REVIEW ARTICLE

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Factors Affecting Development of Dry Powder Inhalers

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The search for alternatives to metered-dose inhalers has driven impetus for finding effective products that do not use chlorofluorocarbon propellants. The purpose of this paper review is to address the factors to be considered in developing dry powder inhalers; particularly the formulation, metering design and flow path in the device and importance of various regulatory requirements are discussed. The advantages and disadvantages of current dry powder inhalers and future approaches for pulmonary drug delivery are also discussed.

Inhalation drug delivery has been used for many years for the delivery of pharmacologically active agents to treat respiratory tract disease. Traditional asthma therapy with bronchodilators, steroids, mast cell stabilizers and anticholinergic drugs has primarily used the pressurized metered dose inhaler (pMDI) however; there is increasing threat because of the environment concerns regarding chlorofluorocarbon (CFC) propellants. In 1989 when the Montreal Protocol was implemented (an International convention that restricts the use of substances that deplete the ozone layer); it defined the need to replace CFC propellants in all pMDIs. The alternative hydrofluoroalkane (HFA) propellants have been difficult to formulate with inhalation drugs because of crucial differences in densities and solubilities of drugs and excipients. The pMDI market now includes both CFC and HFA aerosols with suspension and solution formulations of commonly used drugs such as salbutamol and beclomethasone dipropionate[1]. Large difference in particle size distribution of the emitted doses has also been demonstrated[2]. The problem on beclomethasone dipropionate prescribing is compounded by other CFC free formulations having same nominal dose as the original suspension[3]. Therefore there is a pressing need to clarify the clinical equivalence of newly formulated pMDI products and reduce the problems of HFA reformulation. The dry powder inhaler (DPI), being propellant-free, is an increasingly attractive and less confusing alternative for pMDI as drug delivery devices. There has been tremendous activity in the development of DPI devices over recent years with many innovative systems now at various stages of development[4,5]. Table 1 summarizes some commercially available DPI's and new DPIs currently under development with its dispersion mechanism. DPIs are categorized mainly in two categories like breathe driven/passive DPIs and power assisted/active DPIs. Former uses patient's inspiratory inhalation flow for dispersion of dry powder while later uses some mechanical/electrical power to disperse the dry powder.

The DPIs does not contain CFC propellants to disperse the drug, so they can be regarded as ozone-friendly delivery systems. However, they can not totally replace pMDIs due to limitations of dose delivered and flow rates achieved through the devices for severely diseased patients are probably valid[6], based on the capabilities of currently available powder inhalers. Vidgren *et al.* have shown different deposition patterns in healthy volunteers from the same formulation in four single-dose DPIs[7]. Newman *et al.* have also shown different *in vivo* deposition patterns in healthy volunteers using Turbuhaler inhalers operated at optimal and sub-optimal peak inspiratory flow rates[8]. Clearly, some current designs of DPIs are subject to variations in performance due to differences in inhalation flow rates. Future designs should be independent of patient inhalation for the disper-

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sion of the powder dose.

FACTORS INFLUENCING DPI FORMULATION DESIGN

Physical properties of powders:

DPIs provide powder pharmaceuticals in aerosol form to patients. The powdered drug is either loaded by the user into the DPI before use or stored in the DPI. To generate an aerosol, the powder in its static state must be fluidized and entrained into the patient's inspiratory airflow. The powder is subject to numerous cohesive and adhesive forces that must be overcome to get dispersed. Optimization and control of flow and dispersion (deaggregation) characteristics of the formulation is of critical importance in development of DPIs. These properties are governed by adhesive forces between particles, including Van der Waals forces, electrostatic forces and the surface tension of absorbed liquid layers[9]. The forces are influenced by several fundamental physicochemical properties including particle density and size distribution, particle morphology (shape, habit, surface texture) and surface composition (including absorbed moisture)[10]. Inter-particle forces that influence flow and dispersion properties of inhalation powders are particularly dominant in the micronized or microcrystalline powders (particles smaller than 5 μm). Hickey reviewed the factors influencing the dispersion of dry powders as aerosols[11]. Several cohesive and adhesive forces are exerted on particle characteristics such as size, shape, rugosity and crystalline form, and powder characteristics such as packing density and equilibrium moisture content. Buckton reviewed particle surface characteristics and several other studies have measured the adhesion forces in inhalation powders[12,13]. Peart and co-workers measured electrostatic charge interactions from Turbohalers and drug powders and the results suggest that the inhaler itself and the deaggregation mechanisms influenced the charging phenomena[14]. Electrostatic effects in DPIs have been extensively studies by others[15] and powder flow properties have also been studied[16]. Further particle characteristics have been studied such as the crystallization and amorphous content of inhalation powders[17,18] and the measurement of their surface properties by inverse gas chromatography[19] and computer aided image analysis to plot a Facet Signature[20].

Drug carrier:

Optimization and control of particle-particle and particle-inhaler interactions is of critical importance in the development of efficient DPIs. A paradoxical situation exists in powder formulations – drug particles should be less than 5 μm aerodynamic diameter to ensure efficient lung deposition, but should also exhibit acceptable flow properties required for accurate dose metering. Thus, micronized powders are often blended with 'coarse' inert carriers e.g. lactose, glucose or alternatively palletized as loose agglomerates to improve powder flow. Lactose is often selected as a drug carrier/excipients material because of several advantageous properties like low reactivity and toxicity, low water content and its low cost. Many studies have examined the properties of lactose particles and their interaction with drug particles as part of the process to optimize DPI performance[21]. Blending the drug with a carrier has a number of potential advantages, such as increasing the bulk of the formulation. This allows easier metering of small quantities (typically <100μg) of potent drugs, either at the manufacturing stage (if the doses are pre-metered) or within the device itself for a reservoir device. Provided the content uniformity of the blend is well controlled, this approach can improve the subsequent dosing consistency of the inhaler. The presence of the carrier material, in separating the very fine drug particles, can also improve processing (e.g. flow characteristics) of the formulation. The carrier properties (particle size distribution, particle surface characteristics) can be used to influence/control fine particle mass.

