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Medical Aerosol Inhalers: Past, Present, and Future

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The need to deliver pharmaceutical molecules to the respiratory tract has lead to the development of three major types of medical aerosol inhalers: The nebulizer, invented around the turn of the century, which uses aqueous solutions as its atomization substrate; the pressurized metered dose inhaler, invented in the mid-1950s, which uses a finely divided drug in a chlorofluorocarbon propellant suspension; and the dry powder inhaler, first commercialized in the early 1960s, which

uses a powdered drug form. In general, these dosage forms have served the medical and patient community well, but recent advances in protein chemistry and the ozone depletion issues related to CFC propellants have lead to a renewed interest in the development of more efficient non-CFC inhalers. This article discusses the history of medical inhaler device technology and highlights the new technologies which may replace some of the existing delivery systems.

INTRODUCTION

Using the inhaled route for the administration of both topically active and systemic compounds is becoming increasingly popular. In the case of topical therapy this popularity is undoubtedly related to the fact that the inhaled route gives direct access to lungs. For diseases such as asthma, inhalation has become the primary route of administration of pharmacological agents. In the case of systemic therapy it is the inherent convenience of respiratory delivery coupled to the large surface area and long residence times associated with peripheral lung deposition that has made the lower airways a legitimate portal of entry into the systemic circulation (Niven 1994; Taylor 1994).

Successful administration to the lung requires the generation and delivery of 'fine' aerosols. In order to avoid inertial impaction in the oropharyngeal cavity and reach the lung aerosol particles of 7 μm or less are required. To reach the peripheral lung, the site of absorption for

systemic therapy and the site of action of some topical therapies, particles of the order of 2 to 3 μm are required (Stahlhofen et al. 1980). Thus, one of the major requirements of any medical inhaler is that it generate aerosols containing particles within this "respirable" size range.

However, the design of medical inhalers is not limited to this particle size performance criterion. Successful inhalers must also be acceptable from a pharmaceutical standpoint. This means that the device must store the medication in a suitable fashion and that the drug product must be chemically and physically stable during both storage and atomization. In this respect, problems can arise if the drug substance and/or excipients are not suitably isolated from the external environment or if the drug and excipient are not chemically compatible.

Medical inhalers must also "interact" correctly with the patient, delivering a reliable, uniform, and consistent dose. This

latter criterion, in many respects, limits the choice and success of a particular inhalation dosage form and takes the science of inhalation aerosols outside of the standard aerosol laboratory. For example, portability is an inherent requirement in most medical inhalers because of the need for treatment regimes that require delivery of medication throughout the day and night. Self-contained inhalers are required because medication may be needed in situations where electricity or compressed gas sources are not available. Simple devices that are easy to maintain are required in order that a patient's debilitating condition is not aggravated by strict cleaning and maintenance regimes. Of course the particular combination of reliability, portability and simplicity chosen depends upon the dosing requirements for the particular molecule being delivered. However, above all, simple devices that are straightforward and easy to use are required because, in general, both patients and health care specialists possess very limited knowledge of the subtleties of inhalation science (Kelly 1993).

Finally, cost can be an important factor. For example, for expensive molecules such as proteins it may be economical to use highly efficient, but expensive delivery systems. Whereas with less expensive molecules, such as β_2 agonists, it may be more economical to accept poorer delivery efficiency from a cheaper delivery device.

Table 1 summarizes the requirements for an "ideal" medical inhaler as exemplified by Wolff and Niven (1994).

The size and portability restrictions described above, together with the need to generate aerosols containing fully active drug, severely limits the choices of an aerosol generator for pharmaceutical inhalation delivery. For example, condensation growth methods of aerosol generation cannot be used since volatilization of most pharmaceutical molecules would

TABLE 1. Summary of Criteria for the Ideal Medical Inhaler (Wolff and Niven, 1994)

Reliability, reproducibility, accuracy
Small particle size (1–5 μm)
Simple to use and handle
Multiple dose capability
Resistance to bacterial contamination
Durability
Cost effectiveness
Product stability

cause severe thermal degradation. To some extent the choice of a particular type of generator can also be limited by the particular properties of the compound to be delivered. For example, mechanical atomization of liquid solution of some fragile protein molecules could cause denaturation.

Over the last four to five decades three main types of pulmonary delivery systems have evolved to meet patient needs. In general, none of these systems meet all the above requirements, but rather they reach different compromises between the various criteria. These "inhaler" types are based on either the atomization of liquids, solutions, or suspensions or the dispersion of dry powders. The oldest of these is the pneumatic nebulizer. The nebulizer uses an external power source to break up aqueous drug solutions. In the mid-1950s the pressurized metered dose inhaler (pMDI) joined the nebulizer as a popular dosage form. The pMDI uses a propellant liquid as both its power source and the suspending, or dissolution, medium for the drug. Its inherent portability and perceived ease of use have made it *the* most popular form of inhalation delivery. However, because of the need to deliver relatively large quantities of drug to the airways, the nebulizer and pMDI were joined, in the early 1960s by the dry powder inhaler (DPI). The conventional DPI uses the energy supplied by the patient's inspiration to dispense and disperse a premeasured quantity of drug substance.

NEBULIZERS

Medical nebulizers are probably one of the oldest forms of respiratory drug delivery device. They rely upon the ability of the pharmaceutical formulator to solubilize the drug in a suitable solvent, invariably water. The majority of commercial nebulizer devices were developed from more conventional nasal sprays and they utilize compressed gas to generate liquid aerosol droplets; a technique commonly known as ‘airblast’ atomization. However, as with all “airblast” techniques the droplet sizes generated at the atomizer head are relatively coarse (Lefebvre 1988) and inertial filtration techniques are needed in order to limit the output to “respirable” droplet sizes. This combination of “airblast” and inertial filtration leads to some interesting delivery characteristics. Nebulizers that generate relatively “coarse” aerosols deliver medication quickly but produce high oropharyngeal deposition.

