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Innovations and perspectives of metered dose inhalers in pulmonary drug delivery

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Abstract

The phase-out of chlorofluorocarbons (CFCs) has spurred the development of alternative pulmonary drug delivery systems to pressurized metered dose inhalers (MDIs), such as dry powder inhalers and pocket size nebulizers. Reformulation of CFC–MDIs with hydrofluoroalkanes (HFAs) 134a and 227 is also an opportunity to improve these widely accepted systems with respect to ease of handling, compliance, dosing, and more reliable and efficient lung deposition. MDIs have the advantage to protect the drug substance from external parameters such as temperature and humidity and to meter and de-agglomerate the drug independent from patients inspiratory flow rates. Novel formulation technologies combined with improved valves and actuators should help to overcome dose uniformity and priming problems and will increase the percentage of fine particles capable of reaching the deeper regions of the lungs. Spacer mouthpieces can reduce the cold freon effect and undesired oropharyngeal deposition caused by the rapid evaporation of the propellant and plume velocity of the aerosol cloud. More advanced delivery devices may allow the patient to inhale at predetermined flow rates (fast/slow) to target the deposition of fine drug particles (1–6 μm) to specific sites into the lungs. Breath-actuated devices make these systems more effective and patient friendly. The above features in combination with numerical counters showing the remaining number of shots, and built-in blocking mechanisms to avoid tail-off dependent dose uniformity problems of the last labeled shots, should help to improve both acceptance and compliance of pMDIs compared to other inhalation devices. However, only those inhalation systems, which are accepted and appreciated by patients and offering an ambulatory treatment at reasonable cost, will be successful in a more and more competitive market. These issues must be considered in the development of future devices and formulations.

Keywords: MDIs; Fine particle dose; Lung deposition

1. Introduction

Asthma and chronic obstructive pulmonary disease (COPD) can be treated advantageously via the inhalation route since active substances, such as beta-agonists, anti-cholinergics, corticosteroids

Abbreviations: CFCs, chlorofluorocarbons; HFAs, hydrofluoroalkanes; FPD, fine particle dose; MMAD, mass median aerodynamic diameter; GSD, geometric standard deviation; MDI, metered dose inhaler; DPI, dry powder inhaler.

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and mast cell inhibitors are available directly at the target cells in the lungs (Byron and Patton, 1994). The specific anatomy of the lungs require that compounds are delivered as 'fine aerosols' with a particle size range of $\sim 0.5–6$ μm. Unlike other dosage forms, such as tablets, dose availability from an inhalation device is a result of metering and dispensing in coordination with the patient's inspiratory cycle. Contrary to other routes of application, successful lung delivery depends on a patient's ability to operate the inhalation device in a proper way (Rubsamen, 1995; Newman, 1996). Thus, medicament deposition is not only affected by mechanical drug delivery from the device, but also by its ease of use and 'friendliness to the patient'. The patient must play an active role since inhalation technique, coordination, and compliance will decide whether drug therapy via the pulmonary route is successful or not.

Generation of therapeutic aerosols (Wolfe and Niven, 1994; Dolovich, 1995) producing particles targeting the lungs can be achieved by nebulizers, metered dose inhalers (MDIs) and dry powder inhalers (DPIs). Although only $\sim 5–30\%$ of the total aerosol dose delivered for instance from a MDI or DPI is deposited in the lower respiratory tract (Dolovich, 1995). Doses required to achieve a therapeutic effect are normally only one tenth to one fifth compared to an oral dose. Since portal circulation as well as first pass effect can be avoided, undesirable systemic side effects can be minimized compared to oral drug administration. Despite the development of alternative aerosol drug delivery systems such as multidose DPIs (Brindley et al., 1995; Hill et al., 1996; Smith, 1997; Keller et al., 1997b) and pocket size nebulizers (Clark, 1995; Zierenberg et al., 1996; De Yong et al., 1998), MDIs are by far the most popular inhalation system in the treatment of asthma. The phase-out of chlorofluorocarbons (CFCs) has stimulated the technical progress to improve the performance characteristics of MDIs (Leach, 1995; Smith, 1995; Leach, 1996; Elvecrog, 1997; Dalby et al., 1998; Heald et al., 1998; Lewis et al., 1998; Richards et al., 1998) that may help to support, in the future, their widely accepted use as reliable and cost effective treatment for local and systemic pulmonary drug delivery. Parameters and factors affecting the performance of MDIs as well as developments and trends to improve them (Marshik et al., 1995; Rubsamen, 1995; Upchurch, 1996; Dalby et al., 1998; Heald et al., 1998; Lewis et al., 1998) will be outlined and discussed below.

