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State of the art and new perspectives on dry powder inhalers

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Abstract. – **Modern local therapy for lung diseases is now largely based on pressurized metered-dose inhalers (MDIs). The research of alternatives to MDIs has recently accelerated, primarily due to environmental concerns related to the use of chlorofluorocarbon (CFC) propellants. The most recent and attractive solution to this problem is represented by the development of dry powder inhalers (DPIs), particularly designed to avoid the use of propellants.**

DPIs have been developed for specific products, therefore they possess a reduced versatility in term of application of the same device to different drugs. However, they did introduce new concepts in pulmonary drug delivery, solving some disadvantages of the pressurized devices. They are in their infancy and the efforts of researchers are now impressive. The future will certainly see many other devices containing additional innovative features for the effective respiratory delivery of drug. The goals still remain the delivery of precise and uniform drug doses and increasing the respirable fraction in relation to the dose emitted from the device.

Key Words:

Dry powder inhalers, Aerosols; Particle size, Flow rate.

Introduction

Modern local therapy for lung diseases, that moved the first steps with the development of nebulizers, is now largely based on pressurized metered-dose inhalers (MDIs). The research of alternatives to MDIs has recently accelerated, primarily due to environmental concerns related to the use of chlorofluorocarbon (CFC) propellants. The most recent and attractive solution to this problem is represented by the development of dry powder inhalers (DPIs), particularly designed to avoid the use of propellants.

Nevertheless DPIs, even if they provide the significant advantage of being breath actuated, need further technological development in order to release, independently of the patient inspiratory flow rates, definite and uniform drug doses with high percentages of respirable particles.

Dry powder inhaler devices

DPI's deliver metered small doses of drug in powder form (typically less than 20 mg) in a stream of air drawn through the device by the inspiratory act of the patient. These breath-actuated systems are, thus, useful to overcome another major problem of MDIs, which is the need of coordination between drug aerosolization and inspiratory act[1-3]. Moreover, other aspects of pulmonary delivery via DPIs are advantageous, in particular those linked to the simplification of the system and the stability of the carried drugs, which are present in the device in solid form[4].

The innovative development of DPIs resides in three main elements of the delivery system i.e. the drug formulation, the metering system and the flow resistance of the device. At present the marketed DPIs could be classified as unit-dose or multi-dose reservoir systems. In the first case, the dose is pre-metered in a gelatin capsule that, individually introduced inside the device, is appropriately pierced and emptied by the inspiratory air flow. In the second, several doses of drug are contained in the reservoir of the device or in pre-metered specifically shaped containers. The latter represents an operative evolution of the first type of device, since it reduces patient interventions for loading the capsule in the device. However, the reservoir type re-

quire the design of appropriate and efficient metering systems for the powder, which request sometimes a certain degree of dexterity by the patient.

The type of device determines the formulative approach to the powder preparation. It is well known that aerosol particles need to reach the respiratory region of the deep lung in order to generate a pharmacological response. This result is mostly obtained through particle size reduction of the drug within the appropriate range. Unfortunately, a powder within respirable size range is characterized by poor performance in terms of flow properties which are, on the contrary, crucial for the operative steps involved in powder handling, reservoir filling and dose sampling.

In this sense a powder should possess differentiated properties for the dosing and the delivery operations. Therefore, the formulative procedures must be adapted in order to have a versatile powder that appears coarse during sampling and micronized during delivery. A solution to this problem can be obtained by loosely agglomerating the particles in large and easily de-agglomerating lumps. Nevertheless for the drugs used to treat asthma the very low dose at which they are used makes problematic the metering step. For this reason the most common solution adopted is represented by the use of a coarse free flowing carrier powder (usually lactose) to be mixed with the micronized drug one. The goal is to obtain a drug-carrier mixture that increases bulk and flow properties of the active drug, with the possibility to separate the two different size particles in the mixture during the aerosolization step[5]. This would determine the deposition of the coarse particles in the mouth and of the finest in the lung. The blending of drug with carrier represents a brilliant solution for the improvement of filling and sampling, but carries together additional problems linked to the uniformity of the mixture and the interaction between drug and carrier particles[6]. In fact, mixing is facilitated by strong interparticle forces that easily produce a distribution of drug particles all over the surface of the carrier. Nevertheless the same interparticle forces represent the main obstacle to efficient separation of the drug from the carrier during the aerosolization.

