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Invited Review

Drug delivery to the respiratory tract using dry powder inhalers

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Summary

The inhalation of aerosolised drug has become a well established treatment modality in conditions such as asthma. The pressurised metered-dose inhaler (MDI) is still the most commonly prescribed inhalation system, despite a number of associated disadvantages. The requirement to replace the ozone-depleting chlorofluoro-carbon propellants, present as an integral part of all MDIs, has led to the pharmaceutical industry re-evaluating the potential of dry powder inhalers (DPIs). However, the efficiency of delivery is currently not high, with in some cases only approx. 10% of the inhaled dose of the drug reaching the alveoli. The site of deposition and the deposition patterns of the inhaled aerosol from DPIs is influenced by two major interdependent factors: (a) the patient (anatomical and physiological aspects of the respiratory tract as well as mode of inhalation) and (b) the physical properties of the aerosol cloud (attributable either to the dry powder formulation or the design of the DPI devices). More recently, as engineers have contributed to the design of DPI devices encouraging results have been obtained in clinical trials performed to compare the efficacy and acceptability of DPI with other drug delivery systems. Undoubtedly more cross-disciplinary collaboration of this kind will lead to further improvements in drug delivery from such formulations and may ultimately provide a feasible means of presenting drugs of peptide origin to the body for systemic therapeutic action.

Introduction

Aerosol inhalation as a method of drug delivery to the respiratory tract has become well-established in the treatment of lung disease. This route has several distinct advantages. Medication is directly delivered to the tracheobronchial tree allowing for rapid and predictable onset of action; the first-pass effect is avoided; degradation within the gastrointestinal tract is avoided; lower dosages than by the oral route can be administered with similar efficacy which will minimise unwanted side effects; and it can be employed as an alternative route to avoid drug interaction when two or more medications are used concurrently.

Three main delivery systems have been devised, namely, pressurised metered-dose inhaler (MDI), nebuliser and dry powder inhaler (DPI). Treatment of asthma has improved considerably in recent years owing to the discovery of potent compounds which prevent or alleviate some of the symptoms. However, the efficiency of inhalation therapy is not high since only about 10% of

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the inhaled dose of the drug reaches the alveoli (Newman et al., 1981a). To a certain extent, it may be possible to increase the fraction of dose deposited in the lungs by training the patient in 'correct' inhalation techniques (Power and Dash, 1985). However, the therapeutic efficacy of the inhaled drug is governed by the aerosol characteristics (which are a function of a combination of the formulation and device), inter-patient variability and the technique by which the patient uses the inhaler.

The MDI is still the most commonly prescribed inhalation system. However, it has several disadvantages:

(1) Droplets leaving the actuator orifice can be too large (Moren, 1981) and have an extremely high velocity (Rance, 1974) resulting in extensive oropharyngeal deposition.

(2) The output of the MDI is delivered in the course of vital capacity manoeuvre rather than tidal breathing and hence it is important to synchronise the aerosol discharge with inspiration. In recent studies it was found that 50% or more adult patients have difficulty in using conventional MDIs efficiently even after a careful training (Crompton, 1990; Hilton, 1990; Zainudin and Sufarlan, 1990). In an attempt to solve this problem a spacer devices (Konig, 1985) and breath-actuated MDIs (Crompton, 1988) have been developed.

(3) Dysrhythmias and paradoxical bronchoconstriction (Thiessen and Pederson, 1980) with MDIs have given rise to some controversy about the safety of propellants or surfactants.

(4) The dimensions of the metering valve and the actuator orifice limits the maximum amount of dose delivered to about 1 mg (Ganderton and Kassem, 1992).

(5) The use of chlorofluorocarbon (CFC) propellants are to be restricted in future due to their implication in the ozone depletion.

As a result of these problems it might be expected that the future of the MDIs is limited. There are two possibilities for future development which are currently being actively explored. First, alternative 'ozone friendly' propellants (Daly, 1992) and second, the design and use of alternative inhalers that do not use propellants at all. Nebuliser-generated 'wet' aerosols do not contain propellants but the nebulisers are generally bulky, cumbersome and costly. The ease of operation (precise synchronisation of aerosol discharge with inspiration is not required) and relatively low cost of DPI may therefore result in the development of many new systems over the coming decade, providing future benefits to many patients.

