Technical Report No. 5

Sterile Pharmaceutical Packaging: Compatibility and Stability

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FOREWORD

THIS IS THE FIFTH IN A SERIES OF TECHNICAL REPORTS.¹⁻⁴ This Technical Report was prepared by Dr. Y. John Wang and Dr. Yie W. Chien under the auspices of the PDA Research Committee. It provides a comprehensive review of sterile pharmaceutical packaging systems with regard to product-package interactions, stability and compatibility.

In the selection of pharmaceutical packaging systems one must be aware of the potential physicochemical interactions with the product. These interactions are discussed in detail from both a practical application and a theoretical point of view.

> R. M. Enzinger, Ph.D. Chairman **Research** Committee

¹ "Validation of Steam Sterilization Cycles," Parenteral Drug Association Inc., Technical

 ¹ Validation of Steam Sterinzation Cycles, "Parenteral Drug Association Inc., Technical Monograph No. 1.
 ² "Validation of Aseptic Filling for Solution Drug Products," Parenteral Drug Association Inc., Technical Monograph No. 2.
 ³ "Validation of dry Heat Processes Used for Sterilization & Depyrogenation," Parenteral Drug Association Inc., Technical Report No. 3.
 ⁴ "Design Concepts for the Validation of a Water for Injection System," Parenteral Drug Association Inc., Technical Report No. 3.

Association Inc., Technical Report No. 4.

PREFACE AND ACKNOWLEDGEMENT

The aim of this book is to provide for persons working with sterile pharmaceutical products a detailed account of the compatibility and stability of sterile formulations and packaging components. The intention is to present what is known in concise form, and to indicate how to avoid or resolve problems.

For hospital pharmacists, it is hoped that this book will serve as a valuable handy reference to assist them in identifying and solving the problems of sterile packaging. The tremendous increase in popularity of intravenous admixture programs makes it imperative that greater attention be paid to recognizing such problems. For manufacturing chemists involved in developing sterile pharmaceutical products, it is hoped that their awareness of the current knowledge of relevant physicochemical principles will enable them to design products that will have only minimal problems of compatibility and stability, both for the shelf life of the product and during its preparation and administration in hospital.

The book is arranged by type of interaction between formulation and packaging component, ie., sorption; leaching, and permeation, thus permitting an efficient presentation and analysis of common factors. Some important concepts are presented more than once, to ensure that they are not overlooked.

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I. INTRODUCTION

Sterile pharmaceutical packaging is defined as a primary packaging system that holds and is in direct contact with a sterile pharmaceutical formulation throughout the shelf life of the product. It consists of a container, possibly with a closure, and is considered an integral part of the pharmaceutical product. Examples of sterile pharmaceutical packaging are vials, ampules, plastic bags, plastic bottles, etc. This report encompasses primary packaging systems for such sterile pharmaceutical products as small- and large-volume parenterals, sterile irrigating solutions, and ophthalmic products, but not those for sterile diagnostic products and medical devices.

The primary packaging system should provide adequate protection against any ingress of foreign matter or egress of its contents, and it should possess acceptable physicochemical compatibility and long-term stability with the drug formulation within it until the drug formulation has been administered. Maintenance of a 2- to 3-year shelf-life is desirable. It is worth remembering that no container or closure is completely inert.

To make an intelligent selection of a primary packaging system that is compatible, both physically and chemically, with a sterile drug formulation, one should know about all potential instability/incompatibility problems of a packaging system with a particular drug formulation. This knowledge should derive from careful evaluation of: (1) the composition of the packaging system; (2) the treatment to which it will be subjected; and (3) the composition of the drug formulation.

Physicochemical interactions between sterile pharmaceutical products and their packaging components have been reported in the literature. We discuss these interactions, offering a quantitative analysis of them. Interactions are discussed in three categories: sorption, leaching, and permeation. In each category, discussion of the mathematical equations that are pertinent to an interaction is followed by evaluation and discussion of those critical parameters, such as temperature, that have been shown to influence the interaction. Finally, details of the interactions related to various packaging materials are presented as a handy guide for those involved in selecting a suitable primary packaging system for a formulation to achieve maximum compatibility and stability.

