable salt thereof is provided by at least one controlled-release tablet, said tablet comprising:

(a) a core comprising:
  (i) the metformin or a pharmaceutically acceptable salt;
  (ii) optionally a binding agent; and
  (iii) optionally an absorption enhancer;
(b) a membrane coating surrounding the core; and
(c) at least one passageway in the membrane.

Claim 30. The controlled release oral dosage form of claim 29, wherein said membrane is a semipermeable membrane.

Claim 43. The controlled release oral dosage form of claim 5, which provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 6.0 to 7 hours after the administration of the dose.

78

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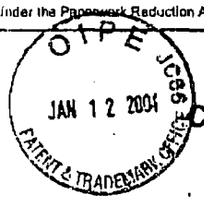

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Re.: Docket No.: 300.1005
Applicant(s): Xiu Xiu CHENG, et al.
Serial No.: 09/705,630
Invention: CONTROLLED RELEASE METFORMIN COMPOSITIONS
Filing Date: November 3, 2000

- Amendment under 37 C.F.R. § 1.312 (7 pages);
- Form PTO 1449 (4 pages); and
-postcard

PART B - FEE(S) TRANSMITTAL

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DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
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Calvin Ashby, III	(Depositor's name)
Calvin Ashby III	(Signature)
March 1, 2004	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/705,630	11/03/2000	Xiu Xiu Cheng	300.1005	6707

TITLE OF INVENTION: CONTROLLED RELEASE METFORMIN COMPOSITIONS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$0	$1360	03/19/2004

EXAMINER	ART UNIT	CLASS-SUBCLASS
YOUNG, MICAH PAUL	1615	424-468000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. *Use of a Customer Number is required.*

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Davidson, Davidson & Kappel, LLC
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Andrx Labs, LLC

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Davie, Florida

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ individual ☒ corporation or other private group entity ☐ government

4a. The following fee(s) are enclosed:
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Director [for Patents] is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) (Date) March 1, 2004

Robert J. Paradise, Reg. No. 41,240

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/705,630	11/03/2000	Xiu Xiu Cheng	300.1005	6707

23280 7590 11/30/2004

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NEW YORK, NY 10018

EXAMINER	
YOUNG, MICAH PAUL	
ART UNIT	PAPER NUMBER
1615	

#20

DATE MAILED: 11/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Supplemental Notice of Allowability	Application No. 09/705,630	Applicant(s) CHENG ET AL.	
	Examiner Micah-Paul Young	Art Unit 1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *11/21/03*.

2. ☒ The allowed claim(s) is/are *5,7-27,29,30 and 43*.

3. ☒ The drawings filed on *03 November 2000* are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the international Bureau (PCT Rule 17.2(a)).
   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient

6. ☐ CORRECTED DRAWINGS (*as "replacement sheets") must be submitted.*
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)
1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Micah-Paul Young
Examiner
Art Unit: 1615

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Application :	09/705630	**Examiner :**	Young	**GAU :**	1615
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[RUSH] **MESSAGE:** Copy mark Figs 1--8 (pages 1-8)
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[XRUSH] **RESPONSE:** File-Up
(PTO-948) Notice Regarding Drawings Mailed on 12/28/04
INITIALS: KVC

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REV 10/04

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
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APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMES APPLICANT	ATTORNEY DOCKET NUMBER
09/705630	11/03/2000	CHENG, XIU XIU	300.1005

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK NY 10018

Examiner
YOUNG, MICAH-PAUL

Art Unit	Paper Number
1615	22

Date Mailed:12/28/2004

Notice Regarding Drawings

Corrected drawings for the above-identified application, received in the USPTO on 11-03-00 are still not acceptable for the reason(s) identified on the attached PTO-948. Applicant is given one opportunity to correct the informalities within a two-month time period from the mailing date of this Notice. **THIS TIME PERIOD IS NOT EXTENDABLE UNDER EITHER 37 CFR 1.136(a) OR 1.136(b). Failure to take corrective action within the set period will result in abandonment of the application.**

ATTACHMENT: PTO-948 Notice of Draftsperson's Patent Review

RETURN CORRECTED DRAWINGS TO:
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Joshua D. Chase
Office of Patent Publication,
Publishing Division
703-305-8430

Form PTO-948 (Rev. 06/03)
Application No. 9/705,630

U.S. DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office

NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW

The drawing(s) filed (insert date) 11-3-00 are:

A. ___ approved by the Draftsperson under 37 CFR 1.84 or 1.152.

B. ✓ objected to by the Draftsperson under 37 CFR 1.84 or 1.152 for the reasons indicated below. Corrected drawings are required.

1. DRAWINGS. 37 CFR 1.84(a): Acceptable categories of drawings: Black ink or Color (3 sets required).
___ Color drawings are not acceptable until petition is granted. Fig(s)___
___ Pencil and non black ink not permitted. Fig(s)___

2. PHOTOGRAPHS. 37 CFR 1.84(b)
___ One (1) full-tone set is required. Fig(s)___
___ Photographs may not be mounted. 37 CFR 1.84(e)
___ Photographs must meet paper size requirements of 37 CFR 1.84(f). Fig(s)___
___ Poor quality (half-tone). Fig(s)___

3. TYPE OF PAPER. 37 CFR 1.84(e)
___ Paper not flexible, strong, white, and durable. Fig(s)___
✓ Erasures, alterations, overwritings, interlineations, folds, copy machine marks not accepted. Fig(s) 1