The pharmacologically active polypeptides and proteins which are being developed such as vaccines and hormones may fail to gain their full potential and wider acceptance if the parenteral route is their sole means of administration. Therefore, with the advent of these drugs/agents, various delivery routes, for example, nasal, rectal are currently under investigation. It is thought that DPI might be a good delivery system for such drugs as the presentation of peptide in this form may provide a pharmacologically active formulation, without the need for the extensive use of excipients.

Clinical Efficiency of Inhalation Delivery Systems

Accurate assessment of drug deposition profiles, both in terms of the quantity of the drug reaching the respiratory tract and its depth of penetration, are critical parameters in evaluating all inhalation drug delivery systems. Inhalation therapy is usually evaluated by measuring the therapeutic response of the inhaled drug doses. Extensive clinical studies have been carried out to compare the efficacy of DPIs with MDIs and nebulisers. In a recent study, for example, it was observed that salbutamol inhaled via the Rotahaler® was just as effective as the same dose inhaled from a nebuliser in producing bronchodilation (Assoulfi and Hodson, 1989). The Rotahaler® offered the advantage of being more portable than the nebuliser. Bricanyl® Turbohaler® was shown to be as effective as other delivery systems in producing bronchodilation. There was a clear preference in favour of Turbohaler® when it was compared with Bricanyl® MDI (Hultquist et al., 1988; Persson et al., 1988; Newman et al., 1989; Osterman et al., 1991)

and Bricanyl® MDI connected to a nebuliser (Svenonius and Ahlstrom, 1988). Patients also showed a clear preference in favour of Turbohaler® when it was compared with Inhalator Ingelheim® (Ribeiro and Wiren, 1990) and Ventolin® Rotahaler® (Warner and Chetcuti, 1987).

Initial reports suggested that total lung deposition from DPIs is smaller than that from MDIs. For example, a similar improvement in lung function was observed when 400 μg salbutamol was given by the DPI and 200 μg by MDI (Muittari and Ahonen, 1979; Mathieu et al., 1992). A study by Zainudin et al. (1990) using radiolabelled salbutamol indicated that 11.2% of MDI dose was deposited in the lungs compared to 9.1% of DPI dose. The British National Formulary (1993) recommends double the dose of salbutamol administered from a DPI than from an MDI. However, recent reports (Hindle et al., 1992; Thorsson et al., 1993) indicate that the recommended DPI dose might not be necessary. Furthermore, the lung deposition of ^{99m}Tc-labelled sodium cromoglycate (SCG) from DPI device (DPID) both in vitro and in vivo was significantly higher than that from a MDI (Vidgren et al., 1988; Table 1). This is probably because the speed of particles delivered from DPI is the same or lower than that of the flow of inspired air, thus making them more prone to follow the air flow than the faster moving MDI particles, thereby reducing upper respiratory tract deposition. Various studies have shown the benefit of slow deep inhalation with MDI (Lawford and McKenzie, 1981; Newman et al., 1981b, 1982).

In most clinical studies, aerosol deposition patterns (both regional and total) are measured using isotopic techniques. Chemical labelling of the drugs commonly used in the management of asthma is often impossible because these molecules rarely contain a moiety which can be labelled with a suitable gamma-emitter and hence cannot be detected outside the body using a gamma camera. Therefore, inert Teflon particles labelled with ^{99m}Tc have been used as model particles in such studies (Newman et al., 1984). Radioactive SCG particles, prepared using a novel labelling method based on a spray-drying technique, have also been used for this purpose (Vidgren et al., 1988). Although the deposition characteristics of spray-dried material are different from those of mechanically micronised drug particles (Vidgren et al., 1987), this method is clearly more physiological than the use of Teflon particles.

TABLE 1

Mean % deposition of ^{99m}Tc-labelled SCG particles [a]

	In vitro			In vivo		
	Device	Upper	Lungs airways	Device	Upper	Lungs airways
MDI	6.4	63.6	30.0	9.5	81.3	9.2
DPI	22.4	38.2	39.4	39.6	44.0	16.4

[a] After Vidgren et al. (1988).

In Vitro Characterisation of Aerosol Cloud

Clinical studies on the dispersibility of different dosage forms, using differently constructed DPIDs, are laborious and costly. Therefore, a number of methods have been proposed for screening the inhalation behaviour of the drug particles and assessing the fine particle fraction of the aerosol cloud in vitro.