In DPIs, the drug is de-agglomerated, or the very fine particles of mixture are separated, by the turbulent flow created by patient inhalation. Other than been designed to work with a pre-metered unit dose or to include a reservoir and a dosing mechanism, the commercial devices are also characterized by the fact that they can contain just the drug or a drug-carrier mixture. In fact, in the Spinhaler® Fisons[7] a mixture of drug, notably cromolyn sodium with lactose, is pre-filled in hard gelatin capsules. After introduction into the device, the capsule is pierced and emptied by means of the inspired air, whose turbulence separates drug and carrier. Similar devices working on gelatin capsules filled with drug-carrier mixtures are the Berotec®, Boehringer Ingelheim, and the Rothaler®, Glaxo-Wellcome[8]. Considerations linked to the slow operative procedures for device loading and the immediate therapeutic needs of an asthma attack, pushed the development towards multidose DPI devices, like Turbohaler®, Astra[9], and Pulvinal®, Chiesi[10], that are based on a reservoir containing the drug that is dosed by the patient with an appropriate and easy to perform manoeuvre on the base of the device. On the other side the Diskhaler®, Glaxo-Wellcome[7], and its development Diskus®[11-13], are based on pre-metered doses in blisters.

Powder formulation for inhalatory delivery

Common to all the pulmonary delivery devices is the need to generate a respirable aerosol. This is particularly evident in DPI technology. The emission from the device of a powder cloud containing a high amount of respirable particles, i.e. particle having aerodynamic diameter lower than 5 µm, is a regulatory requisite. The fraction of the dose having the d_{ae} lower than 5 µm constitutes the respirable fraction[14]. It is quite common to find values of respirable fraction lower than 50% of the emitted dose, mainly due to the difficulty to aerosolize efficiently the powder contained in the device reservoir.

The aerodynamic diameter is a complex parameter since it does not correspond to the real particle dimension, but it is rather the equivalent diameter of a sphere flying as the real particle. This means that the aerodynamic size includes other characteristics of the real particles, like the density and shape, which

affect aerosol performance[15]. It is evident that, at the same volume, low density particles possess better flight properties and that shape is also important for their transport in the air stream. In addition to the fundamental properties of the particle, i.e. size and shape, the derived properties of powders, i.e. flow and packing, must be considered. These affect aerosolization as well since the powder dispersion in individual particles depends on the interactions between the particle themselves, which in turn determine flow and packing properties. Micronized particles are generally cohesive, mainly due to electrostatic interaction affected by environmental conditions (humidity) and electrostatic charge raised during filling and device manipulation. This aspect makes critical the procedure of particle manufacturing for inhalatory delivery. Fluid energy micronization and, in particular the spray-drying techniques, are very useful. The latter allows important modifications of the characteristics of drug particles in the case where their intrinsic properties make them difficult to aerosolize.

When a carrier is required, the knowledge of blending theory becomes very useful to improve the respirable fraction of the dose. As mentioned before, blending is compulsory when the active principle dose is very low and the success of the powder depends on the interaction between drug particles and carrier. This interaction must be able of maintaining the drug attached to the larger carrier particle, nevertheless such adhesion must be reversible in the turbulent air flow conditions generated by the inspiration of the patient through the device.

Several authors have been working on the development of drug particles with optimal properties for deep lung deposition. One of the very promising solutions is the one proposed by Advanced Inhalation Research and is based on the use of large porous particles that are capable of more efficient flight due to the substantial reduction of the density determined by the large increase in surface area that improves their buoyancy in the air stream[16]. This solution allows to obtain same flight performance of very small particles, but with a substantial increase in the real dimensions of the porous particles improving the operations of dose filling and sampling in the device.

Practically, a separation between the volume size and the aerodynamic size was obtained, thus allowing maintenance of the aerodynamic size useful for respiration together with the volume size useful for device preparation.

Finally, as briefly underlined, the micromeritics of the particles is the core of the DPI performance and many procedures could be applied to DPI technology in order to obtain a formulation capable of deep lung penetration.

Device and flow path

Together with the formulative aspects, the design of a device, with the potential to generate an air flow capable to aerosolize the dose in a respirable high fraction, represents a crucial point for the therapeutical success of a DPI.

Ideally a sufficient level of turbulence, able to deaggregate the particles, should be reached with a minimal inspiratory effort by the patient. Optimal flow rate must be obtained in order to reach the maximum performance in terms of respirable fraction.