An additional benefit that may be gained by the use of a carrier such as lactose is the taste/sensation on inhaling, which can assure the patient that a dose has been delivered. Clearly, the influence of the carrier material on product stability must be carefully assessed, and the range of materials available for use as carriers in inhaled products is limited for toxicological reasons. Lactose and other sugars have been studied and used and modification of these materials may allow further formulation optimization. Modifications to the lactose surface have been proposed that would improve the surface characteristics (reduce the rugosity) of the material. Ganderton claims that reducing the rugosity increases the percentage of respirable particles in conventional powder inhalers[22]. Zeng and coworkers has found that the addition of fine lactose particles (mass median diameter 6.96 μm) increased the fine particle fraction of salbutamol sulphate from a powder formulation delivered by a Rotahaler[23]. They suggested that this may be because of the fine particles occupy possible drug binding sites on the larger lactose particles. Lucas *et al.* demonstrated a similar performance modifying effect with a model protein, albumin and a high-dose agglomerated preparation of nedocromil sodium[24]. Other studies have looked at similar effects of lactose size fractions and agglomerates[25]. The properties of lactose such as particle size and surface morphology[26] had a profound effect on the fine particle fraction

of the generated aerosol. Other excipients, like sugars, have also been studies to establish their preformulation characteristics. Braun *et al.*[27] used two grades each of α-lactose monohydrate and dextrose monohydrate with disodium cromoglycate and generated aerosols using a unit-dose device, the Microhaler[28].

Particle engineering:

One of the key factors involved in optimizing DPI performance is the precision particle engineering required to produce a powder formulation that delivers accurate, consistent, efficient doses of drug. Bulk drug modifications, both chemical and physical, have been attempted in order to enhance respirable dose performance. In one study[29], spray-dried salbutamol sulfate was seen to perform as well as micronized material. In the case of sodium cromoglycate, several approaches have been successfully employed to improve flow and dispersion characteristics, including controlled adherent flocs[30,31]. This approach takes advantage of the inherent cohesiveness of the particles.

In a review, Staniforth has outlined the development of improved performance dry powder inhalation systems by preformulation characterization of drug-carrier combinations[32]. Staniforth described the Pascal system, which is an example of carrier formulation technology using a novel single step process termed corrasion. This is a simultaneous milling, mixing and surface modification of mixtures of 98-100% α-lactose monohydrate and 0-2% of the amino acid L-leucine[32,33]. The process is designed to ensure that the drug-carrier bond is sufficiently strong to enable efficient manufacturing processes for the DPI, but also weak enough to facilitate detachment of drug from carrier surface during the inhalation process. Results claim significant increase in fine particle doses compared with conventional formulations.

Lipophilic coating materials have been investigated using disodium cromoglycate as an approach to minimize hygroscopic growth[10]. In addition, crystals of the parent acid and the effect of aspect ratios (longest and shortest dimensions) have been studies[34]. Vidgren *et al.* have shown that spray-dried particles of disodium cromoglycate have better (at least *in vitro*) aerodynamic properties (a higher fraction of dose in a smaller size range) than micronized material[35].

Other techniques such as re-crystallization from supercritical fluids for modifying drug characteristics have been discussed. More conventional ways of modifying drug particle characteristics such as spray drying have been further advanced by the use of new techniques such as supercritical fluid technologies. York and co workers[36] have evaluated the SEDS (Solution enhanced dispersion by supercritical fluids) technique that enables a drug solution to be processed into a micrometer sized particulate product in a singles step operation.

METERING DESIGN

DPIs can be divided into two classes: passive and active devices. Passive devices rely solely upon the patient's inhalatory flow through the DPI to provide the energy needed for dispersion. This method has the advantage of drug release automatically coordinating with the patient's inhalation[37]. The disadvantage is that dispersion typically is highly dependent on the patient's ability to inhale at an optimum flow rate. Depending on the inhaler design, this requirement may be difficult for some patients if the device's resistance to airflow is high[38]. Active devices use mechanisms such as springs or batteries to store energy that can be released to facilitate powder dispersion.

Whether a drug alone or a drug-carrier system is adopted, a key decision in the design of a DPI is whether to use a factory-metered dose or to include a reservoir and metering mechanism in the device itself. Early popular DPIs utilized factory-metered doses. Conventional capsule-filling technology was already well established in the early 1970s by Bell *et al.* who had developed this device for the administration of powdered sodium cromoglycate[30]. Here, the drug mixture is mixed with a bulk carrier to aid powder flow (lactose), is pre-filled into a hard gelatin capsule and loaded into the device. Following activation, capsule is pierced and the patient inhales the dose, which is dispensed from the vibrating capsule by means of inspired air. A similar kind of device (Rotahaler, Glaxo Wellcome) has been developed for the delivery of salbutamol and beclomethasone dipropionate powders. Here, the drug mixture is again filled into a hard capsule and the capsule is inserted into the device, wherein it is broken open and the powder inhaled through a screened tube[39]. Other devices dispense drug loaded into hard gelatin capsules like the Berotec (Boehringer Ingelheim) used for fenoterol[40].

These devices have performed well in clinical use for almost 25 years. Their primary disadvantage is the cumbersome nature of loading the capsules, which may not be easily feasible if a patient is undergoing an asthma attack and requires immediate relief.