Numerous reviews have discussed interactions between pharmaceutical products and packaging components (Autian, 1963a,b; Polack, 1967; Busse and Hughes, 1969; Coates, 1973; Armstrong, 1974; Varsano and Gilbert, 1969). Autian (1963a,b) treated the subject in great depth and provided some guidance for quantitative analysis. Since the early '60s, however, a

better understanding of these interactions has resulted from developments in other fields, such as permeation through plastic films, pharmacokinetic modeling, absorption through biological membranes, and sustained-released dosage forms. This report provides a comprehensive review of those publications that discuss the concepts and mechanisms of these physicochemical interactions and the utilization of these concepts in the development of sterile pharmaceutical products.

II. PRIMARY PACKAGING SYSTEMS

The primary packaging system for a sterile pharmaceutical product consists of a container and a closure system:

A. Containers

Depending on composition of the materials used, containers may be classified as either glass or plastic. Their physicochemical and mechanical properties, as well as the processes involved in their manufacture, may be described as follows:

1. Glass containers

Glass has traditionally been considered the container material of choice for most sterile pharmaceutical products. However, it should not be assumed that glass is a totally inert material or that it is the ideal primary packaging component, either technically or commercially. General reviews on glass container for sterile products were provided by Adams (1977) and Anschel (1977).

a. Nature and composition of glass

Glass is a noncrystalline solid and, thus, shows only short-range order to 10 Å. It is also called a supercooled liquid because, under certain conditions, it can order itself and crystallize, a process known as "devitrification."

Glass consists of a mixture of oxides. The primary glass-forming (network-forming) oxides are SiO₂, B₂O₃, GeO₂, P₂O₅, V₂O₅, and Al₂O₃. Among these, SiO₂ is by far the major component for practically all commercial glasses. Silicone oxide is known to be the component responsible for the three-dimensional network of glass, the silicon dioxide tetrahedron.

Additionally, fluxes such as CaO, Na₂O, K₂O, BaO, or Li₂O, are needed to decrease the softening temperature of glass and, thereby, make it easier to process (Holloway, 1973). A stabilizer, such as Al₂O₃, Sb₂O₃, PbO₂, or ZnO, is also added to make the glass less prone to crystallization or devitrification and, thus, more durable. The general functions of glass formers, fluxes, and stabilizers are shown in Table I. Except for boric oxide, which can enter into the silicon dioxide tetrahedron structure, most of the inorganic oxides, such as those of sodium, potassium, calcium, magnesium, aluminum, barium, and iron, are only loosely bound in the network interstices and are, thus, relatively free to migrate. These migratory oxides can leach into a drug solution that is in intimate contact with the glass container, particularly during the process of thermal sterilization. The dissolved or

	TABLE		
Common Constituents	of Glasses and	Their Effect on	Properties

Constituent	Function	Physical and Chemical Properties
SiO ₂	Network former	Crystalline silica has very high melting point and liquid silica has very high viscosity. High concentration of silica in a glass confers high softening temperature, low thermal expansion, good chemical durability.
B ₂ O ₃	Network former	Will join network structure of silica glasses and reduce viscosity without producing adverse changes in thermal expansion and durability. Is a component of all heat-resisting and "Chemical" glasses.
PbO ₂	Stabilizer	Can link SiO ₄ tetrahedrons.
Al ₂ O ₃	Stabilizer	Can join network in AIO ₄ tetrahedron which are different in size from SiO ₄ . Strongly suppresses devitrification; increases process viscosity.
Na ₂ O	Network modifier (flux)	Markedly lowers softening temperature. Raises thermal expansion and ionic conductivity. Reduces durability.
К2О	Network modifier (flux)	Similar to Na ₂ O, but the larger K ⁺ ion is less mobile than the Na ⁺ ion.
Li ₂ O	Network modifier (flux)	Similar to Na ₂ O, but the smaller Li ⁺ ion is more mobile than the Na ⁺ ion.
CaO	Network modifier (flux)	Inhibits mobility of alkali ions, hence increases resistivity and durability of alkali glasses. Shortens the working range.

