Drug Delivery Devices
Issues in Drug Development

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New techniques for delivery of drugs by inhalation are discussed in this article. Devices that promise to improve the efficiency of lung delivery are described along with some of the regulatory challenges faced by their development scientists. Although high delivery efficiencies are possible, such devices are expensive to develop and may only be feasible in the event that they are partnered with drugs whose therapeutic and economic value is truly enhanced by the effort invested in the process. Appropriate devices must also be selected after paying careful attention to the physicochemical and dosing demands associated with the drug substance to be inhaled. Even newly launched commercial products display large variations in dose delivery to the lung, in spite of increased global efforts to regulate and ensure the uniformity of delivered doses and their aerosol size distributions; this because of variations in the inspiratory maneuvers used by patients and the lack of control exercised over these maneuvers by most new inhalers. Sophisticated electromechanical techniques are discussed as possible ways of overcoming some of the common difficulties associated with ensuring reproducibility of dose and drug delivery to the lung.

Keywords: aerosol; drug; delivery devices; inhalers; lungs

After a long period during which chlorofluorocarbon (CFC)-pressurized metered dose inhalers (MDIs) dominated the market, in the last 15 years several new inhalation devices have been introduced. Other novel devices remain "in the wings," and these may yet be exploited by pharmaceutical companies for specific reasons (1). We are seeing increasing acceptance of the lungs as a route of systemic drug administration, as well as a number of new drugs offering novel therapeutic benefits for several acute and chronic lung disorders (2, 3). These developments represent significant opportunities for pharmaceutical companies, provided they choose delivery systems that adequately "partner" each drug during its development. The regulatory hurdles facing inhaler developers have become more stringent as the global marketplace has extended the impact of the U.S.A.'s Food and Drug Administration; FDA is probably the strictest of the world's regulatory authorities. Multidose inhalers must now be shown to deliver individual doses reproducibly throughout inhaler shelf-life, in temperatures and humidities that represent commonly experienced environmental conditions. Not only must doses be reproducible, but the particle or droplet size distributions from each inhaler must also be shown to be "stable" over the product's lifetime, and the product proven to be manufactured reproducibly (3). This must be done to show that the clinical results that are presented to the regulators at the time of product submission are "representative" of the "to be marketed" inhaler. Some of the recent increased regulatory oversight has been stimulated by environmental demands to replace the CFC propellants in pressurized MDIs with non–ozone-depleting hydrofluoroalkanes (HFAs), at a time when many older drugs and inhalers were becoming subject to competition from the generic industry (1). Not surprisingly, there has been considerable commercial incentive, especially for innovator companies wishing to market new drugs, to attempt to launch such drugs in novel inhalers.

From the drug point of view, inhalers contain mostly short- or long-acting topical bronchodilators (adrenergics as well as anticholinergics), antiinflammatory steroids, and antiallergics such as cromolyn sodium (3). We are also seeing proteins being delivered by this route for their local actions. Drugs like α-1-antitrypsin and other antiproteases, genes, and oligonucleotides are all in clinical trial for local effects in the lung. Nebulized rhDNase was launched by Genentech some 5 years ago for treatment of patients with cystic fibrosis. Antiviral agents and vaccines are also under development for delivery as aerosols to enhance "local immunity" in different parts of the respiratory tract (2–6). In the systemic drug area, only ergotamine has been traditionally delivered through the lung following its presentation as a metered dose (pressurized) inhaler (3). However, biotech companies are attempting to deliver a number of hormones systemically via the lungs (e.g. calcitonin, hGH, PTH), and insulin is presently the subject of large Phase III trials by both Aventis-Pfizer and Novo-Nordisk with their respective inhalation partners Nektar Therapeutics and Aradigm Corporation (5, 7). In summary, the safety of the pulmonary route has gradually gained acceptance for macromolecular delivery (8) and there is a tremendous amount of interest and drug company research activity in this area. This will result in a large number of changes to inhaled drug therapy in the future.

IMPROVING DRUG DELIVERY EFFICIENCY TO THE LUNG

From the point of view of those wishing to pursue inhaled drug development, there are a number of frequent questions that are asked. These are presented, along with some rather general answers, in Table 1. It is clear from this Table that the choice of drug delivery technology to be pursued requires some unique expertise. "Efficient" dose delivery to the lung can be discussed by defining efficiency as the percentage of the dose depositing in the airways (DTL) relative to the delivered dose (dd) or, in some cases, the label claim on the inhaler (Table 1; Efficiency = 100 · DTL/dd). It should come as no surprise to learn that high efficiencies are possible but, of course, the price of moving in that direction can be considerable. Motivating companies to accomplish high delivery efficiencies (in contrast to achieving reproducible but inefficient lung penetration) requires that some penalties are associated with less efficient delivery. In many cases, the lack of a penalty means that these "motivations" do not always exist. However, examples may be related to toxicology (e.g., oral corticosteroid deposition associated with candidiasis and unnecessarily large total drug exposure), therapeutic need (e.g., insulin and other hormones require peripheral lung penetration to enable reasonable bioavailabilities to be achieved; 3, 5), product misuse by patients (e.g., actual use of product encourages additional dosing and an increased incidence of ad-