The development of multi-does DPI has been pioneered by A.B.Draco (a division of Astra) with their Turbuhaler[41] and

by Glaxo Wellcome with the introduction of the Diskhaler[42] and recently the Diskus[43]. The Turbuhaler device is a reservoir-based powder inhaler. The drug is contained within a storage reservoir and can be dispensed into the dosing chamber by a simple back and forth twisting action on the base of the unit. The device delivers carrier-free particles of the β-agonist, terbutaline sulfate, as well as the steroid, budesonide[44].

The Diskhaler (Glaxo Wellcome) has been introduced for the delivery of both the short-acting β-agonist, salbutamol, as well as longer-acting, salmeterol[45]. Also, the steroids like beclomethasone dipropionate and fluticasone propionate are available as disks. These devices have a circular disk that contains a number of powder charges (four or eight), depending on a typical dosing schedule. The doses are maintained in separate aluminum blister reservoirs until just prior to inspiration, thus ensuring the integrity of the powder blend against moisture ingress. On priming the device, the aluminum blister is pierced and the powder charge is dropped into the dosing chamber. The Diskus device represents a further modification of the Diskhaler approach, with the pre-metered doses sealed in blisters on a foil strip. Instead of disk, here coiled strip is used which allows 60 doses of drug to be contained within the device.

There are two main advantages in the use of a pre-metered dose. Firstly, the precision with which the dose can be metered in the factory is superior to the typical precision of metering that can be achieved within a device alone, as required by a reservoir-based powder inhaler. With an efficient delivery system, the enhanced precision of metering will result in improved consistency of the delivered dose and fig. 1 illustrates this point. The graph shows the frequency distribution of doses delivered at 60 l/min from a terbutaline Turbuhaler and a salmeterol Diskus[46]. The pre-metered doses from the Diskus device are more consistent than the doses delivered from the reservoir device. Secondly, the pre-metered doses can be individually sealed and protected from the environment (moisture) until the point of use by the patient. Brindley *et al.* have shown that the drug content per blister and the dose delivered at 60 l/min from the salmeterol Diskus device is unaffected by storage at high humidity[45]. A reservoir that contains all of the doses may be more susceptible to deterioration through ingress of moisture. Some Turbuhaler products are designed to contain a desiccant within the device, to reduce the effects of moisture uptake, although Meakin *et al.* has demonstrated limitations to this approach[47,48].

The advantages of the reservoir metering device approach are the relative ease and cost of manufacturing, since these devices can be 'dump' filled with very high manufacturing throughput. A further advantage of the reservoir approach is the relative ease of including a large number of doses within the device. Newman has also shown that the Turbuhaler inhaler performance *in vivo* compares favorably with pMDIs[49].

FLOW PATH DESIGN

In combination with the design of the formulation and the approach to metering, the third critical factor that determines product performance is the flow path design of the device, particularly the design between exposed dose to be inhaled and the exit from the mouthpiece. An ideal flow path design would allow efficient and consistent emptying from the device across a wide range of flow rates; with sufficient turbulence to disperse/deaggreagate the powder blend and thereby providing an effective pharmacological response. .

Research has shown that the specific design of the DPI in terms of path length, flow angles and orifice diameters influence the resistance of the device[50]. New DPIs may be designed with a low resistance so that all patients can be able to generate high flow rates through it. Resistance of established DPIs has been previously measured[51] and the resultant flow rates were compared. New DPIs such as the Chiesi inhaler[52] (Chiesi Farmaceutici, Italy) and the Innovata Biomed Inhaler[53] (Innovata Biomed Ltd. UK) are evaluated for dosing performance at a range of flow rates.

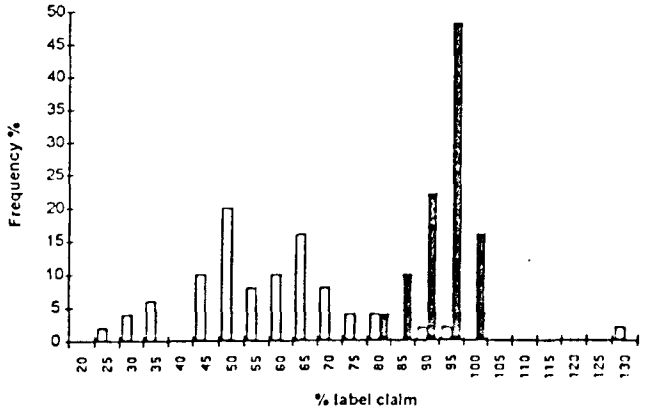

Fig.1: Frequency distribution of doses delivered at 60 l/min.

Percentage Frequency distribution of doses delivered at 60 l/min for salmeterol Diskus (-■-) and terbutaline Turbohaler (-□-) n=50 [Ref.45].

The flow path of the Diskus device is extremely short, with the powder passing through a single 'crucifix' grid to generate the necessary turbulence. As a result of the short flow path, drug losses within the device are minimized, allowing approximately 90% of the metered dose to be delivered while older devices like Turbuhaler typically delivers only 60% of the metered dose, presumably due to greater drug losses within the device[54]. In Turbuhaler, the flow path was carefully designed to maximize turbulence, using a long flow path with spiral channels in order to generate shear forces that would disperse the drug aggregates and produce a good fine particle mass[44]. At 60 l/min, the Turbuhaler can produce up to 50% of the emitted dose as respirable particles (<5 μm), although the percentage is considerably reduced at lower flow rates[55].