2. Pros and cons of metered dose inhalers

The MDI is currently the most widely used inhalation delivery device primarily due to its portability, durability, reliability, long shelf life, microbial robustness (Meier et al., 1996), cost effectiveness and ease of use especially in critical situations. However, despite these advantages, there are some weaknesses (Newman, 1996; Keller et al., 1997a; Howlett, 1998):

- variation in dosing dependent on shaking, priming, actuation time and can content;
- cold feeling after actuation due to the immediate evaporation of the propellant;
- high oropharyngeal deposition due to the ballistic component of the aerosol cloud;
- coordination problems with respect to actuation and inhalation;
- highly variable and sometimes low deposition in the peripheral regions of the lungs ($\sim 5–25\%$ of the labelled dose) dependent on the inhalation maneuver;
- lack of a clear indication of remaining number of doses in the canister.

The CFC-ban turned out to be a challenge (Leach, 1995; Smith, 1995; Leach, 1996) and an opportunity to improve the performance of MDIs regarding the above mentioned delivery drawbacks. Problems may occur especially in those cases where the same in-vitro and in-vivo performance of a CFC-driven MDI has to be matched. Due to the different physical properties of hydrofluoroalkanes (HFAs) such as pressure, density, solvency compared to CFCs new HFA-powered MDIs require complex re-formulation and the use of new valve-types, actuators and mouthpieces (Keller et al., 1997a). A higher vapor pressure usually results in a finer aerosol with a greater initial forward velocity causing a higher

oropharyngeal deposition. This can result in an increased deposition to the whole lung, seen mainly in the central airways (Dolovich, 1995). Smaller metering volumes may also give a finer aerosol with higher respirable fractions and more peripheral lung deposition. Respirable fraction may decline with increasing volume of the metering chamber and increasing drug concentration per shot (Dolovich, 1995). A new HFA 134a MDI can be more uniform and less dependent on actuation number or can fill volume than a corresponding CFC-system (Leach, 1995; Smith, 1995; Leach, 1996; Elvecrog, 1997). However, a comparison of the in-vitro performance of Salbutamol MDIs powered by CFCs, HFA 134a or 227 showed differences in dose-uniformity and suspension homogeneity due to the differences in formulations (propellants), valve-types and mouthpiece/actuators (Keller et al., 1997a).

2.1. Factors affecting efficacy and use of metered dose inhalers

Improvements can be expected for those parameters affecting quality of the spray pattern, the emitted and respirable dose, and the handling/manageability of a MDI by the patient. This includes formulation aspects (suspension or solution), excipients, selection of improved valves, actuators, nozzles, mouthpieces, and auxiliary add-on devices such as spacers (Dolovich, 1995; Leach, 1995; Smith, 1995; Upchurch, 1996; Elvecrog, 1997; Keller et al., 1997a; Heald et al., 1998) and breath triggered actuators (Marshik et al., 1995; Rubsamen, 1995). Most important, however, is the impact of the correct handling by the patient (Newman, 1996). Thus, pulmonary drug delivery by MDIs will be successful if parameters such as those listed in Table 1 are adequately optimised and controlled.

New Pharmacopoeial monographs as issued in USP XXIII and the latest issue of Ph. Eur. and the guideline III75462/93 issued by the CPMP (Commission of the European Communities), describe testing requirements, protocols, and specifications for aerosols (Rogers and Ganderton, 1995), especially HFA-MDIs (Summers, 1998). The guidance for industry on MDI and DPI drug products published by the FDA November 13, 1998 will make it very difficult to approve inhalation products in the USA. A possible consequence of these requirements is that the replacement of CFC-driven MDIs by non-ozone depleting propellants such as HFA 134a and/or 227 is a time consuming and costly effort.

