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DRUG DELIVERY DEVICES

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INTRODUCTION

The inhaled route of administration is widely accepted as being the optimal way of giving drugs, such as bronchodilators and corticosteroids for the treatment of patients with obstructive airway diseases [1]. Compared with systemic administration, the inhalation route offers a faster onset of action and high *in situ* drug concentrations. This results in a lower required drug dose and subsequent lower rates of side effects [1]. There is a wide array of inhaler devices currently available on the market and these are classified as pressurised metered-dose inhalers (pMDIs), breath-actuated (BA) pMDIs, dry-powder inhalers (DPIs), and soft mist inhalers (SMIs). Each class of inhaler device has pros as well as cons (table 1). It is now recognised that inhalers differ in their efficiency of drug delivery to the lower respiratory tract, depending on the form of the device, its internal resistance, formulation of medication, particle size, velocity of the aerosol cloud or plume and ease with which patients can use the device [2]. Efficiency of drug delivery may also be influenced by patient preference, which in turn

affects patients' adherence with treatment and indeed long-term control of the disease [3]. There seems little point in prescribing an effective medication in an inhaler device which patients cannot use correctly. Thus, the choice of the right inhaler for the patient is just as important as choosing the most effective medication.

PRESSURISED METERED-DOSE INHALERS

The development of the first commercial pMDIs was carried out by Riker Laboratories in 1955 and marketing in 1956. Since that time, the pMDI has become the preferred inhalation device for drug delivery to the respiratory tract to treat obstructive airway diseases. The technology of pMDI has evolved steadily over the period of mid-1950s to the mid-1980s. More recently, the pace of technological developments in the general field of drug delivery to the lungs has accelerated, primarily due to the phase out of the chlorofluorocarbon (CFC) propellants. In fact, the transition from CFC to hydrofluoroalkanes (HFA) propellants has been the impetus for further evaluation of the ►

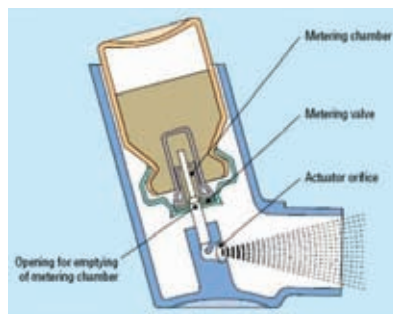


Figure 1. Diagram of the pressurised metered-dose inhaler

technology and performance of propellant driven pMDI. The pMDI has become the most widely used device for delivery inhaled

medications and total worldwide sales by all companies of pMDI products run in excess of \$2 billion per year. The pMDI (fig. 1) consists of an aluminium canister, lodged in a plastic support, containing a pressurised suspension or solution of micronised drug particles dispersed in CFC or HFA propellants. A surfactant (usually sorbitan trioleate or lecithin) is also added to the formulation, in order to reduce the particle agglomeration, and is responsible for the characteristic taste of specific inhaler brands. The key component of the pMDI is a metering valve, which delivers an accurately known

volume of propellant, containing the micronised drug at each valve actuation. Pressing the bottom of the canister into the actuator seating causes decompression of the formulation within the metering valve, resulting in an explosive generation of a heterodisperse aerosol of droplets that consist of tiny drug particles contained within a shell of propellant. The latter evaporates with time and distance, which reduces the size of the particles [4]. Pressurised MDIs have a number of advantages (table 1): they are compact, portable, relatively inexpensive and contain at least 200 metered doses per

Table 1. Advantages and disadvantages of different hand-held inhalation devices

Device	Advantages	Disadvantages
pMDI	Portable and compact Multidose device Quick to use Relatively cheap Cannot contaminate contents Available for most inhaled medications	Contains propellants Not breath-actuated Many patients cannot use it correctly “Cold Freon” effect high oropharyngeal deposition
pMDI + spacer	Easier to coordinate Large drug doses delivered more conveniently than pMDI alone Less oropharyngeal deposition Higher lung deposition than a pMDI	Bulky and cumbersome Require cleaning to reduce electrostatic charge Additional cost to pMDIs Not suitable for all types of pMDI canister
BA-MDI	Portable and compact Multidose device Quick to use Breath-actuated Cannot contaminate contents	Contains propellants “Cold Freon” effect Require moderate inspiratory flow to be triggered
DPI	Portable and compact Quick to use Breath-actuated Usually higher lung deposition than a pMDI Do not contain propellants	Require high inspiratory flow to be triggered May not appropriate for emergency situations Many patients cannot use them correctly Some types are moisture sensitive
SMI (Respimat)	Portable and compact Multi-dose device Probably easier to use correctly than pMDI High lung deposition Does not contain propellants	Not breath-actuated Not currently available in most countries Relatively expensive

pMDI, pressurised metered-dose inhalers; BA-MDI, breath-actuated metered-dose inhaler; DPI, dry-powder inhaler; SMI, soft mist inhaler.