Source: Holloway (1973).

extracted oxides may affect solution pH, catalyze physicochemical reactions, or even enter into the reactions themselves. Additionally, some components of glass are also prone to attack by drug solutions; as a result, flakes may be dislodged into the solution (Avis, 1975).

A true glass can be formed from the combination of SiO_2 and Na_2O . A true glass is, however, soluble in water and is thus called water glass. With the addition of a stabilizer, the water solubility of true glass is greatly reduced and an insoluble soda-lime glass is formed.

1) Soda-lime glasses

Soda-lime glasses account for approximately 90% of all commercial glasses. They are fairly resistant to chemicals, but cannot withstand sudden changes in temperature. Depending on the concentration of Na₂O, B₂O₃,

TABLE II Major Chemical Constituents of Container Glasses and Glasses Used for Handling Ultrapure Solutions

	Typical Concentration (wt %) *									
Glass Type	SIO ₂	AI_2O_3	ZrO ₂	Na ₂ O	K ₂ 0	Li ₂ O	B ₂ O ₃	Ca0	MgO	BaO
Soda-lima A	73	1		17	0.5	-		5	4	
Soda-lime B	74	2		13	0.5		3	11	0.5	_
Borosilicate A	81	2		. 4	0.5		13	_	—	-
Borosilicate B	73	6		7	0.5	_	10	1		2
Alkali-resistant	71	1	15	11	0.5	1				
Chemically Strengthened	66	20	-	9	_	5		-	-	-
High-silica	96	0.5		-			3	—		_
Vitreous-silica	100	_						—		

* In all except high-silica and vitreous-silica glasses, F, CI, SO4, As, and Sb can be present in the range 0.05-0.5%.

CaO, and MgO in the glass network, soda-lime glasses are further classified into A and B types (Table II).

The chemical resistance of soda-lime glass containers can be increased by de-alkalization of the glass surface, generally by exposing the glass to SO_2 gas to remove Na₂O prior to use:

 $Na_2O + SO_2 + \frac{1}{2}O_2 \rightarrow Na_2SO_4$

The sodium sulfate formed remains on the surface of the glass as a fine precipitate that is water soluble and can be rinsed off easily. The de-alkalization treatment can be accelerated if SO2 is used in the presence of H_2O . This treatment reduces the extractable alkali by a factor of 25. By means of SO₂ treatment, a soda-lime B glass (USP Type III or Type NP glass) can be upgraded to a USP Type II glass.

The chemical resistance of de-alkalized glass is comparable to that of borosilicate glass in acidic and neutral solutions, but resistance to alkaline solutions is increased only slightly by de-alkalization treatment. De-alkalized glass containers are widely used for intravenous infusion solutions.

2) Borosilicate glasses

Borosilicate glasses are chemically highly resistant and are known commercially as Pyrex® and Kimax®. Typical compositions of these glasses are shown in Tables III and IV.



	TABLE III
Typical Compositions (in	%) of Chemically Resistant Borosilicate Glasses
	Manufactured by Kimble

Component	KG-33	KG-34	N51A	A 203
SiO ₂	80.3	74.6	74.4	71.6
B ₂ O ₃	13.0	11.3	9.5	9.2
Al ₂ O ₃	2.4	5.0	5.5	5.3
CaO	0.1		0.9	0.8
MgO	-		0.3	0.1
BaO		2.7	2.2	2.1
Na ₂ O	4.2	6.0	6.6	6.4
K ₂ O	-		0.6	0.7
TiO ₂			_	2.8
Fe ₂ O ₃		-	_	0.3
Uses:	Scientific ware, process pipe	Blown bottles	Ampuls vials	Amber ampuls Amber vials
	FA POLICE			C-CONTRACTOR

Source: Bacon (1968).

TABLE IV Typical Composition (in %) of Alkali-Resistant Glasses Manufactures by Corning

	Co	de
Component	7280	7740
SiO ₂	71.3	80.3
B ₂ O ₃	—	13.0
Al ₂ O ₃		2.4
CaO	0.1	0.1
MgO	0.1	
Li ₂ O	0.8	-
Na ₂ O	11.5	4.2
K ₂ O	0.1	
ZrO ₂	15.8	<u> </u>

Source: Bacon (1968).