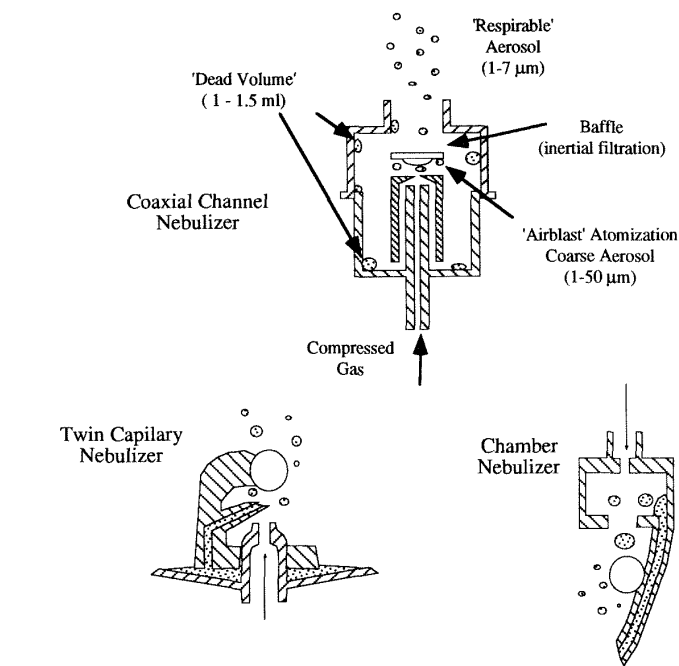
However, nebulizers which deliver “fine” aerosols do so by baffling out and recirculating coarse droplets. Hence they take much longer to deliver a dose of medication. The result is less oropharyngeal deposition, but greater problems with patient compliance due to long nebulization times. Figure 1a presents some typical “pneumatic” nebulizer configurations.

The second method of liquid atomization commonly employed in medical nebulizers is high frequency ultrasound. In this type of device piezo crystals are used to generate high frequencies sound waves of the order of a few MHz. This technique usually generates “respirable” droplets directly (Lang 1962), but baffles are still required in order to prevent solution loss from the central geyser which is formed by the high-energy sound pulses. Figure 1b presents a diagram of a typical domestic ultrasonic nebulizer. It will be noted that in contrast to some large commercial machines the piezo crystal is in direct

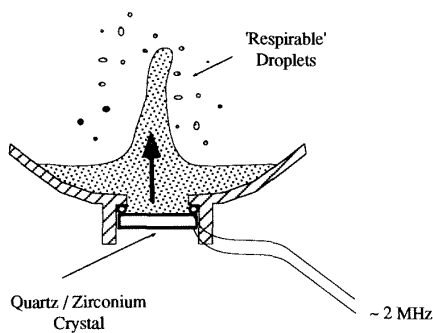
contact with the drug solution and the device does not use a transmission fluid (Leigh et al. 1991). This has the advantage of making the device smaller and easier to use. However, the dramatic changes in load as the nebulizer empties can cause considerable stress on the crystals and in the past this has led to some reliability problems. Current designs, however, use a number of electronic tricks, such as load sensing and automatic frequency matching (Baker and Stimpson, 1994), to control crystal temperatures and reliability is reportedly improved.

The main problems associated with nebulizers are that the devices themselves have large internal solution “dead volumes.” A high percentage of the dose, as much as 50% from a standard 2 mL ampoule, can remain trapped inside the nebulizer. Also, the long nebulization times associated with some nebulizer designs can lead to patient compliance problems. Table 2 presents some recent data (Cipolla et al. 1994) summarizing the output characteristics of a number of nebulizer systems. It will be seen that the overall delivery efficiency varies from 10% to 50%; with nebulization times ranging from 2 to 10 min. When assessing the dose delivered by a nebulizer however, it has to be remembered that most nebulizers deliver aerosol continuously whereas patients only inhale for approximately half of their respiratory cycle. Hence the “respirable” dose actually inhaled is only about a half of that delivered. In general about 10% of the dose placed in the nebulizer actually deposits within the lung (Hardy et al. 1993). Obviously there is room for improvement in nebulizer design.

A number of devices, such as the Pari LC Jet⁺ (Knoch 1994), have optional interrupters or inspiratory control valves which allow synchronization of delivery and inspiration. Other devices such as, the System 22 Mizer (O’Doherty et al. 1990), have holding chambers which fill during



(a) Pneumatic Designs



(b) Domestic Ultrasonic Design

FIGURE 1. Nebulizer designs.

expiration and empty on inspiration. These “storage chambers” rely on the fact that patient’s minute volume is larger than the nebulizer’s volumetric delivery rate. Hence during expiration the chamber fills and

then during inspiration the chamber contents and the nebulizer output are inhaled. However, all of these improvements deal with the problem of synchronicity and current nebulizer designs

all suffer from large “dead volumes” which cause low overall efficiency.

PRESSURIZED METERED DOSE INHALERS

The pressurized metered dose inhaler came into being in the mid-1950s. However, like most spray products which use

liquefied gases as their power source, the pMDI had its roots in work carried out many years before. In 1899, Helbing and Pertch (1899) described the first aerosol generator to be driven by the vapor pressure of a propellant liquid. They used methyl or ethyl chloride as the propellant and the ‘heat of the hand’ caused enough

TABLE 2. In Vitro Nebulizer Performance Using 2.5 ml Pulmozyme® Nebulizer Solution^a (Cipolla et al. 1994)