Optical sizing methods based on microscopy (Hallworth and Hamilton, 1976) of impacted aerosols to measure physical diameters are very slow and may be largely unrealistic and unrepresentative of airway deposition.

Forward light scattering (using laser particle sizing equipment) is a non-invasive technique which provides an estimate of volume median diameter and some index of polydispersity (Hiller et al., 1978; Davies et al., 1980a,b). However, this technique does not take account of the anatomical structure of the human respiratory tract and the aerodynamic behaviour of the particles.

A number of instruments have been used to determine the particle size distribution of aerosols within a model respiratory tract designed to reproduce the anatomical dimensions of an average healthy human airway (Kirk, 1972; Martin et al.,

1988). The most frequently used in vitro method is based on the cascade impaction technique. This is an invasive technique which enables the collection and fractionisation of an aerosol cloud through a simulated 'throat' in a way which imitates the in vivo situation. The cascade impactor utilises the relationship between velocity and mass where larger particles with sufficient inertia are impacted on the upper stages, whereas finer particles penetrate to the lower stages of the separator. Cascade impactors provide a useful aerodynamic measure of particle size distribution which can be used to compare devices and formulations.

Since chemical or physical quantitation of collected aerosol particles from conventional cascade impactors is time consuming, a simplified twin-stage impinger was subsequently developed for more rapid quality control processing of aerosols (Hallworth et al., 1978; Hallworth and Westmoreland, 1987). This device was included in the British Pharmacopoeia (1988) as an official method for characterising aerosols and has recently been incorporated in the United States Pharmacopeia (1992). The twin-stage impinger has two limitations. Firstly, the total sample is divided into only two size categories and secondly, the separation between the two categories is not perfectly sharp. However, the twin-stage impinger has proved to give a good correlation with the clinical performance of therapeutic aerosols (Padfield et al., 1983) and can function as a particle sizing device and as a means of determining total output simultaneously. The respirable fraction of the dose is generally defined as the amount of particles with a d_{ae} of less than 5.0 μm. In the case of the twin-stage impinger, the respirable fraction is assumed to be the amount of particles with less than 6.4 μm diameter. The respirable fraction can be calculated in two ways: first, by the amount of drug collected in the lower impingement chamber as a percentage of nominal dose and second, by the amount of drug collected in lower impingement chamber as a percentage of total amount collected in both chambers. The latter option is preferable since it represents the redispersion or deaggregation ability of the DPID and also takes account of only the drug being delivered into the 'airways'.

It has been suggested that effective use of DPI requires inspiratory flow rates of 60 l min^{-1} or more in the device (in the twin-stage impinger, air is drawn through the instrument at a flow rate of 60 l min^{-1} by means of a vacuum at the outlet). However, a recent study indicates that the peak inspiratory flow required to generate 60 l min^{-1} through, for example, the Turbohaler® is about 3-times higher than that required for the Rotahaler® (Timsina et al., 1992). Therefore, for different DPIDs, it may be more realistic to perform in vitro tests using appropriate flow rates as observed in vivo rather than constant airflow rates.

There are no pharmacopoeial monographs to fit the specific quality assurance requirements of dry powder inhalers. However, in vitro tests for DPIs should include uniformity of dose and respirable fraction in the aerosol cloud. It is also important to identify and confirm the number of doses claimed on the label for multi-dose DPIs (Moren, 1992). A test on the homogeneity of the drug-carrier mixture should also be carried out if a carrier is added in the powder formulation.

The inspiratory flow rate and the turbulence created within the device as the air flows through it breaks the bonds formed between adhering particles. Therefore, the minimum air flow needed should be determined in order to estimate the likelihood that patients with obstructive lung diseases and airflow limitations will be able to discharge the dose. For the same reason, it is also valuable to determine the resistance to airflow through the device.

All in vitro models are simplified and hence the levels of branching of the airways cannot be represented and the potential impactions are of course different from the tissue surfaces comprising the airways. In vivo studies are therefore essential to characterise the mode of deposition and hence clinical response.

The site of deposition and the deposition pattern of inhaled aerosol from the DPIs is influenced by two major interdependent factors:

(a) The patient (anatomical and physiological aspects of the respiratory tract as well as the mode of inhalation).

(b) The physical properties of the aerosol cloud,

which can be sub-divided into those related to (i) the dry powder formulation, and (ii) the design of DPID.