Borosilicate glasses, are also known as USP Type I glasses, can be divided into A and B subclasses (Table II). Class A, Pyrex glass, is more difficult to fabricate and has a lower thermal expansion coefficient than class B. Class B borosilicate glass, as exemplified by the so-called neutral glass, is

A State

commonly used in the manufacture of chemically resistant ampuls and vials for pharmaceuticals.

3) Amber glass

Certain metals can be added to glass to produce such colors as amber, which results from an interaction between added ferric oxides and ferrous oxides and sulfur. Additional components are used to produce three types of amber glass for pharmaceutical use: reddish amber, 4% MnO₂ and 0.01% CrO₃; greenish amber, 0.1% to 1% SO₃; and brownish amber, 2% to 3% TiO₂.

Other colors can be produced by incorporating CoO for blue, NiO for gray, Cr_2O_3 for green, and CuO for bluish-green. These coloring metals in amber glass are potential sources of trace ions, particularly of iron.

b. Classification of glass container by USP

The United States Pharmacopeia (USP) has classified glass containers, according to their degree of chemical resistance, into four types:

- Type I is made from a chemically high resistant borosilicate glass, composed principally of silicon dioxide and boric oxides. This glass has low leachability and a low thermal coefficient of expansion. In general, it is suitable for all parenteral drug products although sulfur dioxide treatment is sometimes utilized to increase its chemical resistance still more.
- 2) Type II is made from de-alkalized soda-lime glass, composed of relatively high levels of sodium oxide (13-17%) and calcium oxide (5-11%) (Table II). The existence of these two oxides makes Type II glass containers chemically less resistant than Type I (which contains 4-7% Na₂O and 1% CaO). A Type II glass container, however, has a lower concentration of migratory oxides than does Type III, and its chemical resistance can be increased by sulfur dioxide treatment, under controlled conditions of temperature and humidity to de-alkalize the internal surface of the glass containers. However, this de-alkalized surface will break down if it is repeatedly exposed to heat sterilization, depyrogenation or alkaline detergents. Thus, Type II glass containers possess relatively good chemical resistance for one-time use. A Type II glass container melts at a lower temperature, can more easily be molded, and has a higher coefficient of thermal expansion than does a Type I glass container. It may be suitable for use as a container for a drug solution that has been buffered to a pH below 7 or one that is not reactive with the glass.
- 3) Type III is also made from a soda-lime glass that contains relatively high levels of sodium oxide and calcium oxide, as do Type II glass containers. However, a Type III glass container has a higher concentration



of migratory oxides than does a Type II container, and it has not been subjected to de-alkalization treatment. It is usually suitable only for anhydrous liquids or for dry drug products.

4) *Type NP* is also made from a soda-lime glass and is not suitable for parenteral drug products.

2. Plastic containers

Plastics fall into two general classes: thermosets and thermoplastics. Because of their unusual versatility, thermoplastics have found wider application than thermosets, especially in the medical/pharmaceutical field.

Thermoplastic polymers are gradually finding use as packaging materials for sterile preparations, such as parenterals and ophthalmic solutions. One of the principal advantages of plastic containers is that they are not as fragile as glass. In addition, the flexibility of polyvinyl chloride IV bags is an advantage in the intravenous administration of large volumes of drug solution, because no air interchange is required.

Prior to the recognition of the potential of plastic materials in health care practice, glass was the dominant material used in the primary packaging of pharmaceutical products. The fragility and weight of glass, coupled with the broad range of properties offered by plastics, have resulted in marked increases in the use of plastics for pharmaceutical packaging during the last two decades (Giles and Pecina, 1975). Today, for example, plastics are used in such sterile primary packaging systems as syringes, bottles, vials, and ampuls (Table V). Fifteen years ago, only glass would have been considered for these uses.

a. Polymerization

Plastic materials are prepared from monomers by polymerization. To achieve polymerization, the monomers must be bifunctional, i.e., the monomers must be capable of forming two covalent bonds. There are two classical ways in which a monomer can achieve bifunctionality: first, a monomer may contain an unsaturated C=C bond, e.g., ethylene $(CH_2=CH_2)$; second, a monomer may possess two different organic functional groups that can react with one another, e.g., an amino acid $(NH_2-CHR-COOH)$.