2.2. Effect of formulation and mouthpiece design on particle deposition

The replacement of CFCs in marketed MDIs primarily focused on the development of 'bioequivalent generic' non-CFC MDIs essentially similar with branded products (Rogers and Ganderton, 1995; Keller et al., 1997a) such as

Table 1
Parameters affecting quality, handling, use, efficiency and compliance of MDIs

Formulation aspects	Valve components	Actuator	Handling	Add-on devices	Patients aspects
Particle size	Valve-volume	Housing	Priming	Integrated mouthpiece	Storage conditions
Concentration	Valve design	Orifice diameter	Shaking	Large volume spacer	Handling conditions
Propellant mix co-solvent	Stem design	Nozzle design	Time between multiple actuation	Breath actuation	Inhalation maneuver
Excipient	Stem diameter	Mouthpiece design	Force for actuation	Breath coordination	Taste of formulation
Stability homogeneity	Gaskets	Drug build-up cleaning	Actuation time	Breath control	Device acceptance

Ventolin® or Becotide®. However, during product development, formulators were confronted with unexpected problems such as insufficient solubility of surfactants in the new propellants, incompatibility of the new propellants with valve gasket materials, water uptake (Williams and Tscherevatchenkoff, 1998), necessity to use smaller spray exit orifice diameters (Keller et al., 1997a; Lewis et al., 1998), etc. These problems on the other hand were a challenge to look for alternatives and formulation technologies used years ago in the development of MDIs. As described first in the US-patent 2.885.427 from 1959, a drug can be dissolved in a propellant/solvent (ethanol) blend, provided no chemical degradation occurs. Hence, it was apparent to check if solutions rather than suspensions could be an alternative for compounds such as beclomethasone-dipropionate (BDP) soluble and stable in HFA/ethanol blends. 3M was one of the first companies which published the reformulation of BDP dissolved in an ethanol/134a blend delivering a respirable fraction (i.e. fractions less than 4.7 μ) of 58% of the ex-actuator dose and a median mass aerodynamic diameter (MMAD) of ~1.1 μ (Leach, 1996). Such an extra-fine BDP–MDI developed by 3M Health Care Ltd. (Loughborough, UK) claims to show the same clinical effects at half the dose of a CFC-suspension formulation (Leach, 1996).

A novel and innovative non-CFC MDI-technology (SkyePharma AG, Muttenz, CH) was developed to increase the fine particle dose (FPD) of non-CFC MDIs formulated either as solution or suspension. BDP being formulated as a non-CFC solution MDI shows similar results compared to those reported by 3M as can be seen from Table 2. The data indicate that, compared to the CFC-driven Becotide®, the increase in FPD is ~2.3-fold, with a reduction in the undesired 'USP-throat' deposition in the cascade impacter. This is due to the generation of fine droplets having a significantly smaller particle size (MMAD) than the particle size of the sprayed dose from the reference product (~1.4 μm versus 3.1 μm).

The FPD of a budesonide and di-sodium-cromo-glycate (DSCG) non-CFC suspension is shown in Table 2 compared to Pulmicort® and Intal®. FPD of a novel budesonide MDI is increased by approximately two-fold associated with a decrease in drug deposition on the USP induction sampling port to about the same extent, whereas MMAD is slightly reduced (~3.1 μm compared to 4.5 μm). Compared with Intal®, the FPD of a novel non-CFC DSCG formulation is approximately two-fold with a similar MMAD. The deposition on the USP-induction sampling port is higher and the mouthpiece deposition smaller compared to the CFC reference product. This is different to the deposition pattern shown by the budesonide formulation.

Aside from the formulation, the geometry, design and orifice diameter of the actuator have an effect on the deposition pattern as it is shown for another DSCG batch (802/345-01R) fitted with an Intal-, Boehringer Ingelheim-, and Skye- actuator-mouthpiece (see Fig. 1). In general, the smaller the orifice diameter, the lager the FPD (Lewis et al., 1998), but with very small spray exit diameters there may be a higher risk of clogging if patients do not follow cleaning instructions. It must be considered in this context, that the manufacture of orifice diameters of 0.25 mm and special nozzle designs with high atomization efficiency is a complex task that requires tight quality control to avoid problems (Keller et al., 1997a).

2.3. Current and future metered dose inhalers improvements

Reduction of undesired oropharyngeal deposition and the cold freon effect can be achieved by added spacers or integrated spacer mouthpieces realized with Azmacort® MDI containing 200 μg triamcinolone-acetonide per actuation (Lewis et al., 1998) or the AeroHaler (Bespak, UK) in combination with flunisolide MDIs (Richards et al., 1998). A more compact concept is realized with Spacehaler® (Evans Medical, Leatherhead, Surrey KT227PQ, UK). A vortex technology reduces both the speed of an emitted CFC aerosol cloud from ~30 to 2 m/s. and the deposition of salbutamol particles on the 'USP-throat' of an Andersen Cascade impactor from ~50 to 5% (Upchurch, 1996). The FPD output with three commonly used MDIs in combination with in-line