The patient

Anatomical and physiological aspect of respiratory tract The anatomical/physiological factors of the human respiratory tract as well as the individual difference in the inhalation techniques have a significant influence on aerodynamic behaviour and hence the deposition of the inhaled particles (Auty et al., 1987; Vidgren et al., 1988). The respiratory tract consists of multiple generations of branching airways (pharynx, larynx, trachea, bronchi, bronchioles and alveoli) which progressively decrease in diameter but increase in number and total surface area. The large surface area of bronchioles and alveoli facilitates the rapid absorption of the inhaled medicament. It is generally assumed that alveolar deposition is therapeutically important (Moren et al., 1985). The degree of airway obstruction and airway geometry also affects the site of particle deposition.

Deposition in the respiratory tract will take place by a combination of inertial impaction (mainly in the larger airways) and gravitational sedimentation (mainly in the smaller peripheral airways and in alveoli). In order to improve drug delivery, it is thus necessary to reduce impaction losses which take place before the aerosol reaches the bronchial tree. The proportion of particles deposited by inertial impaction in the airway increases with particle size and airflow rate (Lippmann, 1977) (deposition is proportional to $\log(d^2F)$, where d = particle diameter and F = inhalation flow rate). It is essential to remember that low flow rate enhances sedimentation and therefore increases deposition in the more distal small airway whereas high flow rates promote impaction and therefore increase deposition in the large airway. In contrast, the higher the flow rate, the greater the turbulence within the DPID and hence the greater the tendency to break up aggregated drugs. However, turbulence can be increased by varying the construction of the device, rather than increasing the airflow rate, by varying the nozzle's internal diameter, for example, Vidgren et al. (1987) demonstrated that the narrower the air channels with the DPID, the more efficient was drug deposition.

Inhalation mode The site of deposition is also affected by the way in which the aerosol is inhaled. The most important factors affecting the mode of inhalation are flow rate, period of breath-holding, volume of air inhaled and volume of lung at the initiation of inhalation and the position of inhaler in relation to mouth. Deposition by gravitational sedimentation increases as the airflow velocity decreases, so that forceful expiration prior to inhalation, deep inhalation followed by a period of breath-holding at total lung capacity maximises aerosol deposition in the lungs.

Inhalation flow rate Energy input from the patient's inspiratory effort is required to deaggregate micronised drug particles or remove them from a carrier surface and facilitate their deposition in the airway. However, the patient's inspira-

TABLE 2

Peak inspiratory flow rates (PIFR)

Device	PIFR (l min^{-1})		Reference
	Male	Female	
Control	333 (218–519)	214 (130–344)	Timsina et al. (1992) [a]
Rotahaler	217 (152–291)	160 (91–236)	Timsina et al. (1992) [a]
Spinhaler	186 (108–243)	134 (69–196)	Timsina et al. (1992) [a]
Inhalator Ingelheim	70 (38–105)	48 (28– 72)	Timsina et al. (1992) [a]
Turbohaler	82 (61–102)	56 (33– 77)	Timsina et al. (1992) [a]
	59 (25– 93)		Engel et al. (1990) [b]
	60 (26–103)		Brown et al. (1991) [b]

Mean PIFR and ranges observed are given. [a] Healthy volunteers. [b] Male and female patients.

tory flow is difficult to control. A recent study of peak inspiratory flow rate (PIFR) with and without DPIDs in healthy volunteers indicated a large variation between males and females as well as between devices (Table 2; Timsina et al., 1992). Therefore, it may be reasonable to assume that effective drug deposition varies between the sexes, and different DPIs. Pitchard et al. (1986) observed the difference between men and women in regional distribution of inhaled particles (size range 2.5–7.5 μm) for a particular inspiratory flow rate.

The relatively high resistance in the Inhalator Ingelheim® and Turbohaler® devices reduces the flow by in excess of 75% during inhalation (Timsina et al., 1992). Similarly, Engel et al. (1990) observed that when inhalation is performed through the Turbohaler®, maximum inspiratory flow is reduced to about 25%. Recent clinical studies have shown that the patients' inspiratory flow rate is a major factor governing the pulmonary deposition (Auty et al., 1987; Richards et al., 1988). This, in turn, depends upon the patient's disease state and age, sex and height. The mean PIFR in healthy humans was found to be 300 l min^{-1} (Coady et al., 1976) and this is supported by the recent finding that measured PIFRs were 333 l min^{-1} in males and 214 l min^{-1} in females (Timsina et al., 1992). In asthma patients this flow rate may be as high as 200 l min^{-1} (Richards et al., 1988). A more recent study (Spiro et al., 1992) reported that the mean flow rates recorded in asthma patients during submaximal inhalation were 154 l min^{-1} (range 54–234) for an MDI and 126 l min^{-1} (range 59–170) for the Diskhaler®. Therefore, the PIFR without the MDI or Diskhaler® could easily be in excess of 200 l min^{-1}.