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TABLE 1. FAQS CONCERNING INHALER DEVICES WITH ANSWERS RELEVANT TO DEVELOPMENT SCIENTISTS

- Can ~ 100% of each "metered dose" be delivered to lung? *No, all devices retain some of the (premetered) drug substance, and much of what is delivered is often deposited in the oropharynx.*
- Can a large proportion of the "ex-mouthpiece dose" be delivered to lung? *Yes, the ex-mouthpiece dose, or delivered dose*, can be made to emphasize only the small "more respirable" particles.*
- Can the dose delivered to the lung (DTL†) be directed preferentially to the peripheral and/or the central airways? *Yes, this is possible for normal individuals but it is not easily achieved for those with lung diseases.*
- Are large payloads possible? *Yes, values for DTL per inhalation ≤ 4mg are possible. Above this value, multiple breaths or continuous inhalation (e.g. nebulizers) must be employed.*
- Can "fragile molecules" be delivered intact? *Yes, although process and formulation constraints are drug-specific.*
- Are ≥ 2-year product shelf-lives possible? *Yes, but formulation packaging and the use of solid-state drug in formulations are extremely important features in cases where reproducibility is a problem.*
- Can the delivered dose, dd, and its emitted particle size distribution, psd, be made reproducible throughout inhaler lifetime? *Yes. If this is not so, the product will not be accepted by regulators.*
- Are all devices suitable for all drugs? *No, the different device platforms are not generally applicable.*
- Are some devices easier to develop? *Yes, but presently these are not the most efficient. High delivery efficiency platforms are more expensive to develop and launch.*

* Delivered dose, *dd*, is the dose leaving the inhaler mouthpiece when the inhaler is used according to the package insert.
† The dose leaving the inhaler that deposits in the airways.

verse events; 3, 4), or drug cost (e.g., drug substance costs constitute a large and prohibitive part of each inhaler's value; 3).

To achieve highly efficient drug delivery to lung requires that the aerosol creation process be controlled so that a fine droplet or particle cloud, containing a known drug concentration in a defined size distribution, is metered reproducibly into the patient's inhaled air stream. Provided a normal individual is inhaling slowly (~ 0.5 L/second), aerosol sizes, expressed as aerodynamic diameters, should preferably be 3 to 7 μm for good tracheobronchial deposition, or between 1 and 3 μm for deposition in the pulmonary regions (6). Breath holding is known to further enhance deposition in the pulmonary or alveolar regions (6). Unfortunately, although device designers can often accomplish some of these requirements, patients rarely comply well with instruction leaflets given with inhalers. As a result, they often require regular counseling to reduce their use of inappropriate inspiratory maneuvers, and in particular, often have difficulty coordinating their inspiration with the creation of the aerosol cloud by the device (3, 4). For this reason, the reproducibility of DTL *in vivo* is often much worse than the apparent reproducibility of the delivered dose assured the regulators during the drug development process (DTL and dd have large and small variance, respectively; Table 1). Furthermore, the presence of acute or chronic obstructive airways disease(s) in patients often precludes the delivery of a significant proportion of each dose to the lung periphery, irrespective of whether a device is selected which enables the predominant production of small aerosol particles (1–3 μm) theoretically capable of penetrating the region in normal healthy volunteers (6).

NEBULIZERS

Thus, the major factors that defeat inhaler design intentions are patient variables. Clearly, in the case of nebulizers used with sedentary patients, especially inhalers designed to deliver metered doses, the inspiratory flow, tidal volume, and frequency of breathing are defined by the gas exchange needs of the patient and we may consider that some "control" exists over the patient's average breathing pattern. If a nebulized aerosol is then produced in a continuous fashion, patients may inhale and exhale its ouput for several minutes while seated. Unfortunately, the way in which drugs are marketed as nebulizer solutions means that some of the potential "control" offered by this situation is usually discarded by companies who market solutions for use with undefined devices, using undefined operating conditions (9). There are two major types of hand-held nebulizer (3, 4). Air blast or "jet" nebulizers are cheapest and most likely to be used clinically, whereas continuous-output ultrasonic nebulizers have fallen out of favor recently for several reasons, including their inability to nebulize suspension formulations (10). Because the pharmaceutical vehicle used in nebulizer formulations is essentially aqueous, patients can use nebulizers for prolonged periods of time, to deliver quite large doses to the lung; tens of milligrams as opposed to micrograms are feasible in many cases. It is important to recognize that jet nebulizers can work quite well to create less than 5 μm, highly respirable, droplet aerosols for delivery of compounds that are either in solution or formulated as microfine-suspensions and placed in nebulizer reservoirs. There is thus no technologic reason why nebulizer therapy should not be used for effective drug delivery to the lung. There are, of course, economic reasons why they may be less than ideal if people are forced to use poorly designed, cheaply manufactured (variable) nebulizers repeatedly, as has been the case in some health centers. One problem then is economic; another may be the issue of convenience, because nebulizer systems are usually not very portable due to the need for a compressed gas supply.