Polymerization can proceed by either of two basic processes, determined largely by the way in which the monomer has attained bifunctionality.

1) Polymerization by addition

Polymerization by addition (or free radical reaction) is commonly performed with monomers that contain an unsaturated C=C bond. These

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TABLE V

Sterile Plastic Devices for Parenteral Drug Administration

Sterile Plastic Device	Plastic Material
Containers for blood product	Polyvinyl chloride
Disposable syringe	Polycarbonate
	Polyethylene
	Polypropylene
Irrigating solution container	Polyethylene
	Polyolefins
	Polypropylene
I.V. infusion fluid container	Polyvinyl chloride
	Polyolefins
Administration set	Nylon (spike)
	Polyvinyl chloride (tube)
	Polymethylmethacrylate (needle adapter)
	Polypropylene (clamp)
Catheter	Teflon
	Polypropylene

Adapted from Turco and King (1979).

monomers have the general chemical structure

$$CH_2 = C < R_1 R_2$$

where R_1 and R_2 can be H, CH₃, phenyl, COOH, COOR, OCOCH₃, C=N, F, Cl, CONH₂, or pyrrolidone.

The polymer produced by addition polymerization may be represented as:

$$(CH_2 - C < R_1)$$

when *n* refers to the average number of monomer units in the polymer molecule. Depending on the chemical types of R_1 and R_2 , a great variety of polymers can be produced (Tables VI and VII). Teflon[®], also known as polytetrafluoroethylene $(CF_2-CF_2)_n$, is a unique polymer produced

TABLE VI					
Polymers Produced by Addition Polymerization of Vinyl-Type Monomers					

Monomer Structur	re Monomer Name	Polymer Structure	Common Polymer Name
H ₂ C=CH ₂	Ethylene	-(CH2-CH2)n	Polyethylene (PE)
CH ₂ =CH	Propylene	$-CH_2-CH_{\overline{n}}$	Polypropylene (PP)
СH ₂ =СН	Vinyl chloride	-+CH₂-CH→n	Polyvinylchloride (PVC)
н₂с=сн	Styrene	-(CH ₂ -CH)n	Polystyrene (PS)
H ₂ C=CH C=O OH	Acrylic acid	-(CH ₂ CH) _n C=0	Polyacrylic acid (PAA)
$H_2C = CH$ C = O OR	Acrylic acid ester	-(CH ₂ CH)- _	Polyacrylic acid ester
H ₂ C=CH C=N	Acrylonitrile	$-(CH_2-CH)_{\overline{n}}$	Polyacrylonitrile (PAN)
CH2=CH	Vinyl fluoride	-+CH₂CH→n F	Polyvinyl fluoride (PVF)
H ₂ C=CH 0 C=0 CH ₃	Vinyl acetate	$\begin{array}{c} -(CH_2CH)_{\overline{n}} \\ O \\ C=0 \\ CH_3 \end{array}$	Polyvinyl acetate (PVAc)
H ₂ C=CH C=O I NH ₂	Acrylamide	$H_2C - CH)_{\overline{n}}$ C = O NH_2	Polyacrylamide (PAAm)
$\begin{array}{c} H_2C = CH \\ N \\ CH_2 \\ CH_2 \\ CH_2 - CH_2 \end{array}$	Vinyl pyrrolidone	$\begin{array}{c} -(\mathrm{H}_{2}\mathrm{C}-\mathrm{C}\mathrm{H})_{\overline{\mathrm{I\!I}}} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$	Polyvinyl pyrrolidone (PVP)

by addition polymerization from a monomer called tetrafluoroethylene, CF2=CF2, in which all four hydrogen atoms in ethylene have been substituted by fluorine.