Nebulizer	Compressor	Nebulizer Time (min)	Respirable Fraction (%)	Nebulizer Efficiency (%)	Delivery (%)
Marquest Customized	Pulmo-Aide	9:32	54.3	58.5	31.7
Respirgard II		(8:51–9:59)	(51.9–55.9)	(51.6–63.8)	(28.4–35.7)
Marquest Acorn II	Pulmo-Aide	10:12	56.7	50.2	28.4
		(9:42–10:36)	(54.7–60.0)	(40.5–57.9)	(22.4–31.7)
Hudson T Up-Draft II	Pulmo-Aide	9:13	50.5	46.4	23.4
		(8:09–10:32)	(47.8–51.0)	(44.6–48.4)	(22.1–25.4)
Baxter Airlife Misty	Pulmo-Aide	6:39	52.7	45.5	24.0
		(5:42–7:12)	(49.5–55.6)	(42.7–48.0)	(23.7–24.4)
Pari LL	Inhalierboy	4:04	44.3	39.9	17.7
		(3:31–4:34)	(40.2–47.6)	(39.5–40.4)	(16.2–19.0)
Pari LL	Master	2:35	60.1	36.1	21.6
		(2:10–2:38)	(57.1–64.3)	(31.9–38.5)	(20.5–22.3)
Pari IS-2	Inhalierboy	9:53	76.6	55.8	42.3
		(9:44–9:59)	(75.1–78.6)	(53.2–59.4)	(40.0–46.7)
Pari IS-2	Master	5:39	80.0	61.7	49.3
		(5:19–5:44)	(79.2–80.6)	(57.4–65.8)	(46.0–52.1)
Pari LC	Inhalierboy	5:16	47.8	51.4	24.6
		(5:12–5:16)	(47.1–48.8)	(50.6–52.7)	(24.1–24.9)
Pari LC	Master	2:30	73.5	29.7	21.8
		(no variation)	(72.7–75.3)	(27.2–33.3)	(20.5–24.2)
SideStream	Freeway	4:28	79.6	44.8	35.7
		(3:59–4:48)	(78.6–81.1)	(40.1–47.6)	(42.7–45.3)
SideStream	CR60	3:08	81.1	54.3	44.0
		(2:58–3:15)	(80.2–81.4)	(53.2–55.6)	(42.7–45.3)
System 22	Freeway	4:33	46.4	22.4	10.3
		(3:47–5:36)	(33.7–56.1)	(18.4–27.1)	(7.3–13.4)
System 22	CR60	3:02	66.0	23.7	15.4
		(2:49–2:58)	(55.2–72.3)	(18.5–29.3)	(13.0–16.9)
Aiolos	Aiolos	1:55	57.4	37.3	21.4
		(1:48–1:56)	(55.3–59.5)	(32.5–40.0)	(19.3–23.0)
Optineb	O ₂ Cylinder	2:12	73.6	48.8	36.0
		(2:02–2:28)	(72.4–75.0)	(39.6–54.2)	(29.1–40.7)

^a The droplet size data were obtained using a Malvern Mastersizer X diffraction analyzer. The values for the Respirable Fraction are calculated from the diffraction-derived size distribution and are the means of nine values (three independent measurements using three individual nebulizers). The values for the Nebulization Time and the Nebulizer Efficiency are the means of three measurements using three individual nebulizers and were determined by stop watch and UV assay, respectively. The range of individual values is given in brackets.

“Respirable Fraction” is the % of droplets generated in the 1–6 μm range.

“Nebulizer Efficiency” is the % of the dose placed in the nebulizer which is actually delivered.

“Delivery” is the % of the dose placed in the nebulizer delivered as “respirable” droplets. The “respirable” dose actually inhaled will be approximately half that delivered, due to the expiratory phase of the breathing cycle.

pressure to develop to atomize the liquid via a small orifice. Some 2 years later Gebauer (1902) discovered that partial vaporization of the propellant liquid prior to final atomization at the spray nozzle produced a finer spray and, in a U.S. patent, he described the use of the first twin orifice expansion chamber. However, it was not until the 1930s and 1940s, with the discovery of freon propellants such as 12, 114, 11, and 22, that these inventions came together to make liquefied gas generators a real and practical proposition. The first, rather crude, "aerosols" developed during the 1940s, were nonmetered systems designed for spraying insecticides. However, in 1956 the pressurized metered dose inhaler, as we now know it, became a possibility when the metering valve was invented (Meshburg 1956). In that same year 3M Healthcare, then Riker Laboratories, combined the Meshburg valve and CFC propellants with a number of respiratory compounds and the pressurized metered dose inhaler was born. Since that time the pressurized metered dose inhaler has become the most popular form of respiratory drug delivery system.

The pMDI delivers a metered "dose" of a CFC drug suspension, or occasionally a solution, containing a predetermined quantity of active drug. It consists of three major components: a reservoir, containing raw drug suspended, or solubilized, in liquefied gas propellant; a metering valve, which when depressed delivers a known quantity of the reservoir contents; and a spray actuator, which combined with the stem of the metering valve comprises a twin orifice expansion chamber and spray nozzle. Figure 2 presents a diagram of a typical pMDI and illustrates the valve 'firing' sequence.

In the rest position the metering chamber of the valve is connected to the propellant reservoir. On depression of the valve this connection is closed and metered discharge begins. The metered dose

is ejected from the metering chamber under the pressure of the boiling liquid propellant. The two phase vapor liquid mixture then flows through the valve stem orifice into the valve stem. While in the valve stem it 'expands', by further vapor formation, before discharge through the spray orifice. The atomization process at the final spray orifice is two phase gas/liquid, i.e. "airblast" (Clark 1991) and is similar to the process involved in nebulization, as described above. However, after droplet formation has taken place the droplets in the emerging cloud quickly evaporate and lose their forward velocity (Clark 1995). It is the CFCs capacity to both generate sufficient vapor to produce efficient two-phase atomization, without the need for an external power source, and to evaporate quickly, after droplet generation has taken place, which makes the pMDI such a successful inhalation delivery system. Of course, the low toxicity of propellants 12, 11, and 114 and their favorable formulation chemistry has added to this success. Nearly all the major respiratory drugs are now offered in the form of pMDIs.

The main advantages of the pMDI are that they are reasonably efficient, if used correctly, and that they are inherently portable and very convenient to use. Table 3 summarizes the deposition efficiency obtained during a number of deposition studies using ^{99m}Tc labeled pMDIs (Dolovich 1993). The fraction of the dose reaching the lung varies from 6.5% to 24%.

However, the major problems with pMDIs are high oral deposition (Newman 1982), brought about by the high droplet velocities associated with the atomization process, and patient coordination/compliance, brought about by the pulsed nature of the pMDI's sprays (Crompton 1982). To overcome the high droplet velocities a variety of spacer devices have been developed. These devices quite literally put