Recently, it has been demonstrated that flow rate better than maximum inspiratory peak is the relevant parameter for the performance of the device[17]. In general, comfortable devices in terms of use, have to be considered only those who require a limited inhalatory effort from the patient in order to reach efficient flow rate.

It has been determined that this effort should not exceed 50% of maximum effort[18]. It would also be beneficial to have a device with low dependence on the inspiratory flow rate since it would render the application quite independent on the inhalation conditions. The marketed DPIs show different resistance to the inspiratory act, aware that high resistance can generate high turbulence but at the same time can render more difficult breathing through the device.

The best solution would be to minimize the flow rate needed to completely empty the reservoir of drug by means of an appropriate design of the flow pathway.

The commercial devices present various interesting solutions, such as the peculiarly designed spiral channels able to maximize turbulence at lower flow (Turbohaler®), the passage of the powder through a grid generating

turbulence (Rotahaler®) or the presence of a small fan in the pathways to help achieve the de-aggregation of agglomerates mechanically as in the Spinhaler®.

However, the realization of long channels, even if potentially capable of generating high turbulence paths, with relatively high Reynolds' numbers, and associated with good deaggregation of the powder, has the disadvantage of a possible increase of the resistance of the device raising the effort of the patient during the inhalation act[19].

Therefore, in this case, the dose delivered to the patient is strictly dependent on the inspiratory flow rate applied with the possibility to have significant amounts of drug deposited inside the inhalation chamber of the device. In general, the pulmonary deposition of a drug in dry powder form is primarily dependent on the drug formulation (or drug/carrier formulation) and the inhaler design.

Thus, if the pulmonary efficiency is compromised, it would be likely difficult for a patient to generate a sufficient flow rate to achieve the complete inhalation of the drug. The different manufacture of current DPIs causes therefore performance variations in relation to the inhalation flow rate needed for each of them to finely disperse the dose of the drug released to the patient[20].

In fact the inspiratory flow rate requested and the particles deaggregation are peculiar characteristics of each device and strictly dependent on physico-chemical properties of the drug like size distribution, morphology and particle density[21].

Powders

Drugs for inhalation can be formulated in two ways: in pure form or mixed with an excipient. Once they have been formulated, they must be accurately metered for inhalation, either in pre-metered unit doses or by dosing mechanisms contained in the inhaler itself.

Formulating powders for inhalation

The dose of pharmacologically active powders for inhalation is usually small, ranging from typically 50 µg in the case of corticosteroids, to 20 mg, in the case of sodium cromoglycate, for instance. Especially in the former case, amounts are so small that to formulate accurate individual doses is a challenge; the solution has been either to pelletize the drug or to mix it with a bulking excipient, such as lactose.

Lactose increases the volume of the powder and makes it easier to accurately meter it. During the blending process, the smaller particles of active drug will coat the lactose particles, so that they act as a carrier for the drug.

Dispensing powders for inhalation

Powder blends can be dispensed in two ways in the DPI: inside a powder reservoir from which doses will be metered, or in pre-metered discrete containers.

Powder reservoir DPIs incorporate a metering system, usually volumetric: the powder exits the reservoir, either under gravity or pneumatic pressure and enters a chamber sized to hold one dose. This is the weakness of these systems, as the metering method is not always accurate. In the case of pre-metered devices, on the other hand, the powder is contained inside a capsule or a blister and the accuracy depends on the quality of the blending and filling processes, a technology which is far more advanced and which affords very little variation.

Airflow

Unlike MDIs, DPIs do not dispense a gas, rather a dry powder. There are a few DPIs which incorporate a pump system, but most portable DPIs rely solely on the energy of the inhalation to entrain, aerosolise and deliver the powder to the patient's lungs. Thus, their mechanism of action is also their Achilles' heel: by making delivery dependent on inhalation flow, performance becomes a function of the energy of the patient's inhalation. If the patient's breathing is severely impaired, or in the case of a child with a low peak inspiratory flow rate, it may happen that not enough energy will be available to entrain the powder.

In a DPI, powder entrainment energy is a function of the quantity of air that the patient draws through the device during inhalation and of the resistance of the device to the passage of air.