4. SIZE OF PAPER. 37 CFR 1.84(f): Acceptable sizes:
21.0 cm by 29.7 cm (DIN size A4) or
21.6 cm by 27.9 cm (8 1/2x 11 inches)
___ All drawing sheets not the same size. Sheet(s)___
___ Drawings sheets not an acceptable size. Fig(s)___

5. MARGINS. 37 CFR 1.84(g): Acceptable margins:
Top 2.5 cm Left 2.5 cm Right 1.5 cm Bottom 1.0 cm
✓ Margins not acceptable. Fig(s) 1-3, 7, 8
✓ Top (T) ✓ Left (L)
___ Right (R) ___ Bottom (B)

6. VIEWS. 37 CFR 1.84(h)
REMINDER: Specification may require revision to correspond to drawing changes, e.g., if Fig. 1 is changed to Fig. 1A, Fig 1B and Fig. 1C, etc., the specification, at the Brief Description of the Drawings, must likewise be changed.
___ Views not labeled separately or properly. Fig(s)___

7. SECTIONAL VIEWS. 37 CFR 1.84(h)(3)
___ Sectional designation should be noted with Arabic or Roman numbers. Fig(s)___

8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i)
___ Words do not appear on a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s)___

9. SCALE. 37 CFR 1.84(k)
___ Scale not large enough to show mechanism without crowding when drawing is reduced in size to two-thirds in reproduction. Fig(s)___

10. CHARACTER OF LINES, NUMBERS, & LETTERS. 37 CFR 1.84(l)
✓ Lines, numbers & letters not uniformly thick and well defined, clean, durable, and black (poor line quality). Fig(s) 1-3

11. SHADING. 37 CFR 1.84(m)
___ Solid black areas pale. Fig(s) ___
___ Solid black shading not permitted. Fig(s)___

12. NUMBERS, LETTERS, & REFERENCE CHARACTERS. 37 CFR 1.84(p)
✓ Numbers and reference characters not plain and legible. Fig(s) 1-3
✓ Figure legends are poor. Fig(s) 1-3
___ Numbers and reference characters not oriented in the same direction as the view. 37 CFR 1.84(p)(1) Fig(s)___
___ English alphabet not used. 37 CFR 1.84(p)(2) Fig(s)___
___ Numbers, letters and reference characters must be at least 32 cm (1/8 inch) in height. 37 CFR 1.84(p)(3). Fig(s)___

13. LEAD LINES. 37 CFR 1.84(q)
___ Lead lines missing. Fig(s)___

14. NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.84(t)
___ Sheets not numbered consecutively, and in Arabic numbers beginning with number 1. Sheet(s)___

15. NUMBERING OF VIEWS. 37 CFR 1.84(u)
___ Views not numbered consecutively, and in Arabic numerals, beginning with number 1. Fig(s)___

16. DESIGN DRAWINGS. 37 CFR 1.152
___ Surface shading shown not appropriate. Fig(s)___
___ Solid black surface shading is not permitted except when used to represent the color black as well as color contrast. Fig(s)___

COMMENTS:

Reviewer J. CHASE
Date 12-28-04

If you have questions, call (703) 305-8404.