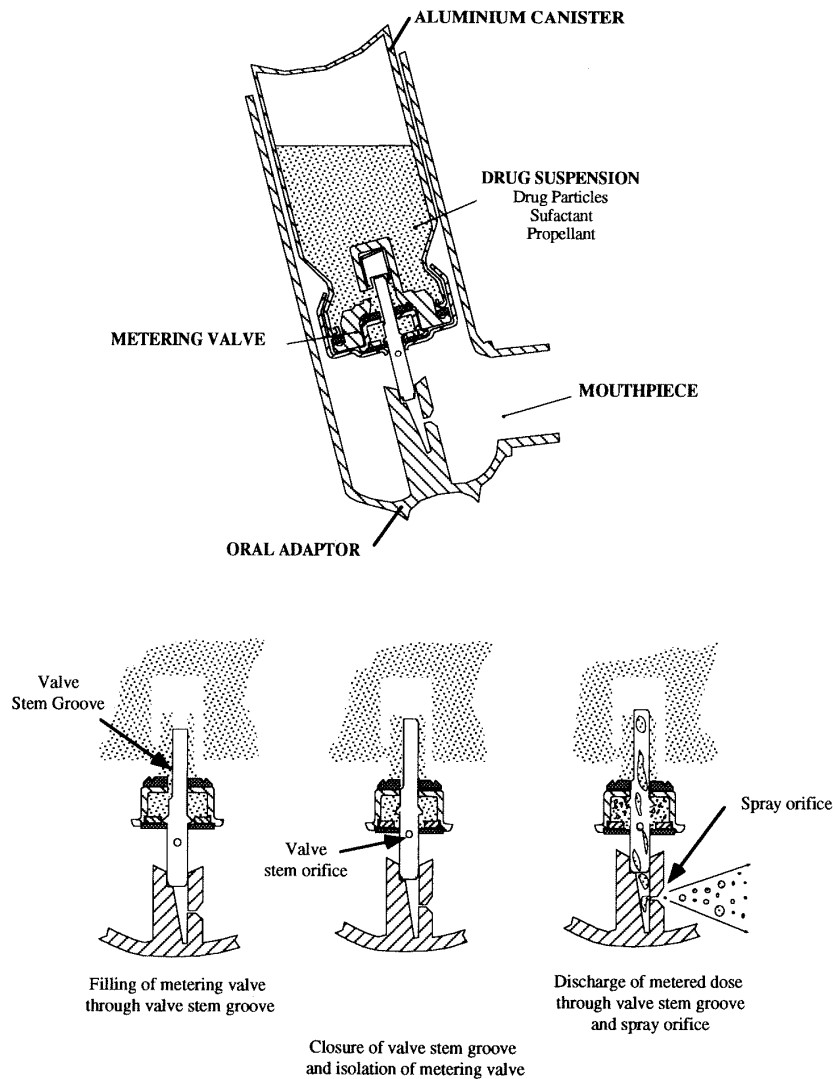


FIGURE 2. The major elements of the pressurized metered dose inhaler.

space between the patient and the pMDI actuator and hence allow the aerosol cloud's velocity and the size of the droplet inside the cloud to decrease substantially before inhalation. Spacers range from

simple tubes, which still require patient coordination for effective use (Newman and Clark 1989), to small and large chambers with inspiratory valves to control the flow of aerosol and hold the aerosol cloud

TABLE 3. In Vitro Lung Deposition Obtained using Radiolabeled Labeled pMDI Aerosol (Dolovich 1993)^a

MDI	Radiolabel	Group	No. of subjects	% deposition in lung	Reference
Atrovent	⁷⁷ Br	Normals	7	11.2	Spiro et al. (1984)
		CB	7	11.7	
Intal	^{99m} Tc-SCG (SD)	Normals	7	9.5	Vidgren et al. (1987)
	^{99m} TcO ₄	Normals	10	11.0	Newman et al. (1989)
	^{99m} Tc	OAD	10	6.5 UT	Newman et al. (1986)
				11.2 CT	
Ventolin	^{99m} Tc-Teflon	OAD	9	8.7	Newman et al. (1984)
	^{99m} Tc-Teflon	Asthma	9	11.2	Zainudin et al. (1990)
	^{99m} TcO ₄	Asthma	10	12.8	Newman et al. (1991)
		Normals	6	24.4	Biddiscombe (1991)
Placebo	^{99m} TcO ₄	Normals	7	10.4 OT	Dolovich et al. (1983)
		COPD	14	8.7 OT	
		Normals	12	6.2 OT	Dolovich et al. (1981)
				12.3 OT	
Nacystelyn	^{99m} TcO ₄	Normals	6	12.3	Hardy et al. (1991)

^a Abbreviations: SD, spray dried; UT usual (closed mouth) technique; CT, correct (closed mouth) technique; OT, optimal (open mouth) technique; OAD, obstructive airways disease; COPD, chronic obstructive pulmonary disease.

until the patient inspires (Dolovich et al. 1983). In general, spacers and chambers increase delivery efficiency to the lungs and reduce oropharyngeal deposition (Newman et al. 1984; Dolovich 1993). They therefore offer great benefits to patients who have problems with inhaler technique and to patients who suffer side effects such as oropharyngeal candidiasis (Salzman and Pyszczynski 1988) from oral deposition of corticosteroids. However, the penalty paid for this efficiency increase is reduced portability and convenience.

Other attempts at improving MDI delivery have focused on the coordination problem alone and a number of breath actuated inhalers have been developed (Arshad et al. 1993). These devices use some form of mechanical pressure sensor to actuate the pMDI automatically during inspiration. However, they are not fool-proof and patient instruction is usually still needed to ensure optimum delivery.

Despite the pMDI's popularity it is currently under threat. As long ago as 1974 Molina and Rowland pointed out the dan-

ger that CFCs present to the Earth's protective ozone layer and since that time growing environmental pressure has resulted in the phased withdrawal and total ban, by 1996, on the use of CFCs. As a result of this ban, new alternative propellants are being developed by the world's leading pharmaceutical companies. These propellants, 134a and 227, are hydro-flouroalkanes and unlike their predecessors they are ozone friendly. However, because of their physicochemical properties what at first may have appeared to be a simple formulation change has taken much effort and inventiveness. There are now over 30 published patent applications dealing with the formulation issues associated with propellants 227 and 134a. Table 4 presents some of the major ones. New toxicology studies have also been carried out and, in an unprecedented alliance, a number of the world's leading pharmaceutical companies formed two major consortia, IPAC 1 and IPAC 2, to oversee the toxicology testing of these new excipients.