Airflow is measured conventionally in litres per minute (though a much more appropriate unit, in the field of human inhalation, would be litres per second). An adult is able to completely fill up the lungs in less

than one second – the fastest rate – but can achieve the same result during several seconds of a more sustained inhalation.

In the fast case, an adult, with a lung capacity of 3 litres of air breathing in with the mouth wide open for one second, will be inhaling at the rate of 180 litres per minute; for two seconds, 90 litres, for three seconds, 60 litres, etc.

Dry-powder inhalers are designed to be used at a certain airflow, or range of airflow rates. By testing inhalers *in-vitro* at their rated airflow (30, 60 and 100 L/min), the results obtained will be a good predictor of *in-vivo* performance.

Air resistance

Devices are more or less resistant to the passage of air. DPIs with very narrow mouthpieces and narrow passageways have high resistance; those with wide channels have low resistance. The lower the resistance, the faster a patient is able to inhale through a DPI and fill the lungs with air; on the contrary, with high resistance, the patient is inhaling against the resistance of the inhaler: the inhaler becomes "felt" and the duration of inhalation becomes longer.

If the patient decides to increase the strength of the inhalation to shorten its duration, discomfort is felt in the chest; some people will even be able to locate in the diaphragm the focus of the pressure difference. Air resistance (R) is measured in cm $H_2O^{½}$/(l/min) and typical values will range from 0.04 for the Rotahaler to 0.18 for the Inhalator. The three airflow rates proposed (30, 60 and 100 l/min) are thus to be used *in-vitro* according to the following resistance levels:

For R < 0.07 cm $H_2O^{½}$/l/min, test at 100 l/min during 2 seconds.
For R = 0.07 to 0.12 cm $H_2O^{½}$/l/min, test at 60 l/min during 4 seconds.
For R > 0.12 cm $H_2O^{½}$/l/min, test at 30 l/min during 10 seconds.

Here is how some inhalers are classified according to this system (Table I):

Other factors being constant, the greater the resistance, the greater the energy to entrain the powder. However, the greater the resistance, the greater the patient's discomfort, if the directive for inhalation is "inhale-as-fast-as-possible", a breathing technique which will impart more energy to the delivery and dispersion of the powder.

We have seen that airflow and resistance have a direct influence on energy. It is useful to show how this happens.

Pressure drop

Pressure drop (DP) is measured in millibar and relates airflow to resistance, in the following equation:

$$DP = \frac{(\text{Airflow})^2}{R}$$

where:

DP is in millibar.
Airflow is in litres per minute.
R is in cm $H_2O^{½}$/(l/min).

Returning to the airflow rates proposed for each resistance interval, the pressure drop for the upper R limit for each airflow rate is:

Table I. DPIs' flows and resistaces characteristics.

Airflow Rate	*Resistance (R)*	*Brand Name*	*Laboratory*
30 lpm	0.18	Inhalator	Boehringer
	0.19	Pulvinal	Chiesi
60 lpm	0.10	Turbuhaler	Astra-Draco
	0.117	FlowCaps	Hovione
100 lpm	0.051	Spinhaler	Fisons
	0.040	Rotahaler	Glaxo
	0.067	Diskhaler	Glaxo

At 100 l/min, DP = (100 × 0.07) = 49 millibar
At 60 l/min, DP = (60 × 0.12) = 51.84 millibar.
At 30 l/min, DP = (30 × 0.12) = 12.96 millibar.

This means that for the rates of 60 and 100 l/min, limiting the resistance of the device in such a way that pressure drop generated by the patient is not greater than about 50 millibar. As the maximum pressure drop intercostal muscles can generate is about 80 millibar, this limit of 50 millibar should be seen as the maximum physiologically acceptable pressure drop in an inhaler, used at 60 l/min or more.

Airflow independence

The question of whether the performance of a DPI is flow-independent or not is presently the most debated issue in conferences and in the literature. It is inescapable than in the case of a breath-actuated DPI, one which does not use motors or pumps to help disperse the powder and deliver it to the patient, therapeutical efficacy depends greatly on inhalation energy.

Some DPIs rely on an exterior power source to disperse the dry powder, which has several advantages: the performance of the inhaler becomes airflow independent - meaning that the powder will always be similarly dispersed, whether strongly inhaled or not - and the quality of the dispersion (the fine particle mass) will be very high. On the negative side is cost and reliability. These DPIs are significantly more complicated to build, have more systems that can break down without warning and are more expensive than simpler breath actuated DPIs.