The accurate determination of the nature of the airflow (laminar or turbulent) passing through the DPID is very difficult because of the complicated construction of the air channels in these devices. However, it has been shown that the smaller the diameter of the air channel, the more turbulent the airflow (Ward et al., 1992). It has also been pointed out that turbulent airflow is more effective than laminar airflow for dispersing the powder mixture (Moren et al., 1985). Hence Inhalator Ingelheim® and Turbohaler® are more prone to produce turbulent airflow and effective dispersion of powder agglomerates or mixtures than the Spinhaler® and Rotahaler®. However, a reduction in the internal dimensions leads to an increase in the resistance of the inhaler to airflow and thus to difficulties for patients in inhaling through the device at a flow rate which produces optimum drug delivery. Such resistance to flow may be particularly undesirable in children (Pedersen et al., 1990) and severe asthmatics. Therefore, there is a clear need for a DPID which provides high levels of turbulence without further increases in resistance to airflow. This could be achieved by introducing grid(s) of varying mesh sizes. The mesh size and positioning of such grids may influence the respirable fraction generated by the device.

The physical properties of the aerosol cloud

The dry powder formulation The behaviour of drug particles during inhalation is strongly dependent on the formulation of the powder(s).

Particle size Theoretically, aerosols may be targeted to a particular lung site by controlling the particle size. However, the complexity of the respiratory tract and the patient's respiratory dynamics cannot be ignored. Nevertheless, there are several clinical studies which demonstrate the importance of particle size on deposition and clinical response (Morrow, 1974; Curry et al., 1975; Rees et al., 1982; Clay et al., 1986). The behaviour of the aerosol in the human respiratory tract is also influenced by the shape and density of the inhaled particles. It is customary to employ aerodynamic diameter (d_{ae}) as a parameter to describe the size of particles moving in the air stream. The d_{ae} is usually calculated by multiplying the value of the mass median diameter by the square root of the effective particle density. It is difficult to specify an 'ideal' size for aerosol particles partly because it is not certain where the particles should be deposited within the respiratory tract, and partly because of the difficulty of predicting the aerodynamic behaviour of the inhaled particles. The deposition pattern may further be complicated by hygroscopic growth (Scherer et al., 1979), particle agglomeration

(Smith et al., 1980), particle charge (Melandri et al., 1977) and particle concentration (as the concentration of particles increases the inter-particle distance decreases with a greater chance for particle collisions to occur). Most researchers agree that aerosol particles in the size range 1.0–6.0 μm are most effective. Particles larger than 10.0 μm generally deposit in the upper respiratory tract whereas particles less than 0.5 μm d_{ae} are exhaled or adhere to the walls of the mouth during exhalation phase. Ideally, it is important to keep particles in the aerosol between 0.5 and 8.0 μm to maximise their delivery and deposition in the lower respiratory tract (Davies et al., 1976). Therefore, the particle size is a primary determinant, not only of the fraction of aerosol deposited in the particular region but also of deposition site itself.

Presence of a carrier Powder flow properties are also dependent on the particle size distribution. Fine particles generally flow less well than coarse ones. The final formulation must flow sufficiently well to be dispensed from a bulk reservoir in an adequately reproducible dose and be capable of being easily handled in an automatic filling machine to produce the unit dose forms for use in the DPID. The two mutually contradictory requirements i.e. smooth flow properties and minimal oropharyngeal deposition are usually compromised by the use of a suitable carrier particle size. The larger carrier particles (30.0–90.0 μm), which are usually lactose, are incorporated with the micronised drug powder to make it less cohesive and freer flowing, thus making it easier to handle during manufacturing processes and improving the emptying from a gelatin capsule during the patient's inspiratory effort. However, the inclusion of the carrier increases the concentration of the aerosol in the inhaled air and may cause irritation, coughing and even bronchoconstriction in its own right. More importantly, the presence of coarser particles may also impair the penetration of the fine drug particles into the lungs, if the drug particles adhere strongly to the carrier particles. The cohesive forces between drug particles and the adhesive forces between drug and carrier particles are the most critical determinants of the redispersion of micronised drug particles in the inspired air (Byron, 1986) and as a result, the availability of the medicament to the lungs. Thus, when a carrier is added, a compromise between powder fluidisation and lung penetration must be taken into consideration.