Most jet nebulizer designs force pressurized gas (usually air) from a nozzle (or jet), at high velocity past a liquid feed tube, so that the nebulizer solution is atomized at the capillary exit. The bulk of the aerosol mist (which may be traveling at up to sonic velocity) impacts against a baffle, drains back into the reservoir in the base, and recirculates. Only very small droplets (< ~ 5 μm, if the system is running correctly) escape the baffle and are available for inhalation. These droplets are produced at device-specific airflow rates and are inhaled along with "dilution air" through a mouthpiece or mask arrangement. Clearly, some 50% of any aerosol produced by a nebulizer that is continuously producing aerosol cannot be available during the patient's exhalation because they are breathing tidally. Moreover, jet and baffle designs of different systems have hugely different efficiencies, resulting in large differences between the times taken to administer a similar DTL, even from the same solution formulation. In all cases, aerosol generation quits before the entire drug has left the reservoir. Most recently, several nebulizer manufacturers (e.g., Pari, Aerogen) have designed systems to minimize drug losses during patient exhalation and minimize the times taken to generate and deposit a given DTL (9). Thus, over the last 10 years these devices have become more efficient delivery

systems, but only if the physician insists that patients use the most modern technology. In general, if we choose reputable devices, define the amount of drug placed into the reservoir in a uniform volume (e.g., 3 ml), and ask patients to inhale and exhale through them until the system quits, then DTL should be somewhere between 8 and 14% of that which was initially instilled into the reservoir. The remainder is lost during exhalation or it is retained in the device. Aerogen, Omron, and Pari market hand-held ultrasonic (piezoelectric) devices that are smaller and less cumbersome than the compressor-driven systems described above. These generate slightly larger aerosols and can accomplish similar values for DTL more quickly than air-blast systems. Although overall efficiencies are likely to continue to improve for high-cost systems (perhaps approaching 20–25% of the instilled dose), the overall efficiency of the present piezoelectric systems is frequently found to be similar to that for jet nebulizers (3, 4). Most recently, some device manufacturers have brought to market computer-controlled systems that monitor each patient's breathing pattern and administer nebulizer output phased with inspiration, whence to enable control over DTL (11).

From a clinical perspective, drugs in nebulizer solutions may be deposited in larger doses than those seen with many metered delivery devices. Also, patients who are seriously afflicted with obstructive lung conditions prefer to use nebulizer therapy, because of the nebulizer's generally more "respirable" output, its continuous generation, and its aqueous, often buffered, vehicle (12). However, assuming that the drug is an appropriate choice, nebulizer therapy can still fail to be effective because of poor nebulizer or compressor selection and an unsuitable choice of operating conditions. Notably, with more recent drug launches, Genentech's "Pulmozyme" package insert is instructive. In effect, this recommends the use of a small number of specific nebulizer systems with this product; only those that were found to be equivalent for *in vitro*/rhDNase delivery during Pulmozyme's development are recommended in the package insert. This "co-marketing approach" is likely to occur more frequently for newly launched nebulizer drugs. Finally, it is important that nebulizer solutions should not be stored in nebulizer reservoirs; stored solutions may grow bacteria which can then be nebulized and inhaled. Devices should be washed and dried between uses, and dishwasher compatibility may thus be important.

DOSE-METERING INHALER SYSTEMS

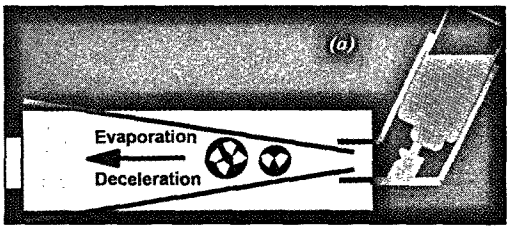
Pressurized metered dose inhalers, dry powder inhalers, or other "bolus aerosol"–producing technologies are considered to be "controlled dose" or "dose-metering" systems because they are sold in forms in which they can only be used with a single drug and formulation. We should appreciate, however, that education and compliance continue to be issues that need to be addressed with all devices, if we hope to be able to control DTL (3, 4, 7). Metered aerosols are designed to be inhaled as boluses, unlike the homogeneous aerosols distributed throughout inhaled air by nebulizers. Bolus aerosols are known to deposit in different places, dependent upon when, in the inhalation, the "bolus" is released. In addition, many bolus pharmaceutical aerosols are unstable physically; that is, they may evaporate and/or have high tendencies to impact, decelerate, and/or sediment over short time periods.