A further disadvantage of a long flow path is a potential increase in the device's resistance. The higher the resistance of the device, the greater the effort a patient has to make in order to achieve a given flow rate[56]. The flow rate achieved may be important in determining the performance of the device[57]. With careful flow path design, and the use of a lactose carrier, some devices such as the Diskus, are relatively insensitive to change in flow rate and deliver a consistent dose over a wide range of inhalation conditions[58]. Device resistance can also affect the patient's comfort in using the inhaler. De Boer *et al.* established that an increase in peak inspiratory flow rate (PIFR) is obtained with decreasing inhaler resistance and that, in healthy volunteers, on average, 55% of maximum effort was regarded as comfortable as a measure of patient's convenience to inhale the dose[59]. Fig. 2 compares the dose delivered from the Diskus and Turbuhaler inhalers at a range of flow rates. The inhaler resistances at each flow rate are also shown in the figure and indicate that the Turbuhaler has a higher resistance than the Diskus inhaler. The graph also shows that the Turbuhaler delivers a smaller production of each dose than the Diskus and is more dependent on flow rate.

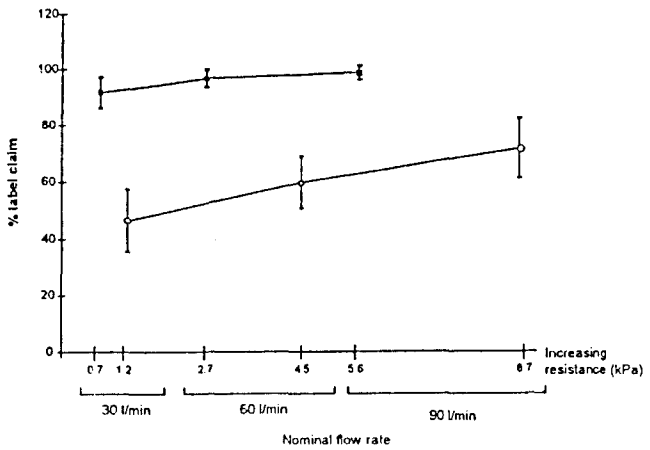

Fig. 2: Measurement of emitted dose from salmeterol Diskus and terbutaline Turbohaler at varying flow rates.

Measurement of emitted dose from salmeterol Diskus (-■-) and terbutaline Turbohaler (-□-) at varying flow rates like 30, 60 and 90 l/min with median and interqratile range for 5 devices each, n=50 [Ref. 43].

REGULATORY AND PHARMACOPOEIAL REQUIREMENTS

The late 1990s have seen the published agreements from the FDA (US Food and Drug Administration)[60] and the European Inhalanda group[61] on the tests required for the approval of new DPIs. US FDA requirements for testing dry powder inhalers are summarized in Table-2. The US Pharmacopoeia specifications for test methods harmonize with the European Pharmacopoeial requirements are now implemented, the FDA guidelines are in consultation draft form, and provide stricter requirements than the Pharmacopoeial tests. The FDA recognizes that the reproducibility of the dose and the particle size distribution are the most critical attributes of DPI. FDA requirements for testing a DPI constitute a demanding list for the approval of a new device[60].

A presentation of FDA Guideline for Product Development Strategy[62] concludes the performance standards for future DPI products have to be built in. Controversy has surrounded the definition of a delivered dose from a DPI and how it should be tested. Because of the differing efficiencies of the devices and their particular formulation characteristics, each device containing the same active ingredient can deliver the same effective or respirable dose from different quantities of active ingredients. This would create significant problems both to prescriber and patient as different labeled (metered) doses could be therapeutically equivalent. The new European Pharmacopoeial Monograph defines the fine particle dose as that fraction of the delivered dose that is <5 μm. However, a new DPI should establish some measure of therapeutic equivalence as part of its marketing information to reduce the prescribers' confusion.

The European Pharmacopoeial Monograph also defines the apparatus used for tests of uniformity of delivered dose and states that the test should be carried out at a fixed pressure drop across the inhaler of 4.0 KPa. Therefore, for devices with differing resistances, the flow rates used for

TABLE 1: COMMERCIALLY AVAILABLE DPIS AND NEW DPIS CURRENTLY UNDER DEVELOPMENT AND ITS DISPERSION MECHANISM

Type of the Device and Name	Dispersion Mechanism
Breath Driven/ Passive Powder Inhalers: Unit- Dose	
Rotahaler (Cipla, GSK)*	Capsule separates with dispersion
Spinhaler (Fisons)*	Pierced capsule rotates on impeller vibratory dispersion
Inhalator (Boehringer Ingelheim)*	Stationary capsule pierced dispersion via capillary fluidization
Aerosolizer (Novartis)	Pierced capsule rotates in chamber dispersion aided by grid
Solo (Inhale Therapeutic Systems)	Dispersion via turbulent airflow pathway
Orbital (Brin Tech International)	Dispersion via centrifugal acceleration mechanism
Microhaler (Harris Pharm)	-
Breath Driven/ Passive Powder Inhalers: Multi-Unit Dose	
Accuhaler (GSK)*	Pierced blister dispersion via turbulent airflow pathway
Diskhaler (GSK)*	Pierced blister dispersion via turbulent airflow pathway and grid
Flowcaps (Hovione)	Capsule based device dispersion via turbulent airflow pathway
Spiros S2 (Elan Corporation)	Dispersion via free floating beads and a dosing chamber
Technohaler (Innovata Biomed)	Dispersion via turbulent airflow pathway
Breath Driven/ Passive Powder Inhalers: Multidose Reservoir	
Turbohaler (Astra Zeneca)*	Dispersion via turbulent airflow pathway
Easyhaler (Orion)*	Dispersion via turbulent airflow pathway
Clickhaler (Innovata Biomed)*	Dispersion via turbulent airflow pathway
Pulvinal (Chiesi)*	Dispersion via turbulent airflow pathway
Twisthaler (Schering Plough)	Dispersion via turbulent airflow pathway
SkyePharma DPI	Dispersion via turbulent airflow pathway
Taifun (Leiras)	Dispersion via turbulent airflow pathway
Novalizer (Sofotec GmbH)	Dispersion via turbulent airflow pathway
MAGhaler (Mundipharma)	Dispersion via turbulent airflow. Formulation present as tablet
Bulkhaler (Asta Medica)	-
Mlat-Haler (MiatSpA)	-
Cyclovent (Pharmachemi)	-
Power Assisted/Active Powder Inhalers: Unit-Dose	
Inhance PDS (Inhale)	Gas assisted - compressed air disperses powder formulation
Omnihaler(ML Lab)	-
Pfeiffer (Pfeiffer GmbH)	-
Power Assisted/Active Powder Inhalers: Multi-Unit-Dose	
Spiros (Elan Corporation)	Electromechanical energy – battery operated impeller
Prohaler (Volois)	Gas assisted – built in pump provides compressed air
MPDS-Inhale (Inhale TS)	-