Attachment to Paper No. ___

☆ U.S. GOVERNMENT PRINTING OFFICE: 2003-301-153

FIG. 1

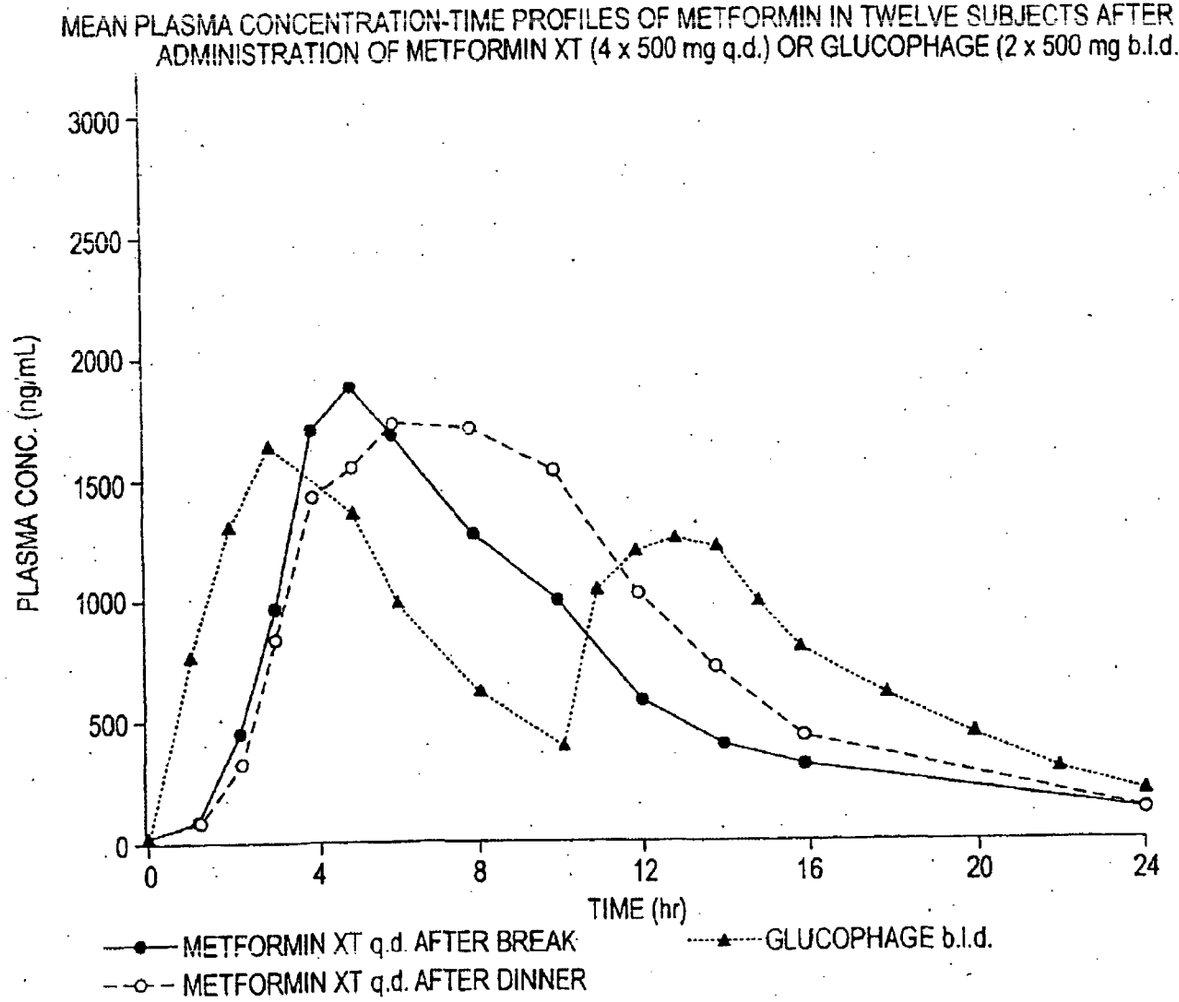


FIG. 2

MEAN PLASMA CONCENTRATION-TIME PROFILES OF METFORMIN IN EIGHT HEALTHY SUBJECTS AFTER MULTIPLE ORAL DOSES OF METFORMIN XT (4 x 500 mg q.d.)