Table 2
Aerodynamic particle deposition of novel non-CFC MDI-formulations containing BDP, budesonide, and DSCG compared to Becotide® 100, Pulmicort® and Intal® powered by CFCs[a]

Product Batch-no.:	Becotide 100® 10072926	BDP 809/L86-04	Pulmicort® YK 702	Budesonide 821/372-05	Intal® FEF2E	DSCG 802/352-01
Propellant formulation label claim	CFCs suspension (100 μg)	Non-CFCs solution (100 μg)	CFCs suspension (200 μg)	Non-CFCs suspension (200 μg)	CFCs suspension (1000 μg)	Non-CFCs suspension (1000 μg)
Mouthpiece (μg)	16.6	7.8	21.4	33.4	419.3	116.8
USP-throat (μg)	55.2	22.0	114.0	46.7	385.7	488.4
FPD (μg)	26.9	60.8	43.3	86.2	147.8	300.0
FPF (%)	26.9	60.8	21.7	43.1	14.8	30.0
MMAD (μm)	~3.1	~1.4	~4.5	~3.1	~4	~3.8
GSD	1.63	1.87	1.63	1.55	1.81	1.65

[a] Aerodynamic particle size distribution was assessed by an Andersen 8-stage cascade impactor according to USP 23 on puff nos. 11–30 and 178–197 from three cans, each. The active compounds were assayed from all sample solutions by HPLC and UV-detection. FPD/FPF was calculated from deposition to stages 2–7+filter, respectively. MMAD and GSD were calculated in a graphical manner from corresponding log probability plots.

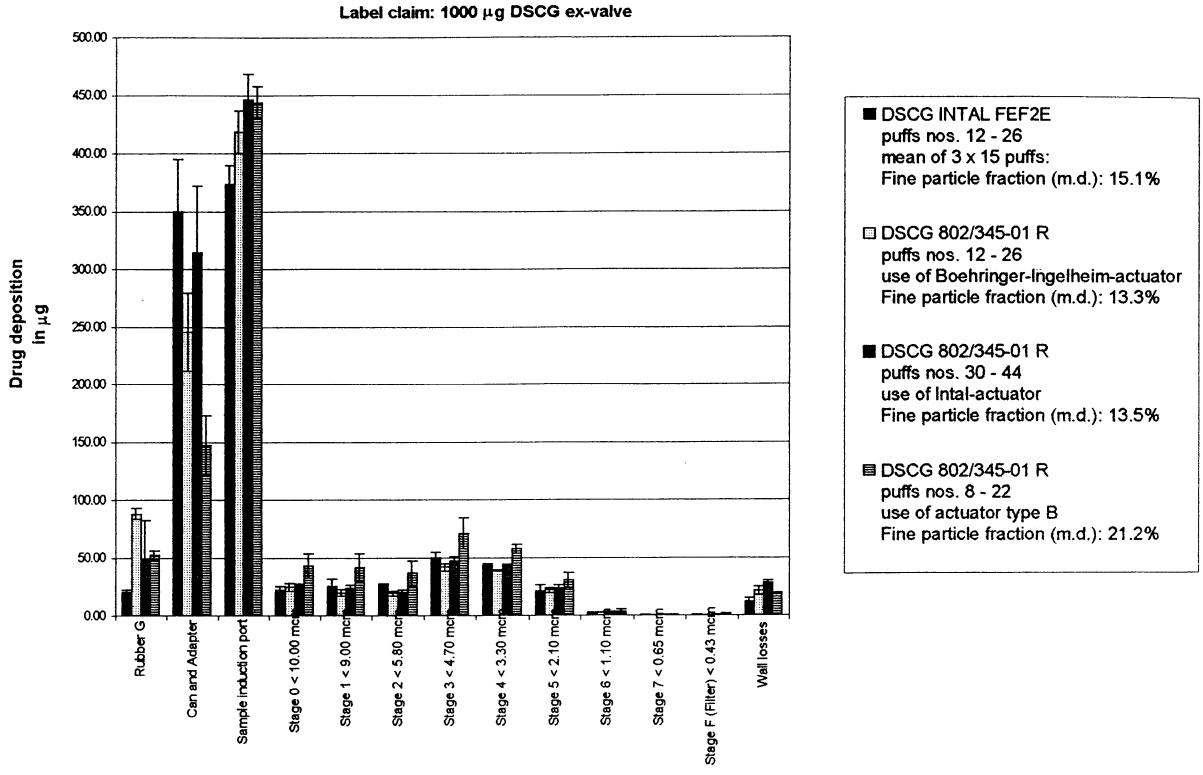

Fig. 1. Effect of different mouthpieces (Boehringer Ingelheim, Intal and Skye-actuator B) on the deposition pattern of DSCG-batch 802/345-01R compared to Intal® when 15 shots each were fired into an 8-Stage Andersen Cascade impactor (ACI) fitted with a USP induction sampling port. Fine particle fractions (FPF) were calculated from stages 2–7 + filter as a percentage of the metered dose set as 100%.