TABLE 4. Major Alternative Propellant Patents (More than 30 formulation patents either filed or published)

Author (Company)		Patent Subject	Patent/Patent appl. No.
Schultz and Schultz (3M Healthcare)	(1990)	Co-solvent	WO 92/06675
Taylor and Burnell (Glaxo)	(1991)	Surface Coating	WO 92/08447
Steel, Somani and Lim (Fisons)	(1991)	Flourinated Surfactant	WO 91/11173
Weil and Dabb (Boehringer)	(1991)	Vapour Pressure Control	WO 91/11495
Fassberg et al. (Schering)	(1992)	'Propellant 227'	EP 92305252.6

DRY POWDER INHALERS

In a United States patent in 1939 Stuart (1939) described what could arguably be called the first dry powder inhaler. Stuart's patent describes a device which was designed to aid the inhalation of aluminum dust for the chelation of inhaled silica. It was intended for use by miners who suffered from silicosis induced by inhaled dust. However, it appears that the device was never commercialized and one has to ask if this is because the risk from inhaling aluminum was higher than that from inhaling silica or, since the device illustrated in the patent used nasal inhalation, because the delivery efficiency to the lungs was inadequate. Ten years later Fields (1949) patented what was probably the first dry powder inhaler to be used for the administration of a pharmaceutical agent. The Aerohaler[®], as it came to be known, was the first truly commercially available dry powder inhaler and was marketed by Abbot laboratories for the delivery of Norisodrine[®], isoprenaline sulphate. The device consisted of "sifter" cartridges containing the powdered drug, a steel ball assembly for "knocking" the dose out of the cartridge and a mouthpiece through which the aerosol was inhaled. There was very little control over the delivered dose, other than patient symptom titration, and

there was no dispersion mechanism inside the device to aid aerosol generation.

In the 1960s this "cartridge and ball" technology was replaced by hard gelatin capsule technology when Fisons Pharmaceuticals and Allen and Hanburys introduced the Spinhaler[®] (Bell et al. 1971) and Rotahaler[®] (Over and Dah 1985) (Figs. 3a and 3b). These latter devices use hard gelatin capsules as the dose storage media, but differing techniques to open the capsule and disperse its powdered contents. In the Spinhaler the capsules are pierced, with the aid of 2 needles, and the contents emptied via a 'friction whirl' (Bell et al. 1971) motion. The aerosol is generated when the powder is drawn through a venturi. In the Rotahaler the two capsule halves are separated, with the aid of a plastic bar, and the contents inhaled through a plastic mesh or grid.

It is important to realize that in contrast to nebulizer formulations, or indeed to some extent pMDI formulations, the formulation of dry powders for use in DPIs is critically important for their effective performance (Ganderton and Kassem 1992). The powder must be able to flow readily in order that the capsule, or powder reservoir, will empty properly, but the powder must also generate a fine aerosol in order that the patient can in-

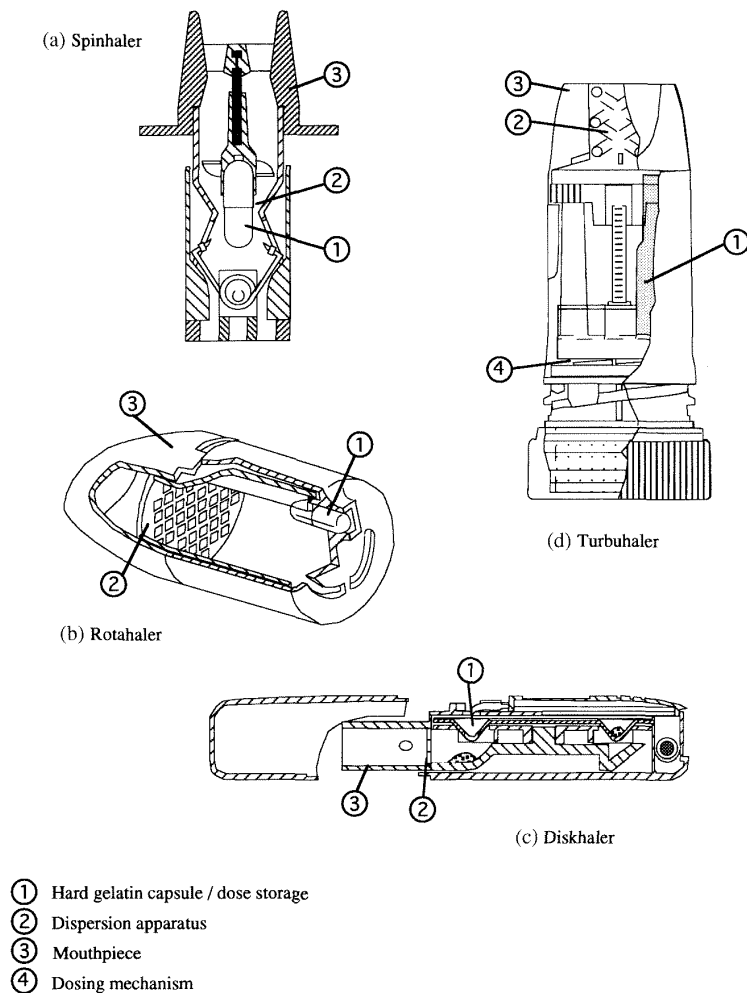


FIGURE 3. The evolution of the dry powder inhaler.

hale a respirable dose. In powder technology terms these two factors are usually mutually exclusive. Fine powders tend to be cohesive and have poor flow properties, whereas coarse powders flow well, but contain little in the way of respirable particles. Traditionally formulators have developed two ways of combating this

problem. The first is to blend coarse “carrier” particles with fine drug particles. This produces a powder which flows and, with the correct dispersion elements in the DPI, generates a reasonable respirable aerosol. The second method is to pelletize the drug. Soft pellets of the drug powder flow well because they are larger than the

constituent particles, but they also generate respirable aerosol when the pellets are broken down inside the DPI. Pelletization can be quite difficult however; too soft and the pellets may break inside the capsule before delivery can be achieved; too hard and the pellets may not be broken down inside the device and hence a cloud of poor respirable quality will be delivered. In general successful DPI design relies as much on the powder formulation as it does on the device engineer.