The use of the coarser carrier particles has been avoided by using aggregates of drug particles (as in Spincaps®) which can be dispensed and packaged accurately while retaining the ease of deaggregation. Similarly, the micronised drug particles have also been made as loose aggregates by spheronisation as in Bricanyl® Turbohaler®.

Literature reports, concerned with the basic principles governing the generation of medical powder aerosols are scarce. As described above, mixing fine drug particles with a coarser carrier is the most common way of formulating dry powders for inhalation. However, the effect of possible formulation variables, such as surface properties of the carrier, optimum carrier size, optimum drug/carrier ratio, relative humidity, electrostatic behaviour, in relation to the respiratory deposition of the inhaled drug/carrier mixture is not known precisely and these have received very little attention. Investigations which provide a basic understanding of the powder properties and their behaviour in turbulent airstream are much needed.

The design of DPID

As mentioned earlier the design of the DPID appears to have significant influence on the drug deposition pattern within the lungs. It is unlikely that ideal DPID will ever be devised. However, there is no doubt that with better understanding of the limitations of the existing devices and the physical laws governing aerosol behaviour, pulmonary delivery of drugs can be optimised.

A comparison between various powder inhalation devices showed that the pulmonary deposition of radiolabelled SCG delivered from various devices was significantly different (16% for Inhalator Ingelheim® to 6.2% for Rotahaler®) and the difference was attributed to device construction (Vidgren et al., 1987). In another study, Vidgren et al. (1990) reported that the mean, whole lung deposition of SCG was about 9% of

administered dose for a multi-dose DPID and Rotahaler®. However, the multi-dose device was more efficient in dispersing the drug into the alveolar region of the lungs. Furthermore, the fraction of the dose retained in the device was significantly higher for the Rotahaler® than for the multi-dose device. Vidgren et al. (1988) observed that a larger amount of drug is retained in the DPID and on the wall of gelatin capsule compared with a MDI (Table 1). It is perhaps not difficult to understand this difference, since the technical construction of DPIDs is more complex than that of MDI actuators. Furthermore, the incomplete emptying of gelatin capsule and sticking of the cohesive drug powder to the plastic walls of DPIDs may also explain the difference observed.

The dosing system of DPIDs is also important, especially in severe acute situations. For example, an inspiratory flow of 33 l min^{-1} through the Turbohaler® delivered an effective dose (Persson et al., 1988), whereas with the same flow rate through the Rotahaler®, the capsule emptying was unreliable and erratic (Bogaard et al., 1989). On the other hand, even a flow rate of 16–19 l min^{-1} through the Inhalator Ingelheim® was found to produce sufficient bronchodilation in children (Pedersen and Steffensen, 1986). Similarly, there was no significant difference in bronchodilatation after inhalation through the Cyclohaler® at 40 or 80 l min^{-1} (Zanen et al., 1992). This means that severe asthma patients can use DPIs with low inhalation flows with beneficial effects.

Fig. 1 illustrates a schematic diagram of currently available DPIDs and a brief description of these devices is presented below and in Table 3.

In the Spinhaler®, the gelatin capsule is mounted in a rotor upon which are several small fan blades. The capsule is pierced by two small needles by sliding the outer casing of the inhaler relative to the inner casing. When the patient inhales, the capsule rotates rapidly and empties its content. In the Rotahaler®, the capsule is mounted in the far end of the inhaler and is broken in half by twisting the outer and inner parts of the inhaler relative to one another. In the Diskhaler®, a disk containing foil blisters is inserted into the device and each dose is activated by sliding the tray out and in and lifting the rear end of the lid so that the needle punctures the blister. The doses are numbered, making it possible for the patient to know how many doses remain. In the Inhalator Ingelheim® devices the gelatin capsule is punctured by pressing a button which is linked to needles, rendering its contents available for inhalation. the drug is inhaled through the pierced holes of a stationary capsule contained in a narrow vertical chamber. The Cyclohaler® has similar features to Inhalator Ingelheim® device. However, the former device has a longer mouth-piece with a plastic mesh, wider air channels and the capsule is inserted in a narrow horizontal chamber. The Turbohaler®