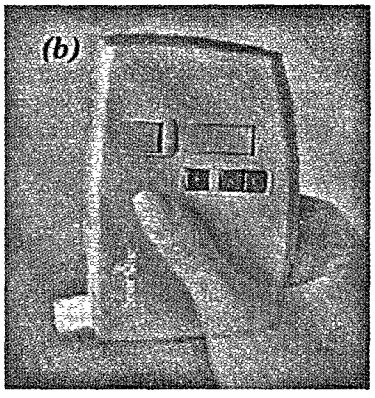
From a drug development perspective, there are numerous formulation issues that can impact the reproducibility of delivered doses and aerosol size distributions from dose-metering inhaler systems. A thorough review of this area is beyond the scope of this article. However, the subject has been discussed elsewhere by the author and others from the point of view of pressurized metered dose inhalers (1, 13), powder inhalers (3, 14–18), and the physical difficulties that are often found when attempting reproducible metering with extremely potent and unstable compounds, like formoterol (19).

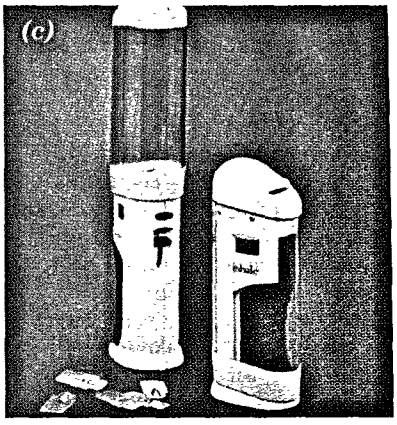
Pressurized MDIs and Accessories

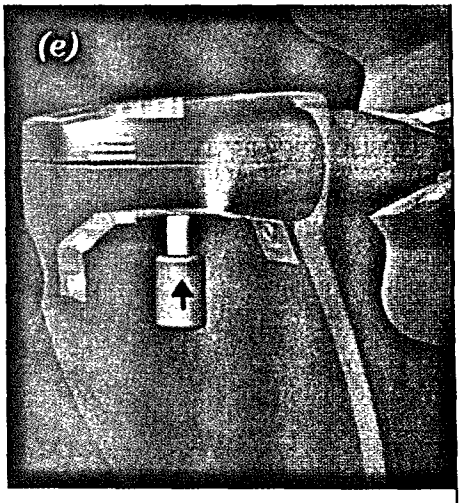
MDIs remain the "gold standard" delivery system in many senses even though considerable efforts have had to be made to redevelop acceptable valve and packaging systems, and to reformulate products with HFA propellants (1). HFA-propelled MDIs are easily portable, tamper-proof, and multidose. They protect the remaining pressurized, liquefied product from oxidation, light, and water ingress while providing an inexpensive, mature technology with accurate liquid dose metering by volume (1, 3). Although reformulated systems have often chosen to mimic the inefficiency of the older CFC-propelled formulations, solution formulations are often feasible which can achieve values of DTL that approach half of the metered dose and exceed 50% of the delivered dose (20); this provided that dose requirements are of the order of 100 μg or less. Moreover, MDIs are apparently easy to use, even though a considerable literature exists to show that *in vivo* values for DTL are variable, because of the difficulties that patients experience trying to coordinate inhalation with actuation of the MDI (4). The aerosol drug dose exits the MDI mouthpiece as a rapidly moving large droplet cloud. However, at about the distance of the back of the throat, the droplet diameter is reduced due to propellant evaporation, and a reasonable proportion of the "polydispersed" aerosol cloud is now small enough to penetrate the lung. It should not be surprising, therefore, that a proportion of each "metered dose" is lost in the actuator mouthpiece, and a further proportion is lost in the oropharynx due to inertial impaction of the "ballistic portion" of the spray. Spacers and reservoirs have come onto the market as compliance aids. These devices are shown diagrammatically in Figure 1; reservoirs can be differentiated from spacers because they contain a valve of some description, intended to retain the aerosol cloud created by the MDI, until the patient inhales. Spacers, on the other hand, contain no such value and simply distance the inhaler mouthpiece from the patient's oropharynx. Both devices can reduce drug deposition in the back of the patient's throat and enable extra time for evaporation to occur (4). Waste drug that would have been captured at the back of the patient's throat can be partly retained in the spacer or reservoir. Notably, there is no reason why MDIs should not be developed with an attached spacer or reservoir for just this purpose, although many of the claims for the advantages of these devices fail to exemplify the problems known to be associated with multiple actuations into reservoirs, untoward delays between cloud generation and inhalation, and the effects of spacer and reservoir electrostatic charges; all of these effects dramatically reduce the DTL per dose from the MDI (13, 21). Notably, MDIs were rarely tested for efficacy or safety with such devices attached and their addition could therefore be construed by drug regulators as an example of product misuse (3, 4).