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TABLE VII
Polymers by from Addition Polymerization of Monomers with both R1 and
R ₂ that are Not Hydrogen Atoms

Monomer Structure	Monomer Name	Polymer Structure	Polymer Name
CH ₂ =C CH ₂ =C CH ₃	Isobutylene	$\begin{array}{c} CH_{3} \\ \leftarrow CH_{2} - C_{3} \\ \downarrow \\ CH_{3} \end{array}$	Polyisobutylene (PIB)
CH ₂ =CH ₃	Methyl styrene	←CH ₂ —CH ₃	Polymethylstyrene (PMS)
Cl CH2=C Cl	Vinylidene chloride	$\begin{array}{c} CI \\ + CH_2 - C _{\overline{n}} \\ - CH_2 - C _{\overline{n}} \\ CI \end{array}$	Polyvinylidene chloride (PVC ₂)
сн2=с	Vinylidene fluoride	$-CH_2-C+n$	Polyvinylidene fluoride (PVF ₂)
СH ₃ СH ₂ =С С=О ОН	Methacrylic acid	CH ₃ -(CH ₂ —C) _n l=0 OH	Polymethylacrylic acid (PMAc)
CH ₂ =C C=O	Methyl methacrylate	СН ₃ -(СӉ₂СНЭ _ћ с==0 0 СН,	Polymethyl methacrylate (PMMA)
0113		CII3	

2) Polymerization by condensation

Condensation (or step-reaction) polymerization commonly occurs with monomers that contain two different types of organic functional groups. It may be illustrated by the reaction of two amino acid monomers:



During the reaction, an amide (C-N) bond is formed and a molecule of water is condensed out. The free carboxylic (-COOH) group remaining can react with the amino group (--NH₂) of another molecule of amino acid, and the free NH₂ group can also react with the COOH group of another amino acid monomer. The polymer chain thus grows from both ends. In fact, a variety of functional group pairs can be involved to form a number of polymers via condensation polymerization (Tables VIII and IX).

The most common examples of condensation-type polymers are polyesters, like Dacron[®] and Mylar[®], polyamides, such as the majority of Nylons[®] (polypeptide is a form of polyamide), and cellulose, a condensation product of monosaccharide units.

Some monomers, such as acrylic acid (CH2=CH-COOH), can react

TABLE VIII
Some Functional Group Pairs Involved in Condensation Polymerization
Reactions

 $\begin{array}{c} -0H + -COOH \\ -0H + -COC1 \\ -0H + -N = C = 0 \\ -0H + -CH - CH_2 \\ \hline \\ \hline \\ -NH_2 + -COOH \\ -NH_2 + -N = C = 0 \\ -NH_2 + -COOCH_3 \end{array}$

TABLE IX Some Polymers Produced by Condensation Polymerization

Polymer Type	Typical Monomer(s)	Polymer Repeat Unit
Polyester	HO-R-COOH	(-O-R-CO-)
	HO-R-OH + HOOC-R'-COOH	(-O-R-O-CO-R'-CO-)
	HO-R-OH + CICO-R'COCI	(-O-R-O-CO-R'-CO-)
Polyamide	H2N-R-NH2 + HOOC-R'-COOH	(-NH-R-NHCO-R'-CO-)
	H ₂ N-R'-NH ₂ + CIOCR'COCI	(-NH-R-NHCO-R'-CO-)
Polyurea	H2N-R-NH2 + OCN-R'-NCO	(-NH-R-NH-CO-NH-R'-NH-CO-)
Polyurethane	HO-R-OH + OCN-R'-NCO	(-O-R-O-CO-NH-R'-NH-CO-)
Polyanhydride	HOOC-R-COOH	(-O-CO-R-CO-)
Polycarbonate	HO-R-OH + COCI2	(-R-O-CO-O-)

Source: Jenkins and Stannet (1972).