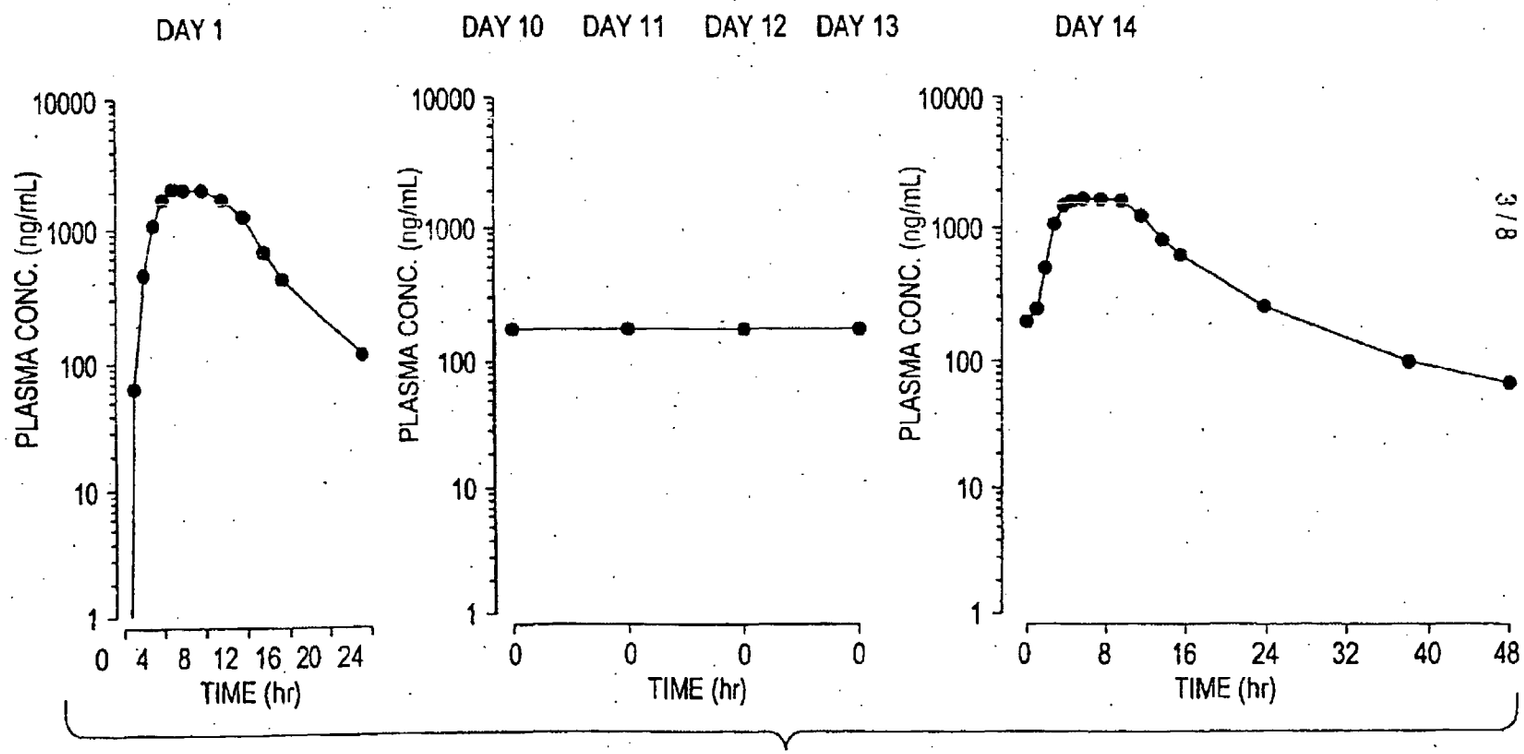


FIG. 3

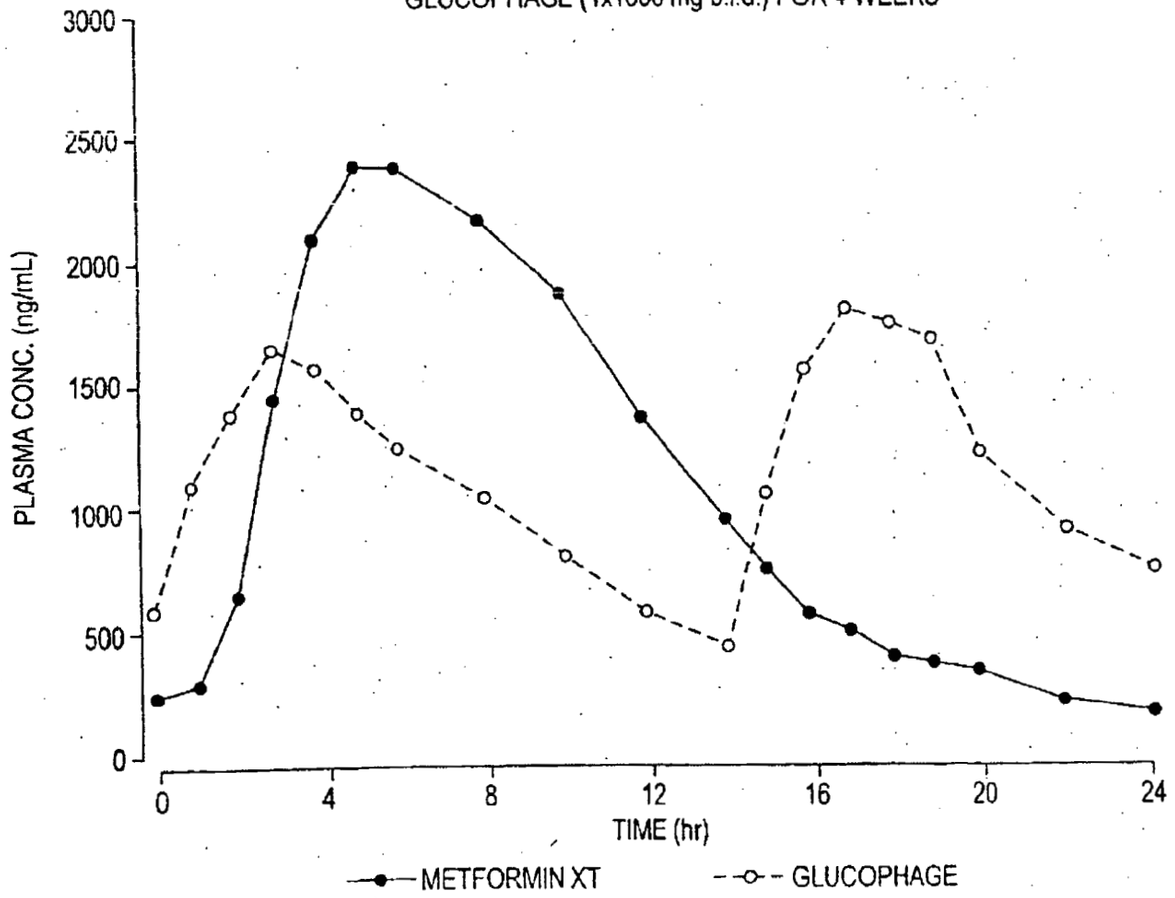


FIG. 4

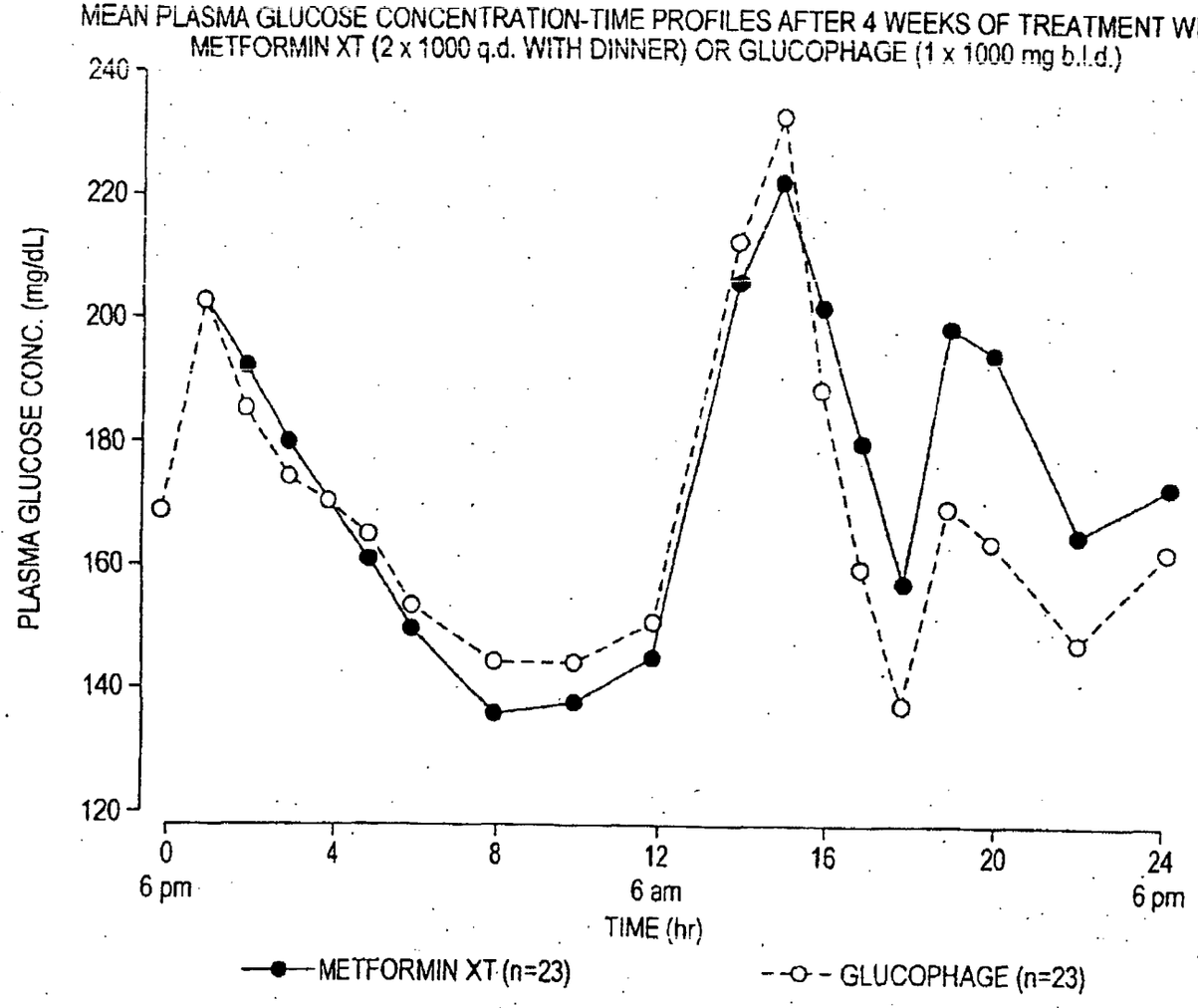


FIG. 5

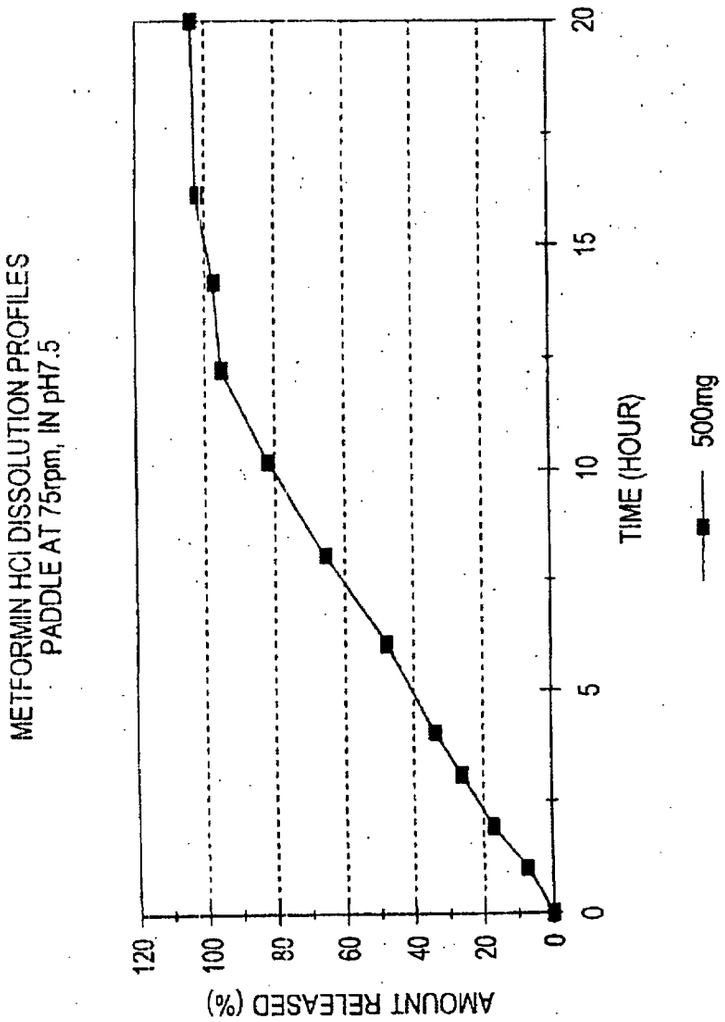


FIG. 6

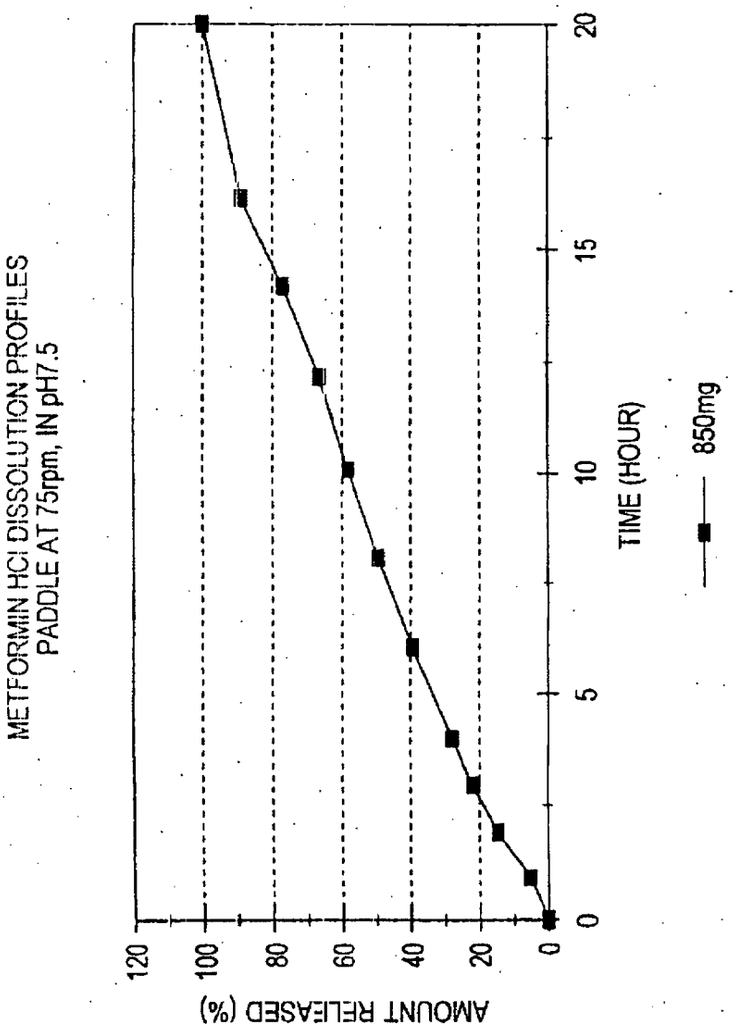


FIG. 7

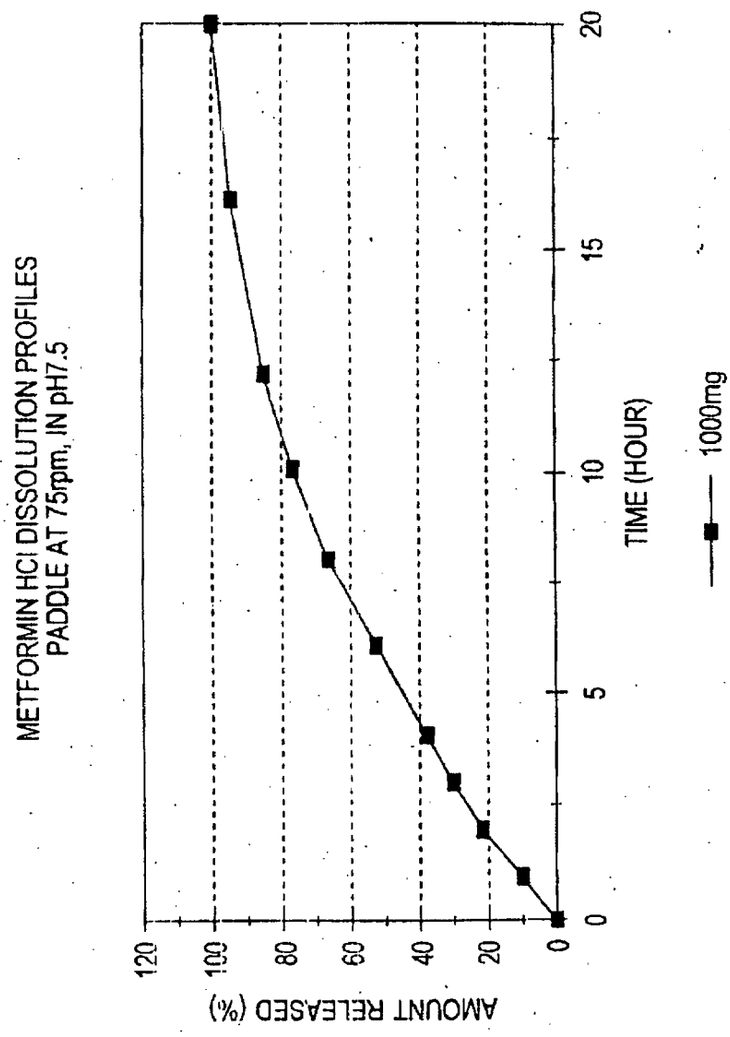


FIG. 8

300.1005

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicants:	Xiu Xiu CHENG, et al.
Serial No.:	09/705,630
Filed:	November 3, 2000
For:	**CONTROLLED RELEASE METFORMIN COMPOSITIONS**
Art Unit:	1615

RESPONSE TO NOTICE REGARDING DRAWINGS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

January 11, 2005

Sir:

In response to the Notice Regarding Drawings, dated December 28, 2004, Applicants submit replacement drawings, Figures 1-8.

If any additional fees are deemed to be due at this time, the Commissioner is authorized to charge payment of the same to Deposit Account No. 50-0552.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

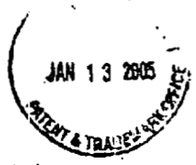
By: _____
Robert J. Paradiso
Reg. No. 41,240

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, NY 10018
(212)736-1940

FORM PTO-1083

Docket No.: 300.1005
Date: January 11, 2005

COMMISSIONER FOR PATENTS
P.O. BOX 1450
Alexandria, VA 22313-1450



In re application of: Xiu Xiu CHENG, et al.
Serial No.: 09/705,630
Filed: November 3, 2000
For: **CONTROLLED RELEASE METFORMIN COMPOSITIONS**
Sir:

Transmitted herewith is a **Response to Notice Regarding Drawings** in the above-identified application.