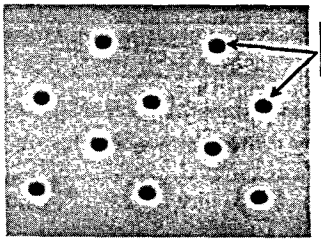
Probably the greatest improvements likely to be associated with MDI usage in the future will involve the marketing of these devices as breath-actuated inhalers. There are many such new devices becoming available at present, although 3M has been marketing Autohaler (a breath-actuated CFC MDI) for a number of years. Figure 1 and its legend describe an expensive option called Smartmist, developed by Aradigm Corporation and registered (but presently not marketed) in the United States, with a number of excellent and sophisticated features (11). The device accepts and seals around regular pressurized MDIs and subjects these inhalers to microprocessor control. A built-in spirometer ensures that the patient receives the drug at the correct point

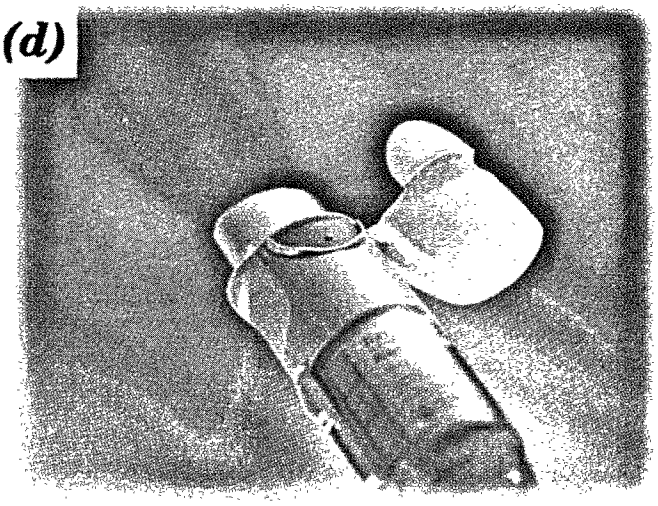


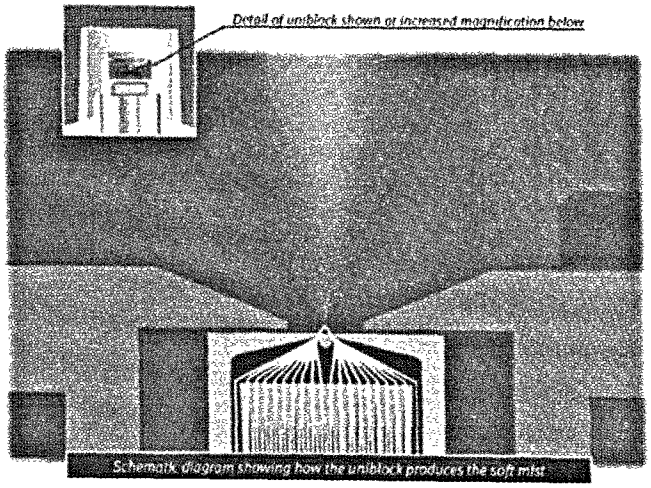












in the inspiration, (e.g., shortly after they commence inhalation from residual volume). It also ensures that they are inhaling slowly as fast inhalation will require repeat attempts; an indicator light will inform the patient if the dose is inhaled (subsequently) at the correct rate. Because the device's memory can be downloaded, the health professional can check whether or not people are complying with recommendations. This type of technology, therefore, is clearly one way of removing some of the control from the patient, and thus ensuring improved benefits by virtue of reducing the variance of in vivo DTL (4, 22); at the very least, it should enable improvements to be made in the analysis of results during and following ambulatory clinical trials.

Dry Powder Inhalers

The present popularity of novel dry powder inhaler (DPI) development commenced at the time that CFC replacement became an issue. These devices are now much more sophisticated than used to be the case when only single-dose, capsule-loading systems existed (e.g., Spinhaler and Rotahaler from Aventis and GlaxoSmithKline, respectively). From a user perspective, the number of different designs that are marketed or in development will itself create problems for physicians and patient educators. We already have difficulty teaching patients to use MDIs; imagine the increasing complexity as the variety of inhaler options increases further. Importantly, from the point of view of DTL variance, most DPIs only deliver drugs when the patient inhales through them. As a consequence, the issue of "coordination" between actuation and inhaling disappears. However, because small volume powder metering is never as precise as the measurement of liquids, and because DPIs are generally less robust than MDIs, there are many alternative (and often inhaler-specific) ways in which patients can misuse these inhalers. As a result, patients may fail to receive therapy for a variety of reasons (e.g., exhalation into the device, loading the device in incorrect orientations and inappropriate storage conditions may affect different DPIs in different ways) (4, 15, 16).