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TABLE X Comparison of Addition and Condensation Polymerization

Addition Polymerization	Condensation Polymerization	
Growth occurs by rapid addition of monomer to a small number of active centers.	Growth occurs by coupling of any two species (monomer or polymer).	
Monomer concentration decreases slowly during reaction.	Monomer disappears well before any high polymer is formed.	
High molecular weight polymer is present at low conversions.	Polymer molecular weight increases continuously during polymerization; high polymer is present only at very high conversions.	
Polymer backbone usually consists exclu- sively of carbon atoms.	Polymer repeat units normally linked by oxygen and/or nitrogen atoms.	

Source: Jenkins and Stannet (1972).

through either the C=C bond or the carboxylic acid group, depending on the polymerization conditions used (Table VI).

Basically, addition polymerization occurs very rapidly after initiation and is essentially a chain reaction, whereas condensation polymerization is a much slower, stepwise reaction process. Some of the fundamental differences between these two major processes of polymerization are shown in Table X.

b. Additives (Adjuvants)

The composition of plastic materials is quite complex. A number of plastics can be prepared for specific applications without the addition of any other ingredient to the polymer, whereas others may contain, besides the polymers, several additives to impart definite quality to the final plastic product. Specific additives are frequently used to modify the mechanical and physicochemical properties of the plastic products. The additives routinely used in thermoplastic materials may be classified as follows (Giles, 1975):

1) Lubricants

Lubricants are used primarily to improve the processibility of plastic materials by lowering the viscosity of melt or by preventing the polymer from sticking to the metal surfaces of the processing equipment.

Most lubricants are used in the processing of polyvinyl chloride, where they are critical to extrusion, calendering, injection molding, etc. Additionally, lubricants have been used in the polyolefins, styrenics, and some thermosets. Considerable activity has recently been noted in the development of lubricants for engineering thermoplastics.

The general chemical class of lubricants used in plastic materials is alkyl acids, e.g., stearic acids, and such derivatives as esters, amides, alcohols and metallic salts. For instance, a commonly used lubricant in the processing of polyethylene is zinc stearate. Paraffin waxes and polyethylene waxes are other popular lubricants. The quantities of lubricant used vary significantly from one plastic material to another.

2) Stabilizers

Stabilizers are used to retard or to prevent the deterioration of plastic materials that may result from exposure to light, heat, and pressure and to improve their aging characteristics. The commonly used families of stabilizers include epoxy compounds (epoxidized soybean oil), organotins (octyltin), and mixed metals (barium and cadmium benzoate). Some of the stabilizers have some solubility in aqueous media, and, consequently, could be extracted into a drug solution.

3) Plasticizers

Plasticizers are materials of low volatility that are added to plastic materials to enhance flexibility, resiliency, and melt flow. They are generally high-boiling organic liquids. They act to reduce the glass transition temperature (Tg) or brittleness of the plastic to a temperature lower than that at which it will be used in an actual application. Rigid PVC (polyvinyl chloride), for example, has a Tg of about 80 °C. Sufficient amounts of plasticizer will produce flexible PVC and decreased the Tg to below 0 °C.

More than 80% of all plasticizers are used with PVC; the rest go into such plastics as cellulosics, nylon, polyolefins, and styrenics. Phthalates are the most popular plasticizers. For example, 30–40% of phthalate ester is added to PVC material to produce a flexible intravenous fluid bag, such as the Viaflex (Travenol/Baxter) and Lifecare (Abbott).

As is true of stabilizers, plasticizers can migrate to the surface of a plastic container and are, therefore, potentially extractable into a drug solution.

4) Antioxidants

Many plastic materials are susceptible to oxidative degradation and require antioxidants to slow down the process and to give them a longer shelf life.

Degradation of a plastic material starts with the initiation of free radicals on exposure to heat, ultraviolet radiation, and mechanical shear, or in the presence of reactive impurities. Antioxidants act by intercepting the radicals or by preventing radical initiation during the shelf life of the plastic materials.

There are two types of antioxidants: Primary antioxidants act to in-

terrupt oxidative degradation of plastics by tying up the free radicals. Such primary antioxidants as the hindered phenolics and the aromatic amines both have a reactive NH or OH group and can donate hydrogen to the free radicals. Phenolics, such as butylate hydroxytoluene (BHT), are the most popular of the primary antioxidants. BHT has a broad FDA approval and is used in polyolefins, styrenics, vinyls, and elastomers, among others.