In this article, the main types of hand-held inhalers will be reviewed, together with the advantages and disadvantages of the different types. Although nebulisers are frequently used to deliver inhaled medications, most current designs are bulky and inconvenient, and treatment administration is prolonged. Therefore, they are better categorised as second-line devices for most patients. As they are not true competitors with hand-held inhalers for outpatients, they have not been considered in this article.

canister that are immediately ready for the use. Furthermore, a large fraction (~40%) of the aerosol particles is in the respirable range (mass median aerodynamic diameter <5 μm) and dosing is generally highly reproducible from puff to puff. Despite numerous advantages, most patients cannot use pMDIs correctly, even after repeated tuition [5–7]; this because pMDIs require good coordination of patient inspiration and inhaler actuation to ensure correct inhalation and deposition of drug in the lungs [5–7]. The correct inhalation technique when using pMDIs involves firing the pMDI while breathing in deeply and slowly, continuing to inhale after firing, and then following inhalation a breath-holding pause to allow particles to sediment on the airways [8]. However, patients frequently fail to continuously inhale slowly after activation of the inhaler and exhale fully before inhalation [5–7]. In addition, patients often activate the inhaler before inhalation or at the end of inhalation by initiating inhaler actuation while breath-holding [5–7]. CROMPTON and coworkers [3, 9, 10] showed that the proportion of patients capable of using their pMDI correctly after reading the package insert fell from 46% in 1982 to 21% in 2000, while only just over half of patients (52%) used a pMDI correctly, even after receiving instruction. Of note, incorrect inhalation technique was associated with poor asthma control, with pMDI misusers having less stable asthma control than good pMDI users [11].

Even with correct inhalation technique, pMDIs have a low inherent efficiency, since no more than 20% of the emitted dose reaches the lungs. This is a direct consequence of the rapid velocity and large size of the droplets in the spray, most of which simply impact on the back of the throat thus causing local, as well as systemic side effects due to rapid absorption [1, 2, 4]. Also, pMDIs require

priming if they haven't been used for a lengthy period of time and have no inhalation control mechanism. In addition, pMDIs contain propellant gases which may cause cough, throat irritation, paradoxical bronchoconstriction and the so-called "cold freon effect", *i.e.* stopping the patient inhaling or inhaling *via* the nose when the cold blast of propellants strikes the back of the throat [1, 2]. Another disadvantage of some pMDI is the absence of built-in counters that would alert the patient to the fact that the inhaler was approaching "empty" and needed to be refilled. Furthermore, not all inhaled medications administered *via* pMDI can readily be reformulated with HFA propellants but some of them continue to use CFCs as the propellant system. HFA-134a is an alternative propellant that contains no chlorine and has a residence in the stratosphere lower than CFCs, so that it has substantially less global warming potential than do CFCs. HFA-134a albuterol has been the first HFA-driven pMDI that has received approval in both Europe and the USA. This preparation consists of albuterol suspended in HFA-134a, oleic acid and ethanol; clinical trials have shown this preparation to be bioequivalent to CFC-albuterol in both bronchodilator efficacy and side effects [12]. Moreover, pMDIs containing a fixed combination of beclomethasone dipropionate and the long-acting bronchodilator formoterol in a solution formulation with HFA-134a and ethanol with co-solvent [13] have been recently developed (Modulite technology,

Chiesi, Italy). Interestingly, this formulation dispenses an aerosol that has a particularly small particle size (mass median aerodynamic diameter ~1 μm), that results in an increased dose delivered to the lungs, particularly to the smaller airways, and decreased oropharyngeal deposition, compared with the same dose of drug administered from a CFC-pMDI [13].