Asterisk denotes commercially available DPIs and new DPIs currently under development. Name in the parenthesis indicates the manufacturer name.

testing the device will be different. This implies that the conditions used for testing the device should relate to the range of inhalation flow rates generated through the device during patient use. It also means that the multistage apparatus for measuring the particle size distribution of the aerosol product might have to be operated at non-standard flow rates and therefore be recalibrated for each different device tested. None of the current impactors used for *in vitro* assessment are ideally suited to the aerodynamic particle sizing of DPIs.

TABLE 2: US FDA REQUIREMENTS FOR TESTING DRY POWDER INHALERS

Drug Product
This includes the device with all of its parts, any protective packaging and the formulation.
Components
Composition
Specifications for the formulation components like active ingredients and excipients
Manufacturers
Method of manufacturing and packaging
Specifications for the drug product
Container and closure system
Drug product stability
Drug product characterization studies
Determination of appropriate storage conditions
Stability of primary (unprotected) package
Effect of varying flow rates
Effect of storage on the particle size distribution
Dose build-up and flow resistance
Effect of orientation
In vitro dose proportionality
Effect of patient use
Effect of moisture
Photostability
Profiling of doses near device exhaustion
Priming
Fill weight
Device ruggedness
Cleaning instructions
Labeling considerations
Defines information to be included on the device label and packaging insert

Several studies have demonstrated improvements in the designs of cascade impactors[63] and emitted-dose-measurements apparatus[64] used for the evaluation of the performance of DPIs. A new impactor is being developed by an industry consortium, the Next Generation Impactor group[65] phase I of the project is an evaluation of new designs.

The requirements form the Medicines Control Agency (MCA)[66] also include stricter controls on the uniformity of the delivered dose than the Pharmacopoeial limits and states that the applicant should be able to attain a mean of ± 20% or better from the nominal content per dose. In addition, the MCA requires each multi-dose unit to have the following two safety features: 1. A counter device or other indicator to give the patient some indication of when it is becoming exhausted and 2. A system to prevent inadvertent multiple dosing because of multiple actuations of the dose measuring device.

The new SkyePharma powder inhaler (SkyePharma AG, Switzerland) containing a reservoir of 300 doses[67] and the Bulkhaler device (Astra Medica AG, Germany) incorporating a refillable cartridge[68] fulfill these MCA requirements. The committee for proprietary medicinal products (CPMP) has published guidelines on DPIs in 1998[69].

The regulatory authorities provide a comprehensive list of requirements for compliance, which must be applied to any new DPI. The complexity of the listed items generates ever-increasing demands on the development process.

NOVEL INHALATION DELIVERY SYSTEMS

Interest in the design of more compact portable inhalation delivery systems is increasing. The patent literature offers numerous examples of applications for novel delivery systems that purport to be potential replacement for the pMDIs, and much is being published in this field[64,65]. Consideration is being given to delivery of biotherapeutic materials, such as some proteins and peptides, by inhalation aerosol[67].

Initial research into the production of microspheres using substances such as poly (D, L- lactide-co-glycide) (PLGA) and poly(L-lactic acid) (PLA)[70] has demonstrated that the administration of microspheres to the pulmonary airways could be a route for sustained-release drug therapy in respiratory disease, although the toxicity of this type of formulation has yet to be established. Another group of workers has studies the pharmacokinetics of mucoadhesive budesonide microspheres administered to guinea pigs, dem-

onstrating an increase in duration of drug action from 6 to 24 hours after lung administration[71].

In recent years, the development of inhalation simulation machines has enabled the measurements of *in vitro* DPI performance using patient's inhalation profiles[72]. The dose dispersion process is driven by a pre-programmed theoretical inhalation profile or a previously recorded patient inhalation profile with varying flow rates and flow accelerations, and the resultant aerosol could is subsequently analyzed for dose and particle size using an impactor or impinger at a fixed flow rate. These machines have increased the understanding of the complex relationship between acceleration of inhalation flow rate and the dose output of DPIs[73]. These machines also facilitate the *in vitro* evaluation of dosing performance of new DPI designs for a range of simulated patient conditions, and thus they are becoming established as part of the ongoing testing of DPIs.

A number of potential new devices are emerging in the powder area, ranging from simple unit-dose devices to more complex multidose systems[74]. In addition, true breath-activated systems, coupled with an auxiliary means for dispersion of the metered powder[75] hold much promise for the future, if they can pass the trials of converting a sound laboratory principle into a commercially successful device. This, of course, will take several years and may well be driven by patients' needs and the acceptability of alternatives to the widely used pMDI.

Recently we have developed liposomal DPI formulation of budesonide[76,77], ketotifen fumarate[78] and terbutaline sulphate[79,80]. Liposomal budesonide was stabilized by lyophilization, delivered as an aerosolized DPI and evaluated by twin stage impinger gave the fine particle fraction of 20%. The developed liposomal budesonide DPI was found to provide desired drug levels in the lungs for a prolonged period of time, which is expected to enhance the therapeutic index of the drug and probably reduce the dose and cost of therapy as well[77].