DPI formulations may either be drug mixed with a large particle size excipient (or diluent, e.g. lactose), to aid with powder flow, or it may consist of drug alone (3, 4). In all cases, the powder formulations are cleverly processed using proprietary techniques that are responsible for the DPI in question having apparently reproducible properties when tested *in vitro* under known, but constant, flow versus time profiles (e.g. for delivered dose and size distribution). From the development perspective, modern "passive" multidose DPIs (in which the patient provides the energy for powder dispersion) fall into two main categories. These either measure the dose themselves (from a powder reservoir) or they dispense and disperse individual doses which are premetered into blisters by the manufacturer. Turbohaler and Diskus, from AstraZeneca and GlaxoSmithKline, respectively, are representatives of the former and latter categories, although many other different designs are presently in development (17, 18, 23). In general, the premetered drug-in-blister approach is the easier type to develop because the reproducibility of the metered dose can be assured during the drug formulation packaging and device assembly processes. Provided then, that the device and formulation design is such that (*1*) the blisters empty well and (2) formulation and drug adhesion to the device is minimal, the delivered dose can usually be shown to the regulators to be reproducible (17, 18). With a device like Turbohaler, however, whose operating principles are well known (23) and will not be repeated here, the powder metering system delivers doses *in vitro* that are much more variable than those derived from premetered blister packs. This intrinsic variability, which increases after storage and/or transport, must therefore be shown in the clinic (for each separate drug formulation) to have no therapeutic or toxicologic consequences. The effort is complicated further if we observe that even with quite sophisticated powder inhaler devices, the mode of use and ambient environmental conditions can often define drug doses reaching the patient's lungs (15, 16). The advice to "keep your powder dry" continues to hold, and in many of these devices, designers and manufacturers have gone to some lengths to reduce the likelihood of water vapor ingress creating problems. With Turbohaler and others, desiccant is included (23) and the overcap should be kept firmly in place when the inhaler is not being used. Exhalation into the device, which should never be practiced, is also often addressed in patient information leaflets.

The systems discussed so far are known as "passive" DPIs, because of their reliance upon "patient power" for the purposes of drug aerosolization. These all deliver variable doses and show delivery efficiencies to the lung which depend on the inspiratory effort the patient expends during inhaler use (inhale faster through these and DTL, even the delivered dose in some instances, increases). Ironically, however, clinical studies with Turbohaler (which shows high *in vitro* variability; 15) show that its *in vivo* dosing variance is smaller than that of the MDI (24), which suffers from high *in vivo* dosing variance, due to coordination problems at the patient interface. *In vitro*, the delivered dose can also often be shown to be dependent on a term known as "acceleration" or the rate at which a given airflow through the inhaler is approached during testing (17). We have illustrated

Figure 1. Photographs and diagrams of some of the inhalers described in the text. (*a*) Diagrammatic representation of MDI actuation into reservoir device prior to inhalation of the aerosol cloud from the reservoir. (*b*) Aradigm Corporation's Smartmist "breath actuator" designed to house an existing MDI product and enable microprocessor control of its operation. Ensures actuation at "correct" point of inspiration, an appropriate inhalation rate and downloading to a PC for compliance checks (11). (*c*) Nektar's Pulmonary Delivery System presently in Phase III trials with insulin as Pfizer-Aventis' Exubera product. The device expels a puff of compressed air through a "transjector" inserted into a prepackaged blister containing spray dried insulin with proprietary excipients. The air puff creates an aerosol cloud for the patient to inhale through a mouthpiece from the integral reservoir atop the device. (d) Boehringer Ingelheim's Respimat "Soft mist inhaler." A disposable, liquid self-metering device for small-volume (15 μl) aqueous and semi-aqueous solutions; *lower part of diagram* shows the conjunction of high pressure conduits leading to two opposed 10-μm jets that create the fine mist as the spray streams converge; the company claim that the long duration (> 1 second) of the trigger-actuated aerosol cloud will enable "greater coordination and lung delivery" (24). (*e*) Diagram of Aradigm's AERx operating principles; premetered drug solutions, in sterile blister-packs are pumped through an array of single-use, laser-drilled jets within the drug storage blister; results in efficient aerosolization and employs breath actuation and inspiration control, as well as patient education features. Device is expensive but has high delivery efficiency, humidity and temperature independence, and feedback on device usage during clinical trials (18, 19). (*f*) Picture of Chrysalis Technologies' prototype offering liquid metering, vaporization and condensation with claimed "pharmaceutical quality" for some drugs. Liquid is pumped and simultaneously subjected to microprocessor-controlled heating, during passage through a "capillary aerosol generator"; device can produce different aerosol droplet sizes commencing with MMADs in the submicron range (21, 22).