The main advantage of DPIs is that they are inherently breath actuated in that they only deliver drug when the patient inhales. However, one of the main criticisms of this type of device is that the doses are packaged discretely and that each individual dose has to be handled by the patient. This makes the device difficult to use. Hence, more recently, Allen and Hanburys have introduced a cartridge multidose powder inhaler (Fig. 3c). The Diskhaler[®] uses a PVC disk containing between 4 and 8 “blisters” of drug. The blisters are pierced using a large plastic “needle” and the contents are inhaled via a plastic dispersion grid. The patient therefore carries between 4 and 8 doses in a single cartridge and does not have to be concerned with loading each individual

dose into the device. One of the most recent commercial additions to the array of dry powder systems goes even further in the multidose convenience direction. The Astra Turbuhaler[®] (Wetterlin 1988) (Fig. 3d) stores its drug powder in a bulk reservoir and uses a miniature metering mechanism, based on volume, to control the delivered dose. Again the powder medication is delivered only when the patient inhales and a dispersing spiral channel in the device’s mouthpiece is used to generate the aerosol cloud. A number of other multidose reservoir devices have been introduced in the world arena. Table 5 lists the DPIs which are currently available in the various pharmaceutical markets throughout the world.

Paradoxically, the main problem with DPIs is the very attribute which is their main advantage. All currently available DPIs utilize the energy in the patient’s inspiration as the power source for aerosol generation. Therefore their delivery and dispersion performance, and hence the dose which they deliver to the lung, is affected by a patient’s ability to inhale at a suitably high flow rate (Newman et al. 1991; Newman et al. 1994). Table 6 summarizes the lung deposition data from 2 recent radiolabel deposition studies. The

TABLE 5. Currently Marketed Dry Powder Inhalers

Unit dose		Unit Multidose		Multidose	
Device (Manufacturer)	Dose Storage Media	Device (Manufacturer)	Dose Storage Media	Device (Manufacturer)	Metering Method
Spinhaler (Fisons)	Hard gelatin capsule	Inhalator (Boehringer)	Hard gelatin capsule cartridge	Clenil (Chiesi)	Flow through chamber
Rotahaler (Allen and Hanburys)	"	Diskhaler (Allen and Hanburys)	4/8 blister cartridge	Turbuhaler (Astra Draco)	Perforated plate
Cyclohaler (ISF/Orion/Phabrita)	"			Easyhaler (Orion)	Blind dimple
Inhalator (Boehringer)	"				

TABLE 6. Typical Deposition and Flow Dependence for Patient Driven Dry Powder Inhalers

Device /Flow Rate (l/min)	% @Location		
	Device	Oropharynx	Lungs
Spinhaler ^a			
60	35.6	58.5	5.5
120	29.4	57.3	13.1
Turbuhaler ^b			
30	11.2	79.2	9.1
60	12.8	69.8	16.8

^a Newman et al. (1994).^b Newman et al. (1993).

paradox is, of course, that it is this very fact that makes them the ultimate in breath activated devices. However, recent data (Hansen and Andersen 1993; Clark 1994) suggests that even relatively sick patients can attain satisfactory flow rates through most devices.

THE FUTURE

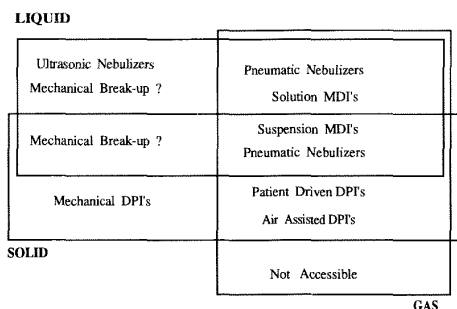
What of future developments then? Figure 4 summarizes the various options available in terms of power source and physical form of the drug substance. Obviously, some drugs will be more suited to a particular physical form due to their chemical or physical nature.

However, as will be discussed below the majority of the options shown in Fig. 4 are being investigated by various pharmaceu-

tical and device manufacturing companies.

One of the major driving forces for the development of these new technologies is, as described above, the forced introduction of alternative aerosol propellants. For the past 5–8 years the pharmaceutical industry has been working to reformulate existing drugs in the new ozone friendly propellants, HFAs 134a and 227. These efforts have led to what could probably be called the most inventive phase of inhalation aerosol delivery since its inception. As stated above there are currently over 30 published patents in the area of alternative propellant formulations and it would seem that the industry is well on the way to filing for the approval of its first CFC replacement metered dose inhaler. 3M Healthcare have announced that they intend to file their first NDA for Dymel[®] 134a/P formulations by the end of 1994. However, the inventions have not been restricted to alternative propellants and both aqueous atomization and dry powder devices have enjoyed a resurgence of interest.

Patents on aqueous atomization cover pure mechanical break-up (Weston et al. 1991), the use of ultrasound (Siemens 1988), and the use of meshes driven by piezoelectric crystals (Takahasi et al. 1988; Ross and Humberstone 1992). In the Weston device (Fig. 5a), hydraulic amplification is used to generate high liquid pressures, typically 400 bar, and atomization is via a small orifice, typically 3–10 μm in diameter. The high liquid pressure and small spray orifice ensure an aerosol cloud of reasonable respirable quality and a number of check valves and the hydraulic piston stroke are used to ensure metered delivery. In order to operate such a device the patient would be required to arm the device, by retraction of the piston, and then discharge the dose during inspiration in a similar manner to current pMDIs. Boehringer Ingelheim developed, and for

**FIGURE 4.** Options for the generation of medical aerosols.

short while marketed, a device, Respi[®]mat, which utilized high-frequency ultrasound to deliver therapeutic doses of an aqueous solution of a bronchodilator in a single actuation (Zierenberg 1992). The main disadvantage of this technique, however, was the large power requirement of the atomizer and the Respi[®]mat device required frequent recharging in order to maintain efficient operation. More recently, Baum et al. (1993) have described a multidose aqueous atomizer which can deliver up to 100 unit doses of

medication. Their device (Fig. 5b) which employs ultrasonic mesh technology (Ueha et al. 1985) to atomize the drug, is small and to an external user would appear as simple to use as a pMDI. The advantage of the ultrasonic mesh technique is that it operates at frequencies of the order of 40 kHz. Its power requirements are therefore low and efficient operation could be maintained by standard dry cell disposable batteries. However, there are product sterility issues with such aqueous multidose devices and if they are