Liposome aerosols are promising vehicles for respiratory delivery of therapeutic drugs and have attracted the attention of many researches, especially in the area of DPIs[81,82]. Liposomal delivery by dry powders has been considered mainly based on the fact that liposomes can be more stable when dried by lyophilization[83,84]. With liposome powders as drug carriers for inhalation therapies, the lyophilized precursor should be micronized to particles of 1-6 μm in diameter for efficient delivery to the lung. Micronization has normally achieved by jet-milling[81,85], which causes particles to break apart on colliding in a high-velocity air-stream. As a measure of circumventing the potentially negative effects of lyophilization and jet-milling advantage might be made of the fact that phospholipids are known to orient into liposomal configuration through a spontaneous, entropic process in a water-rich environment. Such conditions exist in the airways of the respiratory tract, so that it is feasible to postulate that spontaneous liposome formation would occur following pulmonary disposition of microfine phospholipids-based aerosols. This was demonstrated by Desai *et al.* for three model drugs[86] (viz., ciprofloxacin, CM3 peptide and salbutamol sulphate). The effects of several parameters, including lactose concentration, lipid composition and lipid concentration on the encapsulation efficiency of these model drugs were investigated.

Inhalation aerosol characterized by particles of small mass density and large size, permitted the highly efficient delivery of inhaled therapeutics into the systemic circulation. Particles with mass densities less than 0.4 per cubic centimeter and mean diameters exceeding 5 μm were inspired deep into the lungs and escaped the lungs natural clearance mechanisms until the inhaled particles delivered their therapeutic payload. Inhalation of large porous insulin particles resulted in elevated systemic levels of insulin and suppressed systemic glucose levels for 96 hours, whereas small nonporous insulin particles had this effect for only 4 hours. High systemic bioavailability of testosterone was also achieved by inhalation delivery of porous particles with a mean diameter of 20 μm approximately 10 times that of conventional inhaled therapeutic particles[87]. Porous particles comprising therapeutics and pharmaceutical excipients can easily be formed by spry-drying[88], rapid expansion of supercritical fluids[89] and other particle formation technologies. Hence, they can immediately address a variety of needs as therapeutic carriers for inhalation therapies. Their potential for high aerosolization efficiency, long-term drug release and increased systemic bioavailability makes large porous particles especially attractive for systemic inhalation therapies.

CONCLUSIONS

Common to all inhalation dosage forms and delivery systems is the need to generate the optimum 'respirable dose' (particles with aerodynamic diameter <5.0 μm) of a therapeutic agent consistently and reliably. This is a key performance feature in the rational design and selection of a delivery system. Moreover, this performance, in terms of

aerosol quality, should be demonstrated throughout the product's shelf life. In addition to the more usual chemical and physical stability criteria, when considering these delivery systems, it is important that the device design and formulation work have been integrated in the overall design and development of the product. Frequently, therefore, such inhalation delivery systems tend to be compound or company specific.

In summary, in the short term, suitable replacements for pMDIs (be they powder or liquid based) are unlikely, but if some of the systems that are currently being developed are able to achieve the convenience and compactness of the pMDI and have similar (or improved) pharmaceutical performance, they might be in widespread use in the later part of the decade.