pMDI ACCESSORY DEVICES: THE SPACERS

Spacers are extensions to a pMDI with a port at one end to which the pMDI is attached, a facemask or mouthpiece being fitted at the other end. They differ by volume, length, shape, construction material, rigidity (*i.e.*, rigid or collapsible), presence or absence of the valve system, and interface with the airway opening (*e.g.*, mouthpiece, face mask, adaptor to ventilator tubing). Generally, spacers fall into three categories (table 2, fig. 2): 1) open tube spacer; 2) holding chambers, which include a one-way inhalation valve in the mouthpiece, intended to retrain the aerosol within the device until the patient inhales; and 3) reverse-flow devices, in which the spray is fired away from the patients, either into a collapsible bag or into a small volume through which outside air is entrained. Spacers constitute a volume into which the patient actuates the pMDI and from which the patient inhales without necessarily having to coordinate the two manoeuvres [14]. By acting as an aerosol reservoir, these devices ►

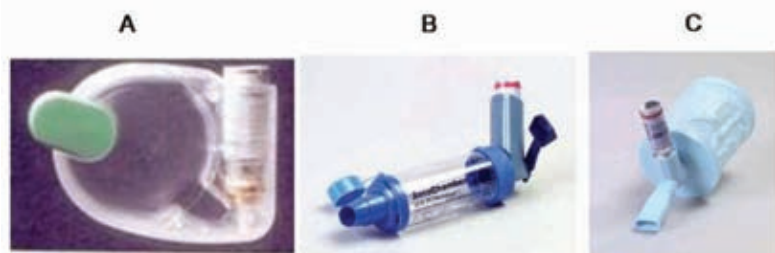


Figure 2. Examples of open tube spacer (the Jet, A), holding chamber (the Aerochamber plus, B) and reverse-flow spacer (Inspirease, C)

Table 2. Characteristics of the main types of spacer devices.

Category	Device	Manufacturer	Volume mL	Material
Tube spacer				
	Boehringer spacer	Boehringer Ing.,Germany	50	Plastic
	Jet	Chiesi, Italy	100	Plastic
	Azmacort	Aventis	110	Plastic
	Aerovent	Monaghan Medical, USA	145	Plastic
Holding chambers				
	Aerochamber plus	Trudell Medical, USA	149	Plastic
	Aerochamber Max	Trudell Medical, USA	198	Plastic
	Vortex	Pari GmbH, Germany	210	Metal
	Optichamber	Respironics Inc, USA	218	Plastic
	FunhHaler	Infamed, Australia	225	Plastic
	NebuChamber	AstraZeneca, Sweden	250	Metal
	Rondo	Leiras, Finland	270	Plastic
	Fluspacer	Menarini, Italy	305	Plastic
	Babyhaler	Allen & Hunburys, UK	350	Plastic
	Volumatic	Allen & Hunburys, UK	750	Plastic
	Nebuhaler	AstraZeneca, Sweden	750	Plastic
Reverse-flow devices				
	Optihaler	HealthScan, USA	70	Plastic
	Aerosol Cloud Enhancer	DHD, USA	170	Plastic
	InspirEase	Schering Co, USA	700	Plastic
	E-Z spacer	WE Pharmaceuticals USA	700	Plastic

From [14] with permission.

slow the aerosol velocity and increase transit time and distance between the pMDI actuator and the patient's mouth, allowing particle size to decrease and, consequently, increasing deposition of the aerosol particles in the lungs [14]. Moreover, because spacers trap large particles, comprising up to 80% of the aerosol dose, only a small fraction of the

dose is deposited in the oropharynx, thereby reducing side effects, such as throat irritation, dysphonia and oral candidiasis, associated with inhaled medications delivered by the pMDI alone [14]. Spacers may improve the clinical effect of inhaled medications especially in patients unable to use a pMDI properly [15]. Indeed, compared with both pMDIs alone

and dry-powder inhalers (DPIs), spacers may increase the response to short-acting β -adrenergic bronchodilators, even in patients with correct inhalation technique [16–19]. On the negative side, spacers represent an additional cost to pMDIs; they are generally bulky, difficult to carry and the encumbrance of some of them ►

may detract from the appeal of pMDIs to the patients, especially among the paediatric population. Some spacers are designed to fit only a single type of pMDI. Moreover, spacers do not completely obviate all errors in inhalation technique; rather, they are the potential for new patient errors, such as incorrect assembly of devices, lengthy delay between pMDI actuation and inhalation from spacer, firing multiple puffs into the spacer before inhaling [14]. Spacers are not immune from inconsistent medication delivery caused by electrostatic charge of the aerosol [14]. The proportion of the drug dose that the patient inhales may vary greatly with different spacers. Data about a spacer, derived from studies with one drug and pMDI, may not apply to other drugs. Changing from one spacer to another may be unimportant with some drugs but be critical for others.