Secondary antioxidants function by reducing the unstable hydroperoxides formed in the plastics degradation process to inert products, thus preventing the proliferation of radicals. They are used in conjunction with primary antioxidants to provide added stability to the plastic materials. The most popular ones are thioesters and phosphites.

Antioxidants can also migrate to the surface of plastic materials and then leach out. Further, the combination of antioxidants with other additives may produce or initiate some undesirable chemical reactions with the drug solution.

5) Antistatic agents

Antistatic agents, such as quaternary ammonium compounds are used to prevent the build-up of static charges on the surface of plastics that causes the plastic materials to cling.

6) Slip agents

Slip agents are added primarily to polyolefin type plastic materials, such as polyethylene and polypropylene, in order to reduce the coefficient of friction of the plastics. These agents impart antitack and antiblock characteristics to the end products.

7) Dyes and pigments

Dyes and pigments impart color to plastic materials. They may leach or be extracted into a drug solution. They are used only infrequently for parenteral products.

The above-mentioned additives may vary in concentration from a few parts per million to as much as 60% of the total weight of the plastic material.

c. Potential problems with plastic containers

During storage the additives described above may possibly be extracted by or leached into a drug solution that is in intimate contact with the plastic container. It is, therefore, important to evaluate the physicochemical compatibility of a final drug formulation in a selected primary packaging system under various storage and time conditions to assure safety and stability of the drug product. Whenever possible, evaluations should be conducted under conditions simulating those to which the product will probably be exposed. Evaluations should take into consideration not only the physical and chemical compatibility of the drug formulation with the

primary packaging system, but should also include an investigation of the mechanical properties of the primary packaging system, e.g., the cracking and stress-cracking of a plastic container that could occur under attack by the drug product, the storage environment, or both. Prolonged exposure to ultraviolet light has been shown to promote the migration of certain additives that could, in turn, accelerate the aging characteristics of the plastic and decrease shelf life of the product.

The use of plastic material for primary packaging systems of parenteral drug products has grown very rapidly during the last two decades. With this phenomenal growth in the use of plastic containers, three potential problems have arisen:

- a. Loss of drug potency and the efficacy of preservation because of sorption of active drug ingredients and preservatives onto the plastic material. Such sorption has been most common in containers made of polyamides, such as nylon.
- b. Egress of volatile constituents, the protective gas in the headspace, or some selective drug species through the wall of the container to the exterior, resulting in decreases in drug potency and stability; or, conversely ingress of atmospheric oxygen, water vapor, or other gases to the interior of the container, causing oxidative or hydrolytic degradation of some susceptible constituents.
- c. Leaching of additives or constituents from plastic containers into the drug formulation, leading to a change in purity, physicochemical instability of the product, formation of particulate matter, or the causation of some adverse effect when the drug is administered.

The use of a plastic material as the primary packaging system for either a pharmaceutical or a food product demands a number of extra considerations that may not be critical to plastics employed for other purposes. Although packaging systems for food products require considerations similar to those for pharmaceuticals, the food products usually have a relatively rapid rate of turnover and, hence, relatively short shelf-life requirements. On the other hand, pharmaceutical products require an extremely long shelf-life stability and the most critical technical and toxicological data for regulatory approval.

The pharmaceutical industry requires, in most instances, a level of safety that is more stringent than that required in the food industry. This is logical when one considers that drugs are taken by a person who is suffering from an illness; any untoward side effects may complicate the existing illness and be detrimental to health. This consideration is of particular relevance for parenteral drug products, which are to be administered directly into the systemic circulation. Although the thermosetting resins have been widely used for making closure systems and also a few specialized containers (e.g., menthol sticks, for almost 50 years), the use of thermoplastics for packaging pharmaceuticals did not start until the late '40s and early '50s. It is widely recognized today that plastics deservedly play a significant role in all facets of pharmaceutical packaging, provided that their advantages can be properly exploited and their potential disadvantages, in terms of physicochemical interactions with the pharmaceutical formulations, are fully evaluated and controlled.