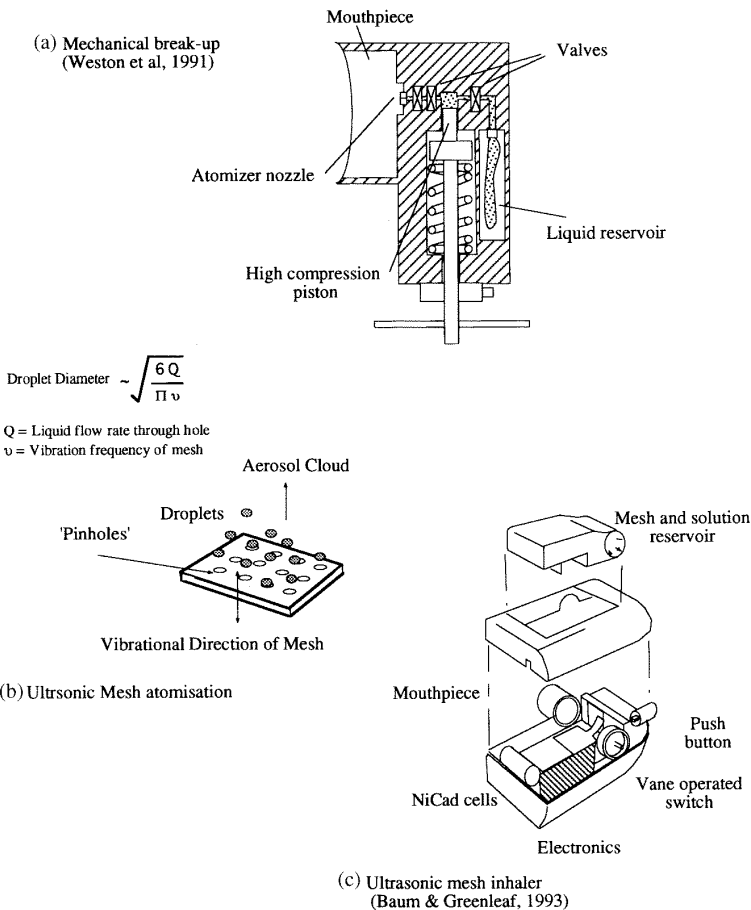


FIGURE 5. Liquid atomizers of the future.

ever to become marketed products multidose aqueous atomizer formulations will probably have to contain preservatives or be packaged in a multidose/unit dose cartridge configuration.

The most prolific area of invention in the past few years has undoubtedly been dry powder inhaler design. Device designs have tried to incorporate the concept of the multidose convenience of the pMDI with efficient and uniform delivery. The two main performance criteria have been dose uniformity and flow independent delivery.

Some of the devices reported in the literature are multidose, but maintain the breath activated nature of the current DPIs (Clark et al. 1990; Braithwaite 1992). In the Braithwaite device the dose is metered by a small “dimple” (Fig. 6a). In the Clark device the dose is “shaved” from a compacted powder-bed by the action of a knife or blade, the dose weight is controlled by the pitch and angular displacement of the blade, figure 6b.

Jago Pharma AG (Switzerland) have developed a multidose device which uses a dosing ‘notch’ to meter the powder, but

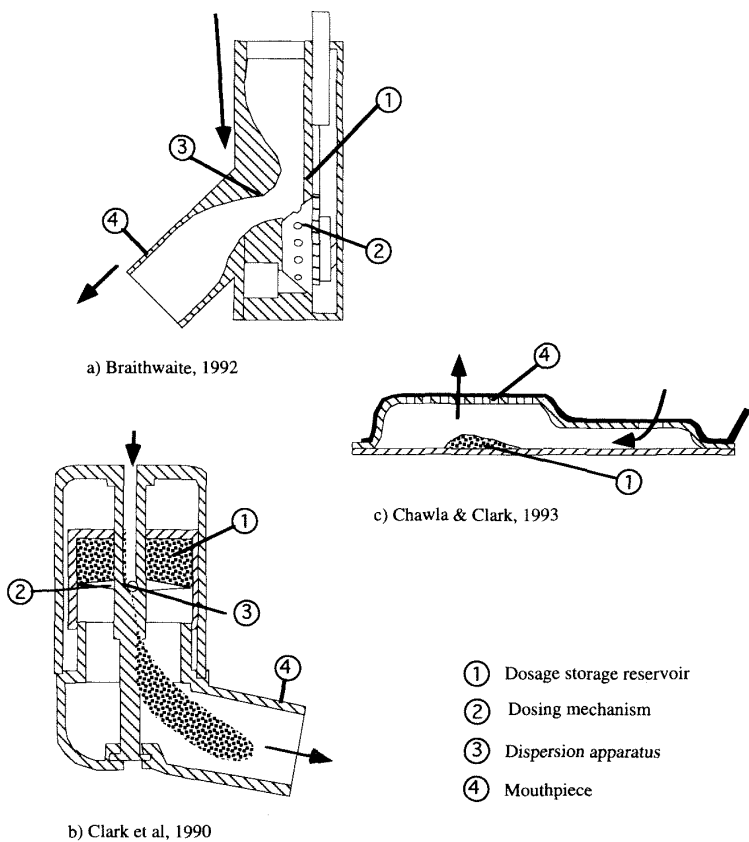


FIGURE 6. Patient driven dry powder inhalers of the future.

also incorporates a novel breath activated piston. The dosing “notch” is only moved to the dispensing position, by the action of the piston, when the patient has reached an inspiratory flow high enough to properly disperse the powder formulation.

In yet another novel attempt to bring simplicity to inhalation devices Chawla and Clark (1993) have patented a disposable inhaler (Fig. 6c). This system uses a unit dose preformed blister containing drug powder as its own inhaler. After removing a foil seal the patient inhales directly from the blister, through a small array of holes, and then disposes of it. Device cleaning and maintenance are therefore avoided.

However, despite these many advances in DPI design, it is probably the “power assisted” multidose dry powder inhalers which represent the real ‘new wave’ of powder aerosol delivery.

Two groups, Boehringer Ingelheim and 3M Healthcare, have described systems which utilize tapes containing microscopic dimples or fibre like structures as the drug storage media (Figs. 7a and 7b). In the Boehringer Ingelheim device (Gupte et al. 1992) the drug powder is stored on a valour tape, or plastic microstructure, at a density of 1–1.5 mg/cm² and it is delivered by a small compressed air pulse. The device is purely mechanical and the patient is only required to arm a small piston and initiate delivery in the same way as they would a pMDI. In the 3M Healthcare device (Schultz et al. 1992) the drug is stored on a polyester or polypropylene film at a density of 25–100 µg/cm². The dose is delivered with the aid of a mechanically, or electrically, operated hammer. The hammer is reset when the patient opens the mouthpiece and actuation is via a pressure sensing vain. Delivery is therefore flow independent and is automatically synchronized with inspiration. However, as with the breath activated pMDIs discussed above, it is likely that

some degree of patient training will still be required if effective delivery is to be ensured. Both of the above devices obviously rely on the uniform distribution of the drug in the microstructure storage media to ensure delivered dose uniformity. The delivered dose is also limited by the void space in the microstructure. These systems are therefore limited in terms of the maximum dose which they can deliver.