BREATH-ACTUATED MDI

Breath-actuated (BA)pMDIs have been developed to overcome the difficulty with hand–lung coordination posed by conventional press-and-breathe pMDIs. Examples of this type of device include the Autohaler (3M, St Paul, MI, USA), and the Easi-breathe (Teva Pharmaceutical Industries Ltd) (fig. 3). Breath-actuated MDIs contain a conventional pressurised canister, and have a flow-triggered system driven by a spring which releases the dose during inhalation, so that firing and inhaling are automatically coordinated. These inhalation devices can achieve good lung deposition and clinical efficacy in patients unable to use a pMDI correctly because of coordination difficulties [2]. Errors when using BApMDIs are less frequent than when using a standard pMDI [3, 5]. However, BApMDIs do not solve the cold Freon effect and would be unsuitable for a patient who has this kind of difficulty using pMDI.



Figure 3. Examples of breath-actuated pMDIs.

In addition, some of these devices may require a higher inspiratory flow than pMDI for triggering.

The Autohaler is a BA-pMDI that is available with albuterol and beclomethasone in HFA propellant. It has a manually operated lever that, when lifted, primes the inhaler through a spring-loaded mechanism, allowing the aerosol to be dispensed with an inspiratory flow of about 30 L·min⁻¹. Clinical studies have demonstrated that the lung deposition of β -adrenergic bronchodilator administered *via* the Autohaler is similar to that obtained when the drug is correctly inhaled *via* a pMDI and greater than that resulting from conventional pMDIs in patients with poor inhalation technique [20]. Moreover, it can be used effectively by patients with poor lung function, patients with limited manual dexterity and elderly patients [2]. The Easi-Breathe is a novel patient-triggered inhaler that dispenses albuterol and beclomethasone. This inhaler is primed when the mouthpiece is opened. When the patient breathes in, the mechanism is triggered and a dose is automatically released into the airstream. The inhaler can be actuated at a very low airflow rate of ~20 L·min⁻¹, which is readily achievable by most patients [21]. Not surprisingly, practice nurses have found it easier to teach and patients to learn to use than a conventional pMDI [21]. In vitro studies have shown that particle size distribution and percentage of

respirable fine particle obtained using the Easi-Breathe device was similar to those obtained by using the conventional pMDI [22], although comparative clinical efficacy data are not yet available.

DRY POWDER INHALERS

Modern powder inhalers were first introduced in 1970 and the earliest models were single-dose devices containing the powder formulation in a gelatine capsule, which the patient loaded into the device prior to use. Since the late 1980s, multi-dose DPIs have been available, giving the same degree of convenience as a pMDI. DPIs (fig. 4) are delivery devices containing drugs in powdered formulation that have been milled to produce micronised particles in the respirable range. These delivery devices allow the particles to be de-agglomerated by the energy created by the patient's own inspiratory flow [23, 24]. The powdered drug can be either pure or blended with large particle size excipient (usually lactose) as a carrier powder [23, 24]. The empty condition is generally apparent, alerting the patient to the need for replacement. Some DPIs, such as the Diskus (GlaxoSmithKline, CITY, UK) or the Turbuhaler (AstraZeneca, CITY, Sweden), have a multidose capacity. These multidose DPIs fall into two main categories: they either measure the dose themselves (from a powder reservoir) or they dispense individual doses which are pre-metered into blisters by the ▶

Table 3. Characteristics of the main dry-powder inhalers

Device	Company	Type	Dose counter	FPF airflow independence	Device resistance	Advance warning of last dose	Protection from humidity	Lactose carrier (taste feedback)	maximum number of doses
Aerohaler	Boehringer Ingelheim	Single-dose	n. a.	-	+++	n. a.	-	✓	6 (blister pack)
Aerolizer	Novartis	Single-dose	n. a.	-	+	n. a.	✓	✓	1
Clickhaler	Innovata Biomed	Multi-dose	✓	✓	+++	✓	-	✓	200 (resevoir)
Diskus (Accuhaler)	GlaxoSmith-Kline	Multi-dose	✓	✓	++	✓	✓	✓	60 (blister pack)
Easyhaler	Orion Pharma	Multi-dose	✓	-	++++	-	✓	✓	200 (resevoir)
Handihaler	Boehringer Ingelheim	Single-dose	n. a.	-	++++	n. a.	✓	✓	1
Jethaler	Hitachi	Single-dose	n. a.	-	+++	n. a.	-	✓	200 (resevoir)
Novolizer	Meda Pharma	Multi-dose	✓	✓	++	✓	✓	✓	200 (resevoir)
Pulvinal	Chiesi	Multi-dose	-	✓	++++	✓	✓	✓	200 (resevoir)
Spinhaler	Aventis	Single-dose	n. a.	-	+	n. a.	-	-	1
Turbuhaler	AstraZeneca	Multi-dose	✓	-	++++	✓	✓	✓	200 (resevoir)
Twisthaler	Schering Plough	Multi-dose	✓	-	+++	✓	✓	✓	120 (resevoir)