[] Small entity status of this application under 37 C.F.R. 1.9 and 1.27 has been established by a verified statement previously submitted.
[] A verified statement to establish small entity status under 37 C.F.R. 1.9 and 1.27 is enclosed.
[X] No fee for additional claims is required.
[] A filing fee for additional claims calculated as shown below, is required:

	(Col. 1)	(Col. 2)		SMALL ENTITY			LARGE ENTITY	
FOR:	REMAINING AFTER AMENDMENT	HIGHEST PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	FEE	OR	RATE	FEE
TOTAL CLAIMS	* Minus 20** =			x $ 9	$		x $ 18	$
INDEP. CLAIMS	* Minus 3*** =	0		x $ 42	$		x $ 84	$
[ ] FIRST PRESENTATION OF MULTIPLE DEP. CLAIM				+ $140	$		+ $280	$
				TOTAL: $		OR	TOTAL: $	

* If the entry in Co. 1 is less than the entry in Col. 2, write "0" in Col. 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

[X] Also transmitted herewith are:
[ ] Petition for one-month extension under 37 C.F.R. 1.136 (in duplicate)
[X] Other: **Eight sheets of drawings**

[ ] Check(s) in the amounts of $.00 is/are attached to cover:
[] Filing fee for additional claims under 37 C.F.R. 1.16
[] Petition fee for one month extension under 37 C.F.R. 1.136
[] Other:

[X] The Assistant Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 50-0552. A duplicate copy of this sheet is enclosed.
[X] Any filing fee under 37 C.F.R. 1.16 for the presentation of additional claims which are not paid by check submitted herewith.
[X] Any patent application processing fees under 37 C.F.R. 1.17.
[X] Any petition fees for extension under 37 C.F.R. 1.136 which are not paid by check submitted herewith, and it is hereby requested that this be a petition for an automatic extension of time under 37 CFR 1.136.

Robert J. Paradiso, Reg. No. 41,240
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

I hereby certify that this correspondence and/or documents referred to as attached therein and/or fee are being deposited with the United States Postal Service as "first class mail" in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" on January 11, 2005.

DAVIDSON, DAVIDSON & KAPPEL, LLC

By: Guendoline Decosta
Guendoline Decosta

COMPLETED

PTO/SB/81 (01-06)
Approved for use through 12/31/2008. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY and CORRESPONDENCE ADDRESS INDICATION FORM

Application Number	09/705,630
Filing Date	November 3, 2000
First Named Inventor	Chen et al.
Title	Controlled Release Metformin Compositions
Art Unit	1615
Examiner Name	T. Ware
Attorney Docket Number	141-596

I hereby revoke all previous powers of attorney given in the above-identified application.

I hereby appoint:

☑ Practitioners associated with the Customer Number: 47888

OR

☐ Practitioner(s) named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Please recognize or change the correspondence address for the above-identified application to:

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OR

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	Address				
	City		State		Zip
	Country				
	Telephone		Email		

I am the:

☐ Applicant/Inventor.

☑ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE of Applicant or Assignee of Record

Signature	Roberta Loomar	Date	July 12, 2007
Name	Roberta Loomar	Telephone	954-762-6211
Title and Company	Vice President, Chief Compliance Officer and Assistant General Counsel; Andrx Corporation		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☑ *Total of 1 forms are submitted.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/96 (04-07)
Approved for use through 09/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Chih-Ming Chen et al.

Application No./Patent No.: 10/866,866 Filed/Issue Date: March 15, 2005

Entitled: CONTROLLED RELEASE METFORMIN COMPOSITIONS

Andrx Labs, LLC, a Limited Liability Company
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☑ the assignee of the entire right, title, and interest; or

2. ☐ an assignee of less than the entire right, title and interest
(The extent (by percentage) of its ownership interest is_____ %)

in the patent application/patent identified above by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

OR

B. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Chih-Ming Chen et al. To: Andrx Corporation
The document was recorded in the United States Patent and Trademark Office at
Reel 011679, Frame 0517, or for which a copy thereof is attached.

2. From: Andrx Corporation, A Florida Corporation To: Andrx Corporation, A Delaware Corporation
The document was recorded in the United States Patent and Trademark Office at
Reel 013792, Frame 0227, or for which a copy thereof is attached.

3. From: Andrx Corporation To: Andrx Labs, LLC
The document was recorded in the United States Patent and Trademark Office at
Reel 013788, Frame 0187, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Roberta Loomar — July 12, 2007
Signature — Date

Roberta Loomar — 954-762-6211
Printed or Typed Name — Telephone Number

Vice President, Chief Compliance Officer and Assistant General Counsel
Title

PTO/SB/21 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	3

Application Number	09/705,660
Filing Date	November 3, 2000
First Named Inventor	Chen et al.
Art Unit	1615
Examiner Name	T. Ware
Attorney Docket Number	141-596

COMPLETED

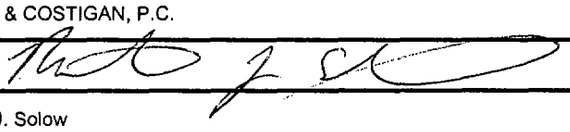
ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
- ☐ Fee Attached
- ☐ Amendment/Reply
- ☐ After Final
- ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
- ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☑ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
- ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☑ Other Enclosure(s) (please Identify below):

Statement Under 37 CFR 3.73 (b)
Return Receipt Postcard

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	HEDMAN & COSTIGAN, P.C.		
Signature			
Printed name	Matthew J. Solow		
Date	July 19, 2007	Reg. No.	56,878

CERTIFICATE OF TRANSMISSION/MAILING

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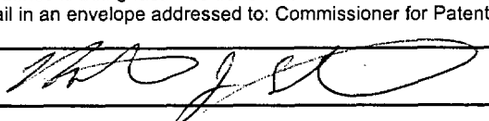
Signature			
Typed or printed name	Matthew J. Solow	Date	July 19, 2007