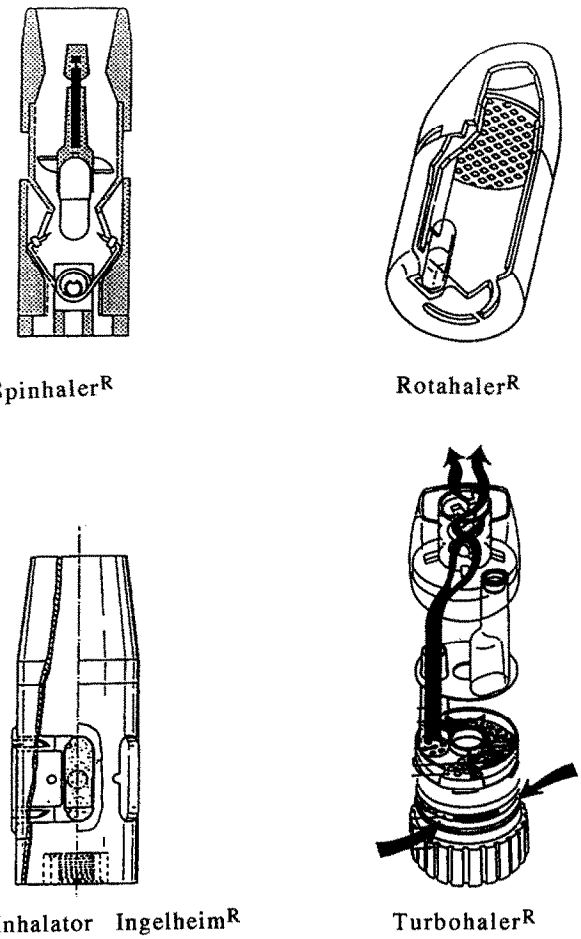

Fig. 1. Some currently available dry powder inhaler devices

TABLE 3

Currently available DPIDs

Device	Drug	Preparation	Carrier present	Dose system
Spinhaler®	sodium	20 mg,	no, loose drug	unit
(Fison)	cromoglycate	Spincaps	aggregates	
Rotahaler®	salbutamol	200, 400 μg	yes, lactose	unit
(Glaxo)	(as sulphate)	Rotacaps	ratio 1:67.5	
	beclomethasone	100, 200, 400 μg		
	dipropionate	Becotide Rotacaps		
Diskhaler	salbutamol	200, 400 μg	yes lactose	unit, 8
(Glaxo)	(as sulphate)	Ventodisks	ratio 1:67.5	blisters in a disk
	beclomethasone	100, 200, 400 μg		
	dipropionate	Becodisks		
	salmeterol	50 μg	unit, 4	
	xinafoate	Serevent	blisters in a disk	
Inhalator	fenoterol	100, 200 μg	yes, glucose	unit
Ingelheim®	hydrobromide	Berotec	ratio 1:24	
Inhalator				
Ingelheim M®				unit, 6
(Boehringer Ingelheim)				capsules
Cyclohaler®	salbutamol	200, 400 μg	yes, lactose	unit
(Pharbita)	(as sulphate)	Cyclocaps	ratio 1:67.5	
Turbohaler®	terbutaline	500 μg	no, loosely	multi
	sulphate	Bricanyl	packed drug	100 doses
			aggregates	
	budesonide	200, 400 μg		50, 100
		Pulmicort		doses

dispenses the drug free from carrier. Each dose is primed by rotating a turning-grip back and forth at the base of the inhaler. The device is fitted with a dose indicator and the device is disposable after the doses have been used.

Within the range of currently available DPID,

TABLE 4

Some of the desirable properties of a DPID

(1)	It should be simple to use (incorporating single hand operation with a comfortable firm grip and simple dose dispensing).
(2)	It must be compact and economical to produce.
(3)	The device should facilitate the delivery of drug particles with only minimal loss in the oropharynx, the device and the exhaled air.
(4)	The device should provide a safeguard against accidental overdose.
(5)	Multi-dose system operated by volumetric dosing principle with mechanical assistance appears to offer a number of advantages when compared to those dependent upon inserting a capsule into a device.
(6)	The device should incorporate a distinguishing feature for partially sighted or blind patients.
(7)	The device should provide maximum aerosolisation with the minimum effort on the part of the asthmatics, especially children and elderly.
(8)	The drug reservoir in a multi-dose DPID should preferably be transparent to indicate the amount remaining.
(9)	The device should allow accurate reproducible dosing of drug particles preferably without the need of a carrier.

it is difficult to assess clinical superiority of one device over another since the response may be patient-specific. However, it can be seen that currently no single device has all of the desirable properties listed in Table 4. There are several examples in patent literature which describe attempts to design new, mainly multidose, DPIDs.