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REFERENCES

1. Leach, C.L., In; Byron, P.R., Dalby, R.N. and Farr, S.J. Eds., Respiratory Drug Delivery V, Interpharm Press, IL, 1996, 133.
2. Ganderton D., **J. Aerosol Med.,** 1999, 12, 119.
3. Howlett, D.J. In; Byron, P.R., Dalby, R.N. and Farr, S.J. Eds., Respiratory Drug Delivery VI, Interpharm Press, IL, 1998, 123.
4. Atkins, P.J., Barker, N.O. and Mathisen, D., In; Hickey, A.J., Eds., Pharmaceutical Inhalation Aerosol Technology, Marcel Dekker, Inc., New York, 1992, 155.
5. Dunbar, C.A. and Hickey, A.J., **Pharm. Tech.,** 1997, 21, 116.
6. Dolovich, M.B. and Ramsdale, E.H., **Can. Med. Assoc. J.,** 1990, 142, 1036.
7. Vidgren, M., Karkkainen, A., Karjalainen, P., Paronen, P. and Nutinen, J., **Int. J. Pharm.,** 1988, 42, 211.
8. Newman, S.P., Moren, F., Trofast, E., Woodman, G. and Clarke S.W., In; Newman, S.P., Moren, F. and Crompton, G.K. Eds., A New Concept in Inhalation Therapy, Medicom, UK, 1987, 104.
9. Hinds, W.C. In; Hinds, W.C. Eds., Aerosol Technology: Properties, Behaviour and Measurement of Airborne Particles, Wiley, New York, 1982, 127.
10. Hickey, A.J., Gonda, I., Irwin, W.J. and Fildes, F.J.T., **J. Pharm. Sci.,** 1990, 79, 1009.
11. Hickey, A. J., Concessio, N.M., Van, M.M. and Platz, A.M., **Pharm.Tech.,** 1994, 18, 58.
12. Buckton, G., **Adv. Drug Del. Rev.,** 1997, 26, 17.
13. Podczek, F., In Drug Delivery to the Lungs VII, The Aerosol Society, UK, 1996, 70.
14. Peart, J., Staniforth, J.N., Byron, P.R. and Meakin, B.J., In; Byron, P.R., Dalby, R.N. and Farr, S. J. Eds., Respiratory Drug Delivery V, Interpharm Press, IL, 1996, 85.
15. Mazumder, M.K., Bhattacharyya, D., Guo, W. and Hickey, A.J., In; Byron, P.R., Dalby, R.N. and Farr, S.J. Eds., Respiratory Drug Delivery VI, Interpharm Press, IL, 1998, 369.
16. Dawson, M.L. and Clarke, J.G., In Drug Delivery to the Lungs IX, The Aerosol Society, UK, 1998, 68.
17. Phillips, E.M., Byron, P.R. and Naini, V., In; Byron, P.R., Dalby, R.N. and Farr, S.J. Eds., Respiratory Drug Delivery V, Interpharm Press, IL, 1996, 103.
18. Buckton, G., In; Byron, P.R., Dalby, R.N. and Farr, S.J. Eds., Respiratory Drug Delivery VI, Interpharm Press, IL, 1998, 145.
19. Thielmann, F., Levoguer, C. and Domingue, J., In; Byron, P.R., Dalby, R.N. and Farr, S.J. Eds., Respiratory Drug Delivery VIII, Interpharm Press, IL, 2002, 611.
20. Kaye, B.H., In; Byron, P.R., Dalby, R.N. and Farr, S.J. Eds., Respiratory Drug Delivery V, Interpharm Press, IL, 1996, 95.
21. Patel, A.N., In; Byron, P.R., Dalby, R.N. and Farr, S.J. Eds., Respiratory Drug Delivery VII, Interpharm Press, IL, 2000, 381.
22. Ganderton, D., **J. Biopharm. Sci.,** 1992, 3, 101.
23. Zeng, X.M., Martin, G.P., Tee, S., Ghoush, A.A. and Marriott, C., **Int. J. Pharm.,** 1999, 182, 133.
24. Lucas, P., Clarke, K.A., Tobyn, M.J. and Staniforth, J.N., In; Byron, P.R., Dalby, R. N. and Farr, S.J. Eds., Respiratory Drug Delivery VI, Interpharm Press, IL, 1998, 243.
25. Boerefijn, R., Ning, Z. and Ghadiri, M., **Int. J. Pharm.,** 1998, 172, 199.
26. Clarke, M.J., Tobyn, M.J. and Staniforth, J.N., In; Byron, P.R., Dalby, R. N. and Farr, S.J. Eds., Respiratory Drug Delivery VII, Interpharm Press, IL, 2000, 645.
27. Braun, M.A., Oschmann, R. and Schmidt, P.C., **Int. J. Pharm.,** 1996, 135, 53.
28. Pearce, J.O., **EP Patent No.,** 0333334A2, 1989.
29. Chawla, A., Taylor, K.M.G., Newton, J.M. and Johnson, M.C.R., **Int. J. Pharm.,** 1994, 108, 233.
30. Bell, J.H., Hartley, P.S. and Cox, J.S.G., **J. Pharm. Sci.,** 1971, 60, 1559.
31. Auty, R.M., Brown, K., Neale, M.G. and Snashall, P.D., **Brit. J. Dis. Chest,** 1987, 81, 371.
32. Staniforth, J.N., In; Byron, P.R., Dalby, R.N. and Farr, S.J. Eds., Respiratory Drug Delivery V, Interpharm Press, IL, 1996, 65.
33. Malcolmson, R.J., Buckton, G., Darcy, P., Cox, R.L., Renwick, C.E. and Embleton, J.K., In; Byron, P.R., Dalby, R.N. and Farr, S.J. Eds., Respiratory Drug Delivery VI, Interpharm Press, IL, 1998, 365.
34. Chan, H. K. and Gonda, I., **J. Pharm. Sci.,** 1989, 78, 176.
35. Vidgren, M., Vidgren, P., Uotila, J. and Paronen, P., **Acta Pharm. Fennica,** 1988, 97, 187.
36. York, P. and Hanna, M., In; Byron, P.R., Dalby, R.N. and Farr, S.J. Eds., Respiratory Drug Delivery V, Interpharm Press, IL, 1996, 231.
37. Kjellman, N.I.M. and Wirenstrand, B., **Allergy,** 1981, 36, 437.
38. Dunbar, C. and Hickey, A.J., **Pharm. Technol.,** 1997, 21, 116.
39. Clark, A.R., **Aerosol Sci. Technol.,** 1995, 22: 374.
40. Pedersen, S. and Steffensen, G., **Eur. J. Respir. Dis.,** 1986, 68, 207.
41. Wetterlin, K. **Pharm. Res.,** 1988, 5, 506.
42. Sumby, B.S., Churcher, K.M., Smith, I.J., Grant, A.C., Truman,