the dependency of the fine particle dose on flowrate for marketed cromolyn sodium capsules in Spinhaler (UK product; lactose-free formulations) by using a constant throughput of 4 L of ambient room air at different flow rates. Whereas the delivered dose changed minimally (20 ± 3 mg), the fine particle dose (dose < 5 μm aerodynamic diameter) differed by more than an order of magnitude in the range 30–100 L/minute (15, 16). Not surprisingly, all these dependencies are functions of both the inhaler and the formulation. For example, Turbohaler (with terbutaline sulfate) shows a strong dependence on flowrate, whereas Rotahaler and Diskhaler (albuterol sulfate) exhibit much less effect (14). To some extent this is predictable because the latter devices are rather inefficient and their designs ensure only that they empty fairly well, not that they disperse powder efficiently. Nevertheless, the wide variety of DPI designs that will ultimately be available (each with its own idiosyncrasies) will make it difficult for practicing physicians to predict all of the possible effects of different inhalation maneuvers on individual patient values for DTL. Generally, efficient powder dispersion requires that the energy from the patient's inspiration be transferred effectively to the powder as it passes through the device. This, in turn, requires the maintenance of turbulent conditions and significant mechanical interactions (impaction, abrasion, etc.) within the aerosol flowpath. Thus, the moderate to high airflow resistance designs (e.g., Turbohaler and Handihaler from AstraZeneca and Boehringer Ingelheim, respectively) tend to be more efficient delivery devices (Turbohaler approaches 25% delivery to the lung when used in accord with manufacturer's advice) than the low resistance systems (Spinhaler, Diskus, and Diskhaler from Aventis, GlaxoSmithKline, and GlaxoSmithKline, respectively), but higher efficiencies may also be associated with steeper dependence of fine particle dose on air flowrate.

In the case of drugs like cromolyn sodium, it is possible to argue that variations in inhaler efficiency are of little clinical consequence. On the other hand, there is plenty of evidence for inhaled insulin, now in Phase III clinical trials, and for peptides like LHRH analogs, that a direct correlation exists between values for fine particle dose and systemic bioavailability or efficacy (2). In these cases, therefore, we need to reduce inter- and intrapatient variability in DTL as well as reduce the variability of regional drug deposition in the lung. Presently, regulators reviewing new inhaled drug submissions are at least likely to request dose response information that shows the effect of different values for DTL, and relates them to the likely performance of the to-be-marketed inhaler. Thus, better control over the drug dose to lung may be desirable for both MDIs and DPIs. This demand for improved reproducibility has been answered in the DPI arena by two Californian companies, Nektar Therapeutic Systems (previously Inhale) and Dura Pharmaceuticals from San Diego (now Elan). Both have been developing more sophisticated powder inhalers (25) and Nektar's PDS (Pulmonary Delivery System; Figure 1) appears likely to reach the market shortly. These "active" DPIs provide an energy source to disperse a premetered powder dose more efficiently and reproducibly than any of the passive systems described so far. Nektar's PDS uses a miniature mechanical air pump to compress, and then release, a bolus of air through a "transjector" into a carefully controlled and formulated dose of powder, held in a blister package. This creates an aerosol cloud in a small antistatic chamber atop the device, which the patient is advised to inhale completely and slowly. The Dura device (25) uses a breath-actuated high-speed motor to drive an impeller in a chamber containing a premetered powder dose, so that aerosol creation and powder inhalation occur independently but sequentially. Both systems have been shown to have efficiencies greater than 50% with certain formulations and are designed to minimize the effect that the patient has on the particle size distribution of the aerosolized drug dose.

Novel Solution Metering Inhaler Devices

Figures 1d, 1e, and 1f show some of the new solution metering devices that are currently in development for use with inhaled drugs. Several other companies are active in the area (Aerogen, Aradigm, Batelle Pharma, Chrysalis Technologies, Boehringer-Ingelheim, and Sheffield Pharmaceuticals; 26–34). All are developing "propellant-free" inhalers that offer the advantage of liquid metering (for dosing precision) and an energy source to enable patient-independent, reproducible "active" aerosol production. Some devices are mechanical while others are electromechanical. The latter appear to have some added challenges from a development perspective, because of the need to demonstrate the reliability of both mechanical and electrical systems independently, and in combination, within the inhaler. Most seek to employ aqueous or part-aqueous drug solutions, a fact which introduces the need for solution sterility (in the United States) and appears to demand the inclusion of bacteriostatic agents if a solution reservoir is first to be opened and then used as a source for multiple doses. Boehringer Ingelheim have now launched their mechanical Respimat device in Germany (early in 2004), containing a combination of fenoterol and ipratropium in aqueous solution. The principles of operation are shown in Figure 1 and its legend (32). The company claim that the long duration (> 1 second) of the trigger-actuated aerosol cloud, which forms a slow moving "soft mist" at the device mouthpiece, should enable easier coordination between firing and inhalation, and improve the lung delivery efficiency relative to MDIs. The device has been reported to produce a median aerodynamic diameter between 4 and 5 μm and to show lung delivery efficiencies of approximately 50% in trained volunteers.