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
09/705,630	11/03/2000	Xiu Xiu Cheng	300.1005

CONFIRMATION NO. 6707

OC000000025054548

47888
HEDMAN & COSTIGAN P.C.
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

Date Mailed: 07/27/2007

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/23/2007.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

COMPLETED

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
09/705,630	11/03/2000	Xiu Xiu Cheng	300.1005

CONFIRMATION NO. 6707

OC000000025054486

23280
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

Date Mailed: 07/27/2007

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/23/2007.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Office of Initial Patent Examination (571) 272-4000, or 1-800-PTO-9199
OFFICE COPY

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2000

Application or Docket Number

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	42	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	42 minus 20=	* 22
INDEPENDENT CLAIMS	2 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	355.00	OR	BASIC FEE	710.00
X$ 9=		OR	X$18=	396
X40=		OR	X80=	
+135=		OR	+270=	
TOTAL		OR	TOTAL	1106

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1)		(Column 2)	(Column 3)
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X40=		OR	X80=	
+135=		OR	+270=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1)		(Column 2)	(Column 3)
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X40=		OR	X80=	
+135=		OR	+270=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1)		(Column 2)	(Column 3)
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X40=		OR	X80=	
+135=		OR	+270=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

PALM INTRANET

Day : Sunday
Date: 10/20/2002
Time: 16:15:43

Application Number Information

Application Number: **09/726193**
Assignments
Filing Date: **11/29/2000**
Effective Date: **11/29/2000**
Application Received: **11/30/2000**
Patent Number:
Issue Date: **00/00/0000**
Date of Abandonment: **00/00/0000**
Attorney Docket Number: **300.1023**
Status: **61 /FINAL REJECTION MAILED**
Confirmation Number: **6199**

Examiner Number: **77687 / FUBARA, BLESSING**
Group Art Unit: **1615**
Class/Subclass: **424/400.000**
Lost Case: **NO**
Interference Number:
Unmatched Petition: **NO**
L&R Code: Secrecy Code:**1**
Third Level Review: **NO**

Waiting for Response Desc.
Mail Final Rej.

Secrecy Order: **NO**
Status Date: **07/15/2002**

Title of Invention: **CONTROLLED RELEASE METFORMIN FORMULATIONS**

Bar Code	Location	Location Date	Chrg to Loc	Charge to Name	Emp. ID	Infra Loc
09726193	16C3 TC 1600 CENTRAL FILES, CM1-3C10	08/01/2002		No Charge to Name	TINVENTO32	CM1/03/C 10

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | Inve

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Revenue Accounting and Management

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Start Date: Any Date End Date: Any Date

Accounting Date	Sequence Num.	Tran Type	Fee Code	Fee Amount	Mailroom Date	Payment Method
04/09/2001	00000071	1	101	$710.00	04/05/2001	CK
04/09/2001	00000072	1	105	$130.00	04/05/2001	CK
04/09/2001	00000073	1	103	$396.00	04/05/2001	CK
04/17/2001	00000164	1	581	$40.00	04/05/2001	CK
07/12/2002	00000010	1	117	$920.00	07/08/2002	CK
07/12/2002	00000011	1	148	$110.00	07/08/2002	CK
03/06/2003	00000105	1	1251	$110.00	03/04/2003	CK
03/14/2003	00000002	1	1806	$180.00	03/03/2003	CK
11/26/2003	00000076	1	1253	$950.00	11/24/2003	CK
03/05/2004	00000001	1	1501	$1,330.00	03/03/2004	CK
03/05/2004	00000002	1	8001	$30.00	03/03/2004	CK
05/10/2004	00000252		8007	$20.00	01/04/1970	DA 500552

ISSUE SLIP STAPLE AREA (for additional cross references)

POSITION	INITIALS	ID NO.	DATE
FEE DETERMINATION		71426	1/24/01
O.I.P.E. CLASSIFIER		69652	
FORMALITY REVIEW		69134	
RESPONSE FORMALITY REVIEW	JS		4-13-01

INDEX OF CLAIMS

✓	Rejected	N	Non-elected
=	Allowed	I	Interference
—	(Through numeral)... Canceled	A	Appeal
÷	Restricted	O	Objected

Claim Final	Claim Original	Date
	1	=
	2	
	3	
	4	=
4	5	= =
	6	
2	7	= =
3	8	
4	9	
5	10	
6	11	
7	12	=
8	13	
9	14	
10	15	
11	16	
12	17	
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16	21	
17	22	
18	23	
19	24	
20	25	
21	26	
22	27	= =
	28	
23	29	= =
25	30	= =
	31	
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If more than 150 claims or 10 actions staple additional sheet here

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SEARCHED

Class	Sub.	Date	Exmr.
424	473	12-20-01	TW
	468		
	474		
	475		
	479		
	480		
	482		
514	635		
	588		
	591		
	592		
	593		
updated		5-18-03	TW
Above to date		12-12-03	MPH

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.
424	473	12/12/03	MPH
	468		
	474		
	475		
	479		
	480		
	482		
514	635, 588, 591, 592, 593		

SEARCH NOTES
(INCLUDING SEARCH STRATEGY)

	Date	Exmr.
Inventor search	12-20-01	TW
IBRS updated	5-18-03	
CAS/STN		
Index Bioscience Pharmacology Sptext		
Consult 1645 STIC	5-14-03	TW
Above to date	12-12-03	MPH

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