K.G., Marriott, R.J. and Booth, S.J., **Pharm. Tech. Int.,** 1993, June, 20.
43. Gunawardena, K.A., Pleace, K.J. and Clay, M.M., **Amer. J. Respir. Crit. Care Med.,** 1994, 149, A21.
44. Pedersen, S., **J. Aerosol Med.,** 1994, 7, S-46.
45. Brindley, A., Sumby, B.S., Smith, I.J., Prime, D., Haywood, P.A. and Grant, A.C., **Pharm. Tech. Eur.,** 1995, 7, 14.
46. Malton, A., Sumby, B.S. and Smith, I. J., **Eur. J. Clin. Res.,** 1995, 7, 177.
47. Meakin, B.J., Cainey, J.M. and Woodcock, P.M., **Int. J. Pharm.,** 1995, 119, 103.
48. Meakin, B.J., Cainey, J.M. and Woodcock, P.M., **Eur. Respir. J.,** 1993, 6, 760.
49. Newman, S.P., **J. Aerosol. Med.,** 1995, 8, S21
50. Britto, L. In; Byron, P.R., Dalby, R.N. and Farr, S.J. Eds., Respiratory Drug Delivery VI, Interpharm Press, IL, 1998, 312.
51. Clark, A.R. and Hollingworth, A.M., **J. Aerosol Med.,** 1993, 6, 99.
52. Pitcairn, G., Lunghetti, G., Venture, P. and Newman, S., **Int. J. Pharm.,** 1994, 102, 11.
53. Nantel, N.P., In; Byron, P.R., Dalby, R.N. and Farr, S.J. Eds., Respiratory Drug Delivery V, Interpharm Press, IL, 1996, 386.
54. Byron P.R., In; Byron, P.R. Eds., Respiratory Drug Delivery, CRC Press, Boca Raton, FL, 1990, 167.
55. Meakin B.J., Cainey, J.M. and Woodcock, P.M., **Int. J. Pharm.,** 1995, 119, 91.
56. Clark, A.R. and Hollingworth, A.M., **J. Aerosol Med.,** 1993, 6, 99.
57. Olsson, B. and Asking, L., **J. Aerosol Med.** 1994, 7, S43.
58. Prime, D., Slater, A.L., Haywood, P.A. and Smith, I.J., **Pharm. Tech. Eur.,** 1996, March, 23.
59. De Boer, A.H., Winter H.M.I. and Lerk, C.F., **Int. J. Pharm.,** 1996, 130, 231.
60. US FDA (CDER) Draft Guidance for Industry Metered Dose Inhalers (MDI) and Dry Powder Inhalers (DPI) Drug Products. CMC Documentation.
61. Inhalanda Pharm. Eur. Suppl. 1999, 0671, 984.
62. Donawa, M.E. and Horhota, S.T., In; Byron, P.R., Dalby, R.N. and Farr, S.J. Eds., Respiratory Drug Delivery VIII, Interpharm Press, IL, 2002, 371.
63. Van Oort, M. and Downey, B., **US Pharm. Forum,** NJ, 1996, 22, 2204.
64. Collins, S. In; Drug Delivery to the Lungs IX, The Aerosol Society, UK, 1998, 60.
65. Wright, P. In; Drug Delivery to the Lungs VIII, The Aerosol Society, UK, 1997, 107.
66. Summers, M.P., In; Recent Advances in Dry Powder Inhalers, Management Forum Ltd. UK, 1996, 142.
67. Keller, M., Muller-Walz, R., Gilchrist, P., Lefrancoise, G. and Haeberlin, B., In; Byron, P.R., Dalby, R.N. and Farr, S.J. Eds., Respiratory Drug Delivery VII, Interpharm Press, IL, 2000, 511.
68. Berner, B., Fyrnys, B., de Boer, A., Gottenauer, W. and Wolf-Heuss E. In; Byron, P.R., Dalby, R.N. and Farr, S.J. Eds., Respiratory Drug Delivery VI, Interpharm Press, IL, 1998, 475.
69. Committee for Proprietary Medicinal Products, 1998, CPMP/QWP/158/96.
70. El-Baseir, M.M. and Kellaway, I.W., **Int. J. Pharm.,** 1998, 175, 135.
71. Sakagami, M., Kinoshita W., Makino, Y. and Fujii, T., In; Byron, P.R., Dalby, R.N. and Farr, S.J. Eds., Respiratory Drug Delivery VI, Interpharm Press, IL, 1998, 193.
72. Burnell, P.K.P., Maltona, A. Reavilla, K. and Ballb, M.H.E., **J. Aerosol. Sci.,** 29, 1011.
73. De Boer, A.H., Bolhuis, G.K., Gjaltema, D. and Hagedoorn, P., **Int. J. Pharm.,** 1997, 153, 67.
74. Hill, M., Vaughan, L. and Dolovich, M., In; Byron, P.R., Dalby, R. N. and Farr, S. J. Eds., Respiratory Drug Delivery V, Interpharm Press, IL,1996, 230.
75. Schultz, R.K., Miller, N.C., Smith, D.K. and Ross, D.L., **J. Biopharm. Sci.,** 1992, 3, 115.
76. Joshi, M.R. and Misra, A.N., **AAPS Pharm. Sci. Tech.,** 2001, 2, article 25.
77. Joshi, M. and Misra, A.N., **Meth. Find. Exp. Clin. Pharmacol.,** 2001, 23, 531.
78. Joshi, M and Misra, A.N., **Int. J. Pharm.,** 2001, 223, 15.
79. Joshi, M.R. and Misra, A.N., **Indian J. Exp. Biol.,** 1999, 37, 881.
80. Joshi, M.R. and Misra, A.N., **Indian Drugs,** 1999, 36, 245.
81. Schreier, H., Mobley, W.C., Concessio, N., Hickey, A.J., and Niven, R.W., **STP Pharm. Sci.,** 1994, 4, 38.
82. Ho, J. In; Shek, P.N., Eds., Liposomes in biomedical applications, Harwood Academic Publishers, Amsterdam, 1995, 199.
83. Mobley, W.C. and Schreier, H., **J. Control. Release,** 1994, 31, 73.
84. Sun, W.Q., Leopold, A.C., Crowe, L.M. and Crowe, J.H., **Biophys. J.,** 1996, 70, 1769.
85. Mobley, W.C., Pharm. Res., 1998, 15, 149.
86. Desai, T.R., Wong, J.P., Hancock, E.W. and Finlay, W.H., **J. Pharm. Sci.,** 2002, 91, 482.
87. Edwards, D.A., Hanes, J., Caponetti, G., Hrkach, J., Ben-Jebria, A., Eskew, M.L., Mintzes, J., Deaver, D., Lotan, N. and Langer, R., **Science,** 1997, 276: 1868.
88. Sacchetti, M., and Van Oort, M.M., In: Hickey, A.J., Eds., Inhalation Aerosols, Dekker, New York, 1996, 233.
89. Tom, J.W. and Debenedetti, P.G., **J. Aerosol Sci.,** 1991, 22, 555.