A dry powder device with air-assisted dosing mechanism has recently been patented (patent no. WO 9210229). On actuation, a small amount of air flows through the drug reservoir and dose metering chamber and subsequently the drug powder is filled into the dosing chamber. The metered dose is pushed into the passage through the exit port and carried by the inhaled airstream via the swirl chamber. It is thought that the turbulent airflow in the swirl chamber deaggregates the powdered medicament. Another device (patent no. GB 2165159) contains a storage chamber with 100–200 doses. The dosing unit is comprised of several depressions for measuring the dose. Once dispensed the drug is deposited in a cavity and the inhalation airflow carries the medicament to the mouth-piece and ultimately to the lung. A multi-dose DPI device dispenses its metered dose of dry powder in a cup with holes (patent no. EP 0424790). Another reservoir device with a dosing cavity of predetermined volume is also found in patent literature (patent no. EP 0166294). The metered dose is carried by the inhaled airflow through the screened mouthpiece. All the above four patented DPIDs resemble a conventional MDI in their physical appearance. The possibility of designing a 'true' multidose Diskhaler® is also being examined (patent no: GB 2242134). The device uses a similar drug and lactose formulation to the Diskhaler® but with an increased number of doses in the device (up to 60 or even possibly 100). Each blister on the strip has a peelable lid which is removed automatically with each dose advance and used blisters and lids are wound up separately.

As discussed earlier, with all DPIDs the effectiveness of aerosolisation depends entirely on the patient's inspiratory effort. A major challenge in the future development DPIDs is to decrease the dependence of the devices on the patient's inspiratory flow. To decrease this dependence a consistent and reproducible external energy source must be available for dosing and deagglomeration of the powder.

Two patents have been filed for 'assisted' DPID designs (Schultz et al., 1992). In the first, a 'tape-based' powder inhaler, the drug powder is bound on to a tape, allowing the patient to carry a 'cassette' of medicine. Up to 200 doses can be held in a cassette and a refill can be loaded into the device body. The patient advances the dose by opening the cover of the mouth-piece. During inhalation, a spring-loaded impactor strikes the rear of the tape and the released powder passes through a deagglomerator. Closing the mouthpiece resets the system for the next use. The second prototype device (see above) uses air-assisted deagglomeration where the micronised drug, without a carrier, is metered from a reservoir into a metering hole. At actuation, a small puff of compressed air simultaneously empties the metering hole and disperses the drug powder. These impactor-based and air-assisted mechanisms may overcome the problem of delivery efficiency in relation to patients' inhalation flow rates.

There are several variables to be considered when designing a DPID. The influence of the diameter and the length of the inhalation channel as well as the mouth-piece but the positioning of the mouth-piece for optimum efficacy for DPID are all amongst the parameters which can be varied. Furthermore, the orientation and inclination of the device at the point of operations, and the effect on reproducible dose dispensing has not been reported. Additionally, the design features of the dosing unit (multiple or single cavity) on drug delivery should be investigated.

Conclusion

Encouraging results have been obtained in clinical trials performed to compare the efficiency and acceptability of DPIDs with other inhalation drug delivery systems. DPIs seem to provide a clear advantage over other systems and are widely accepted by both patients and clinicians as an effective means of drug delivery to the lower

respiratory tract and are now an established alternative to MDIs and nebulisers. The development process of DPIs should involve the design of a formulation and a delivery device which provides a maximum redispersion with minimum effort on the part of the user. However, as discussed above, this is not as straight-forward as it may appear and there are many technical difficulties associated with optimising drug delivery to the lungs. It is only by systematically studying the dependence of DPID design, powder formulation and operating variables on the inhalation process that improvements in inhalation drug therapy can be obtained. Therefore, a multi-disciplinary project spread across several academic disciplines, including for example, engineers, powder technologists, inhalation scientists and clinicians may constitute the basis of a rational development and optimisation strategy.

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