Aradigm Corporation's AERx device is also described in Figure 1 (26, 27, 34). This device has been shown to achieve ~70% delivery efficiency to lung, as well as independence of its aerosol properties from common ranges of temperature and humidity, for some formulations. The electromechanical device is expensive but is reusable and, like the Nektar PDS (Figure 1), is in Phase III clinical trials with insulin (in this case, a solution formulation). One of the keys to the development of this technology is to enable reproducible blister packaging of individual small (~50 μl), sterile, solution doses in a proprietary, laminated blister strip, part of which is equipped with an array of high precision, laser-drilled nozzles. The Aradigm AERx device also enables dose control by partial actuation (e.g., fractions of each blister can be dispensed as aerosols). The company makes similar technology available in cheaper mechanical manifestations (e.g., without the electronic components that enable breath actuation, spirometry, and patient training; 34).

Battelle Pharma in Ohio has recently explored the possibility of employing electrospray technology to produce fine mists of several different solution formulations. This technique produces a small aerosol with the potential for efficient lung delivery by adding a high voltage to sprayed aerosol droplets in a similar fashion to that employed in some commercially available mass spectrometers. As the droplets evaporate in entrained air, the surface charges on each droplet repel each other and cause the droplets to shatter, thereby producing a smaller aerosol cloud. The technique has limitations; it is unlikely that all solvents and solutes are suitable and electric charge is known to affect aerosol deposition, both *in vitro* and *in vivo*; however, early results have shown promise (28). Aerogen, from California, is attempting to commercialize a piezoelectric device, AeroDose, containing a vibrating screen, onto which is dispensed drug solutions from a sealed reservoir (31). The technology is similar to that in develop-

ment by Sheffield Pharmaceuticals; their metered solution inhaler (MSI) device also dispenses liquid formulations and generates aerosols ultrasonically, this time from a vibrating "horn" which generates aerosol in a similar fashion to an ultrasonic nebulizer (33). It seems possible to the author that the former, vibrating screen, technology may have the advantage of leaving less dry residue in the device between doses. Nevertheless, both technologies are likely to suffer from the need to provide and validate device-cleaning schedules to satisfy regulators that aerosolized impurities from residues retained in the device between doses, do not pose a safety problem during use by patients.

One final approach, which offers the intriguing possibility that almost the entire aerosol dose could reach the lung, perhaps even the lung periphery, is being tested by Chrysalis Technologies in Virginia (Figure 1 and legend). By simultaneously pumping the metered solution through a heated (microprocessor-controlled) "capillary aerosol generator," the device enables thermally stable drugs and vehicles to be evaporated and subsequently condensed in entrained air in a controlled fashion. Different formulations require different heating profiles, and manipulation of the entrained air at the capillary exit appears to enable control of particle nucleation and ultimately, the final aerosol size (0.25–2 μm has been reported; 29, 30). It is unlikely that all drugs can be aerosolized in this way without degradation. Nevertheless, this is the only technique that appears to offer the possibility of truly high delivery efficiencies for solutions metered in fractions of a milliliter.

CONCLUSIONS

Drug delivery to the lung by aerosol inhalation can only be accomplished in high doses (tens of milligrams) by repetitive inhalation. In such cases, administration from a restricted menu of ultrasonic or jet nebulizers is most appropriate. Doses less than or equal to about 4 mg can potentially be delivered from a variety of single-dose–metering inhalers. The MDI and passive DPI are presently the least expensive to develop. However, unless significant modifications are added to these technologies, they rarely offer high delivery efficiencies to lung. New aerosol drug development efforts need to seek to identify the clinical importance of efficient "targeted" drug delivery to different regions of the respiratory tract. Novel technologies should be chosen in cases in which significant clinical advantage is expected to result from efforts to increase delivery efficiency and/or the targeting of specific regions. New electromechanical inhalers offer high delivery efficiencies, a choice of particle size distributions, and improved methods of ensuring patient compliance. Whether these are worth the high cost of development will depend on the added value that they bring to drug therapy in each specific case.

Conflict of Interest Statement: P.R.B. has a consulting/advisory relationship with several of the companies whose devices are mentioned in this article and sits on the advisory boards of Boehringer Ingelheim $20,000, Aradigm Corporation $5,000, Nektar Therapeutics $60,000, GlaxoSmithKline $4,000 and is PI of a large grant from Chrysalis Technologies $8M to investigate condensation aerosol technology for pharmaceutical purposes and has also made invited presentations at all of these companies for which he has received honoraria and owns stock in Aradigm Corporation.

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