A recently patented device (Galli 1993; Bruna et al. 1994) overcomes this limitation in the magnitude of the delivered dose by utilizing a multidose powder reservoir (Fig. 7c). In this device a large chamber, isolated from the external environment by elastomeric seals, contains the powdered drug and a ‘brush and sweeper’ arrangement loads the drug into a dosing hole. The delivered dose is controlled by the bulk density of the formulation and the volume of the dosing hole. The metered dose is discharged with the aid of a small compressed air pulse which is generated when the patient squeezes the device. This device, as other devices of similar design, requires a free flowing powder in order to ensure delivered dose uniformity. This requires not only good formulation, but also good control over the moisture uptake of the powder.

Mecikalski and Williams (1994) describe a device which overcomes the drug storage problem by using a cartridge approach similar to that of the Diskhaler (Fig. 7d). The drug is stored in a multidose cartridge and then dispersed by an electrically driven impeller. The impeller is activated by a pressure sensor that senses the patient’s inspiratory flow rate. The use of a dosing cartridge has the advantage that the delivered dose uniformity is primarily controlled at source, in the factory, by the cartridge filling machine and it is therefore not subject to whims of the drug powder, such as changes in flowability and bulk density. The

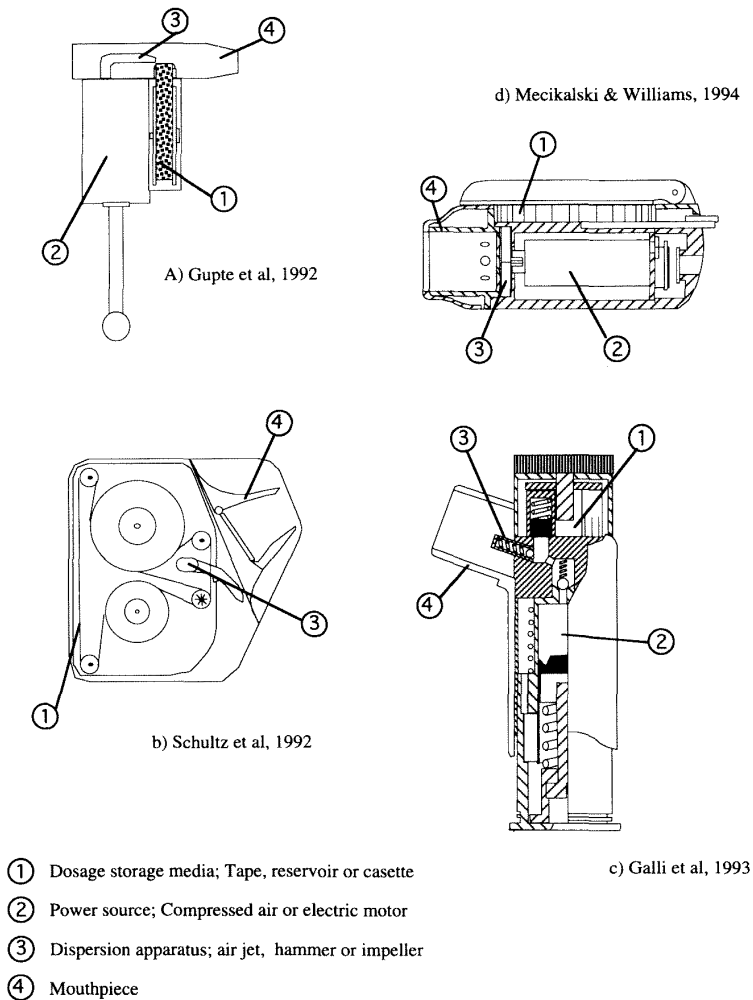


FIGURE 7. “Power assisted” dry powder inhalers of the future.

Mecikalski device also has the advantage that its delivery is flow independent and breath activated (Hill 1994).

In yet another approach Jager-Waldau et al. (1994) utilize the cartridge approach to control dose uniformity and drug in-gritty, but use a small compressed air

pulse similar to Galli et al. to deliver the dose of medication.

SUMMARY

In summary the design of medical inhalers has to be a compromise between

many factors. Efficient and uniform delivery being the main performance criteria, but ease of use, patient acceptance, and compliance being just as important. Over the years three major classes of inhaler have evolved to meet patient needs: the nebulizer, which uses aqueous solutions as its atomization substrate; the pressurized metered dose inhaler, which uses highly volatile propellant liquids; and the dry powder inhaler, which uses a powdered drug form. Each class of device has its advantages and disadvantages from both pharmaceutical and clinical perspectives. pMDIs are undoubtedly the most popular and convenient form, although clinical issues relating to incorrect use and environmental issues relating to the ozone layer have increased the use of DPIs. Nebulizer devices appear to be restricted to the very sick, very young and those who have compliance problems with the other two dosage forms.

As a direct result of the ozone depletion controversy there has been a resurgence of interest in the search for the "ideal" medical inhaler. However, would be inventors should beware; it costs many millions to develop a new inhaler and many technical and clinical difficulties have to be overcome. The development path is also very unclear. In some respects it is necessary to couple inhaler development and a new pharmaceutical molecule in order to enlist the necessary funds and resource for clinical development. However, this very alliance can be the downfall of a device if the clinical efficacy of the compound fails to be confirmed. The development of an inhaler with an existing compound can also be fraught with difficulties. Since a direct efficacy comparator exists a considerable advantage has to be demonstrated before the necessary impetus to develop and market a device can be gained. The paradox is that it is usually necessary to carry out some

clinical development before a "considerable" advantage can be demonstrated.

In summary, invention is 5% of the solution, development, both pharmaceutical and clinical, is the remaining 95% and it is what is really at the heart of the successful introduction of any new medical inhaler.

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