3: present; -: absent; n.a.: not applicable; +: low; ++: medium; +++: high; ++++: very high; FPF, fine particle fraction; adapted from www.admit-online.info, with permission.

manufacturer. Turbohaler and Diskus, respectively, are representatives of the former and latter categories, although many other different designs are presently in development.

Several DPIs are available (table 3) and, generally, they do have many advantages over pMDIs. Dry powder inhalers are actuated and driven by the patient's inspiratory flow; consequently, DPIs do not require propellants to generate the aerosol, as well as coordination of inhaler actuation with inhalation [23, 24]. However, a forceful and deep inhalation through the DPI is needed to de-aggregate the powder formulation into small respirable particles as efficiently as possible and, consequently, to ensure that the drug is delivered to the lungs [23, 24]. Although most patients are capable of generating enough flow to operate a DPI efficiently [25], the need to inhale forcefully and, consequently, generate a sufficient inspiratory flow, could be a problem for very young children or patients with severe airflow obstruction.

Although DPIs offer both the patients and physicians advantages over pMDIs, they do have some limitations of design, cost-effectiveness and user-friendliness. For instance, single dose DPIs require that single doses are individually loaded into the inhaler immediately before use. This is inconvenient for patients and does not allow direct dose counting. In addition, the inhalation manoeuvre has to be repeated until the capsule is empty, which may give rise to under-dosing and to high dose variability. Furthermore, high humidity may cause agglomeration of the particles of powder thus reducing the delivered dose. Some DPIs do not have any triggering mechanism, which makes optimal drug delivery entirely dependent on an individual patient's uncontrolled inspiratory manoeuvre. Although DPIs are considered easier to use than pMDIs, a systematic literature review revealed that up to 90% of

patients did not use their DPI correctly [26]. Common errors made by patients were lack of exhalation before inhalation, incorrect positioning and loading of the inhaler, failure to inhale forcefully and deeply through the device, and patients' failure to breath-hold after inhalation [26]. Furthermore, unless clearly instructed, some patients did not know that they must firmly seal their lips around the mouthpiece, causing them to attempt an "open mouth" inhalation technique that will not deliver any dose [26]. All these errors may lead to insufficient drug delivery, which adversely influences drug efficacy and may contribute to inadequate disease control [26].

SOFT MIST INHALERS

The development of SMIs has opened up new opportunities for inhaled drug delivery. Technically, these inhalation devices fall within the definition of a nebuliser, as they transform aqueous liquid solution to liquid aerosol droplets suitable for inhalation. However, at variance with the traditional nebuliser designs, SMIs are hand-held multi-dose devices that have the potential to compete with both pMDIs and DPIs in the portable inhaler market. At present, the only SMI currently marketed in some European countries is the Respimat (Boehringer Ingelheim, Ingelheim, Germany; fig. 5). This device is a propellant-free, multidose inhaler that emits a metered dose of drug solution of 15 µL. The Respimat does not require propellants since it is powered by the energy of a compressed spring inside the inhaler [27]. Individual doses are delivered *via* a precisely engineered nozzle system as a slow-moving aerosol cloud (hence the term "soft mist") [27]. Scintigraphical studies have shown that lung deposition is approximately double that from a CFC-driven pMDI [27]. More importantly, the aerosol emitted from Respimat is released very slowly, with a velocity of approximately four-times less ►



Figure 4. Variety of dry-powder inhalers for drug delivery.

than that observed with a CFC-driven pMDI [27]. This greatly reduces the potential for drug impaction in the oropharynx. In addition, the relatively long duration over which the dose is expelled from Respimat (about 1.2 s compared with 0.1 s from pMDIs) would be expected to greatly reduce the need to coordinate actuation and inspiration, thus improving the potential for greater lung deposition. Although Respimat has been used relatively little in clinical practice to date, clinical trials seem to confirm that drugs delivered by the Respimat are effective in correspondingly smaller doses in patients with obstructive airway disease [28].