spacer devices (Dalby et al., 1998) was higher with the OptiVent® (HealthScan Products Inc., Cedar Grove, NJ) than with the AeroVent® (Monaghan Medical, Plattsburgh, NY).

Breath actuated devices, like the Autohaler® (16; 3M Health Care Ltd, Loughborough LE111EP, UK) and Easi-Breathe® in combination with the Optimiser (Baker/Norton, Harlow Essex, CM195TJ, UK) can be very helpful to overcome problems associated with handling and operation of MDIs by patients. In addition, it is most likely that due to reproducible actuation a more uniform dose is released than by manual actuation. Thus, less variation regarding the emitted dose may be accomplished.

Gamma scintigraphy studies have demonstrated reduced delivery at inspiratory flow rates exceeding 60 l/min with increased deposition of the aerosol in the central airways (Dolovich, 1995; Richards et al., 1998). Clinical response and pharmacokinetic measurements of MDIs inhaled at fast and slow rates indicate a more peripheral deposition and higher drug absorption at inspiratory flow rates of ~30 l/min (Rubsamen, 1995; Farr et al., 1996). These results demonstrate that the inhalation maneuver can affect whether a drug is directed more towards central or peripheral deposition, and this may change the balance between primarily a topical effect (e.g. bronchodilatation) or promoting systemic absorption, depending on the drug substance. These aspects should be considered for efficient and reliable drug therapy.

SmartMist®, a microprocessor controlled device (Aradigm/Miris Medical Corporation Hayward, CA, USA), is said to provide the means for

analyzing the inspiratory flow profile after automatically actuating an aerosol from an MDI based on predefined conditions of flow-rate and cumulative inhaled volume met by the patient (Rubsamen, 1995).

Consequently, a possible future step for controlled pulmonary drug delivery are auxiliary devices which are capable of delivering a dose of medicament at a preset optimal inspiratory flow that preferentially targets either the central or peripheral lung region. Additionally, such devices should assure that oropharyngeal deposition is minimized.

3. Systemic drug delivery via pressurized metered dose inhalers

Propellant driven aerosols can be used for the systemic delivery of peptides, e.g. the LHRH analogue leuprolide (Wood and Knowles, 1994), proteins (e.g. bovine gammaglobulin), vaccines to the respiratory tract and DNA-plasmids (Brown and Pickrell, 1995). Selected surfactants with solubility in aerosol propellants may be utilized to produce small particle size aerosols of antigenically intact proteins. They can be prepared by lyophilizing aqueous solutions of surfactants and proteins and suspending the resultant material in the propellant, where the protein may exist in 'reverse micelles' surrounded by small quantities of water and a molecular layer of surfactant molecules (Brown and Pickrell, 1995). The sprayed particles or droplets of an aerosol cloud having a size distribution with a MMAD of less than 1.5 μm will be deposited preferentially in the peripheral lung, possibly leading to sufficient systemic absorption to produce the desired therapeutic effect. This was shown in a study with aqueous morphine-sulfate solution (25 mg/ml, equivalent to a loaded dose of 1.1 mg) administered via inhalation by AERx (Farr et al., 1996).

For systemic drug delivery, control of the particle size range of the emitted dose within $\sim 1-2.5$ μg, should assist in targeting of the aerosol cloud, preferably to the alveolar region where drugs can be absorbed more efficiently into the systemic circulation. These aspects are important for pulmonary delivery of potent analgesics, e.g. fentanyl, formulated as MDI fitted with a valve that has temporal and metering control mechanism (Purewal et al., 1990).

The examples given above show that pulmonary drug delivery is a viable alternative to parental administration of some drugs. However, variability issues may have to be addressed and better controlled, e.g. by reducing oropharyngeal deposition and control of aerosol generation during inhalation with respect to inhaled flow rate and volume (Rubsamen, 1995).