CHOICE OF AN INHALER DEVICE

More than 100 inhaled device-drug combinations are currently available

on the market. The number is likely to increase as more CFC-free pMDIs become available and companies develop device for generic drugs. This choice increases the level of confusion experienced by clinicians, nurses and pharmacists when trying to choose the most appropriate device for each patient. Thus, physicians' experience is amongst the most important factor which influences decision making for inhaler choice in asthma therapy. Inhalers are often prescribed on an empirical basis rather than on an evidence-based approach. Following their own experience, doctors are much more likely to prescribe the same old inhaler which they have always prescribed, rather than new, improved inhalers entering the market.

Criteria to be considered when choosing an inhaler device differ, depending on the audience

addressed [29]. From the viewpoint of the inhalation technologist, consistent and safe dosing, sufficient drug deposition and clinical effect guide the inhaler choice. The patient's ability to inhale through the device, the intrinsic airflow resistance of the device and the degree of dependence of drug release on inspiratory airflow variability are all important determinants when considering constancy of dosing [29]. From the point of view of the clinician, clinical efficacy and safety should be the most important determinants to consider when choosing an inhaler [29]. However, in the real world, clinical efficacy must be balanced against cost-effectiveness and inhalers with insufficient performance may be prescribed simply because they are cheap. Patients' preferences and acceptance of the inhaler should also be considered when deciding



Figure 5: The Respimat soft-mist inhaler

on a specific inhaler, since these will have major implications for compliance.

Several general principles of inhaler selection and use have recently been reviewed in detail by a joint committee of the American College of Chest Physicians and the American College of Asthma, Allergy and Immunology [30]. Briefly, pMDIs are convenient for delivering a wide variety of drugs to a broad spectrum of patients. For patients who have trouble coordinating inhalation with inhaler actuation, the use of spacer may obviate this difficulty, though most of these devices are cumbersome to store and transport [30]. The use of spacer, however, is mandatory for infants and young children. DPIs are usually easier for patients to handle than pMDIs and a growing number of drug types are available in several DPI formats [30]. The key issue for dry powder inhalation is adequate inspiratory flow rate. The most ill patients and the very young may not be candidates for a DPI. While not included in this review, a nebuliser could be used as an adequate alternative to pMDI with a spacer by almost any patient in a variety of clinical settings from the home to the intensive care unit. However, nebulisers are more expensive, cumbersome, and relatively time-consuming to use compared to hand held inhalers.

These attributes should limit the use of nebulisers whose effect can be matched by hand-held devices in almost all clinical settings.

Recently, the Aerosol Drug Management Improvement Team (ADMIT), a consortium of European respiratory physicians with a common interest in promoting excellent delivery of inhaled drugs, was formed with the remit of examining ways to improve treatment of asthma and COPD in Europe [31]. ADMIT recommends that instructions for correct inhalation technique for each inhaler device currently on the market should be compiled by an Official Board with instructions made readily accessible on the web [7]. Local asthma associations and patient groups could also be involved in promoting the importance and teaching and reinforcing of correct inhalation technique. Information could be disseminated by the use of dedicated literature, school visits by healthcare professionals and pharmacists, as well as through patient advocacy groups [7].

CONCLUSIONS

To date, advancement in management of obstructive airway diseases, such as asthma and COPD, has been pharmacologically driven rather than device-driven. Since it is likely that in the future inhaled bronchodilators and corticosteroids will remain the cornerstone of obstructive airway diseases therapy, development of inhalers may become more important than development of new drugs. Problems with drug delivery have been identified due to inappropriate use of inhaler devices, particularly pMDIs where patients need to coordinate inhaler activation with inspiration. However, as inhalation is likely to remain the delivery route of choice for the foreseeable future, there is a need to develop inhaler devices which are easy to use and deliver ►

a consistent dose of drug to the lungs which may improve patient compliance with treatment leading to better control of the disease. Continued and repeated education of both health care professionals and patients in correct inhalation

technique is essential, and the results checked at regular intervals by a member of medical staff. Substantial changes in educational efforts are clearly required and should be particularly addressed towards the general practitioner

and nurse who in turn teach patients how to use their inhaler correctly. Finally, it is important to remember that an inhaler should only be prescribed with the absolute certainty that the patient can use it correctly. ■

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