4. Regulatory aspects

Approval of inhalation products requires submission of data, which are the result of extensive and expensive in-vitro and in-vivo testing. As a consequence, proposals for new testing methods, specifications, and guidelines to demonstrate qualitative and therapeutic equivalence of generics versus innovator products (Rogers and Ganderton, 1995) were discussed at many scientific meetings (Summers, 1998). Since the valve is arguably the most critical part of an MDI system, further requirements regarding testing of valve extractables, dose uniformity, and respirable particles were specified in the CPMP-guidelines (Commission of the European Communities) and the current edition of the European Pharmacopoeia.

Although generic salbutamol MDI is marketed in Europe and other countries, many years passed before the FDA approved generic salbutamol MDIs (synonym albuterol) for the US market. This raises the question of how best to assess the performance and quality of inhalation products and the criteria that must be met to approve them (Commission of the European Communities; Rogers and Ganderton, 1995; Summers, 1998). Since drug delivery via inhalation is beneficial and advantageous especially in the treatment of pulmonary diseases, a more reasonable approach and consensus by the agencies, health group organizations, and industry is needed to specify the type of data and requirements necessary for regulatory approval. However, the recent guideline on MDI and DPI drug products published by the FDA is

contra-productive and undermines the attempts to harmonize test methods and specifications.

Dose labeling is still an unresolved problem and difficult to define. Attempts have been made to improve characterization of aerosol efficiency since the label claim does not appear to provide any valuable information with respect to the dose administered and available to the patient. A future goal might be the labeling of the dose which is deliverable from a device as a respirable dose according to a world-wide accepted standard impactor system with distinct cut-off sizes at various flow rates showing better in-vitro and in-vivo correlation's than current impactors. Alternatively, Thiel has proposed the use of a respirability index that reflects the drug amount discharged from an inhaler, that will reach the lungs, more closely compared with FPD fraction (FDF). It is defined as an estimate of the percentage of drug delivered from an inhaler that will be deposited in the lungs which one obtains from Stahlhofen–Rudolf calculations using values for inhaled volume, inspiratory flow-rate, breath-hold, along with measured values for MMAD, GSD and non ballistic fraction for that discharge (Thiel, 1997).

5. Discussion and conclusion

Within the last few years, it has been recognized that inhalation therapy could become more than just a simple route of administration to treat asthma and related diseases. Inhalation therapy is in the midst of a renaissance due to a deeper understanding and awareness of pulmonary functions and diseases such as asthma, emphysema, COPD, and cystic fibrosis. In addition to the delivery of the traditional therapeutics like beta-adrenergic agonists, anticholinergics, corticosteroids, the therapeutic effects of other well-known substances such as heparin (Köhler, 1994), amiloride, and furosemide are being investigated when administered via the pulmonary route. New drug entities such as leucotriene inhibitors, cytokinin-, elastine-, tachykinine-, bradykinine-, endotheline- antagonists and gene vectors, are potential candidates for modern local lung therapy (Wasserman and Renzetti, 1994). Systemic aerosol drug administration via the pulmonary route can be expected for insulin, growth hormones, potent analgesics, anti-migraine compounds and predominantly new biotech products currently in development (Farr et al., 1996; Brown and Pickrell, 1995; Smith, 1997). In this context, it is apparent that pulmonary drug delivery of proteins and peptides (Wood and Knowles, 1994; Brown and Pickrell, 1995) such as insulin (Farr et al., 1996) would require innovative drug delivery systems delivering more precise dosing, more efficient drug dispersion, and better patient compliance (Rubsamen, 1995; Farr et al., 1996; Smith, 1997).

The phase out of CFCs has spurred the industry to improve current MDI-systems despite increased regulatory requirements and the question of patents on HFA-formulations and propellants. Improvement in drug application and handling can be achieved with MDIs powered by non-CFC propellants in combination with new valves, spray velocity reducing actuators (Spacehaler®), breath triggered actuators (Autohaler®, Easi-Breathe®), and auxiliary built-in or add-on devices (OptiVent®, AeroVent® SmartMist®). Thus, the modern MDIs have made a substantial step forward by introducing significant improvements in the pharmaceutical performance. This should maintain the MDI as the preferred dosage form for inhalation therapy. The above features in combination with a numerical counter showing the remaining number of shots to improve feed back to the patient and compliance, should be a next step towards improved pulmonary drug delivery by MDIs which, however, should be affordable at a reasonable cost.

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