Other types of DPIs are able to achieve flow-independence; in one particular model, the designer made a conscious decision to direct the inhalation energy to the emission of the powder and fully achieve it at a low airflow: if 100% of the drug is emitted at 30 l/min, then this will necessarily be the case at 60 l/min as well and the requirement for flow-independence will be met. The cost of this choice is therapeutical efficacy: by directing energy exclusively at the emission of the drug, none is left to maximise dispersion and fine particle fraction (fine particle fractions between 20 and 25% are reported for this device).

The issue of flow-independence makes it imperative to determine two parameters for all breath-actuated DPIs:

- Below which flow rate does the DPI performance fall dramatically?
- Above which flow rate does the DPI performance become fairly stable?

By "DPI performance" what is meant here relates to total emitted dose and to fine particle fraction. The higher these numbers, the better. Obviously, in the ideal DPI, the first flow rate should be as low as possible. A DPI should be able to start emitting its dose with flow rates as low as 20 l/min. The second airflow rate, that at which emission will become fairly stable, should be at an airflow little different from the first level, say 30 l/min. This means that the inhaler will have basically the same performance in terms of emitted dose, at most airflow rates.

Relating improvements in the fine particle fraction to changes in airflow is more difficult, because presently available analytical systems are calibrated for only 2 airflow rates (28.2 and 60 l/min). The uncertainty of re-calibration is a deterrent against the procedure and we do not intend to use neither the twin-impinger nor the Andersen at non-standard airflow rates.

The ideal DPI

From the observations made in this issue, the following characteristics of the ideal DPI can be identified (Table II):

This is the ideal inhaler and it does not exist in the real world. Some features are incompatible. For instance, reservoir-based DPIs offer the best convenience to the patient, because they hold up to 200 doses; on the negative side, their required metering systems have been unable to match the precision of pre-metered doses.

Real airflow independence is possible with an additional power source (batteries or mechanical air pump), but devices are more complex and expensive and the probability of breakdown increases. Breath-actuated inhalers can also be designed in such a way that the full dose is administered even at a very low flow, but as we have seen, fine particle fraction is not maximised.

Ultimately, the choice of an inhaler can be determined by an objective evaluation using

Table II. Characteristics of the ideal DPI.

Item	*Feature*
Efficacy	Must deliver a high quantity of respirable, fine particle drug (< 5 μm), independently of the patient's inhalation airflow and with complete emission.
Reproducibility	Must deliver reproducible doses, both of the total emitted dose and of the fine particle fraction.
Assurance of delivery	Must inform the patient that the full dose is being taken has been taken.
Stability	Must ensure that the drug remains stable for a long period of time when stored inside the device
Convenience	Must be simple and comfortable to use. Should not require more than two preparatory steps before inhalation. Must be portable and unobtrusive. Must contain a large number of doses.
Reliability	Must have a minimum of parts and mechanisms that can break down. Should be a mechanical device, in preference to battery-operated.
Cost	Should permit re-loading and in that case, must permit a large number of actuations. Should permit a low cost per actuation.
Versatility	Should technically be able to deliver several drugs.

the above table as a checklist, but also by subjective preference.

Novelty in DPIs

Recently Inhale Therapeutic Systems introduced a device that consists of a chamber where a stable cloud of drug is produced and from where the patient extracts the aerosol with a slow and easily controllable breath. This system is designed to be "flow rate independent", which means it can deliver a metered dose of drug relatively independent of a patient ability to inhale forcefully. The device is composed of two main components: the body and the inhalation chamber. The basic concept of the system is to apply mechanical energy to disperse and aerosolize the dry powder drug which is contained in specifically designed blisters. The key components of the technology are the dispersing element contained in the body of the inhaler and the inhalation chamber. After introduction of the dose inside a special aperture in the body of the inhaler, the activation of a mechanism opens the blister and a special lever on the front of the body activates the aerosolization of the powder inside the inhalation chamber. The cloud is stable for several seconds after aerosolization. A patient then opens the chamber cap and inhales the stationary cloud with a slow, deep inhalation. This eliminates the need for patient coordination between generation of the aerosol and the breathing activity and encourages slow, deep inspiration for deep lung delivery.

Another device "flow rate independent", developed by Dura Pharmaceuticals and named Spiros® is composed of two main components: the inhaler and the powder storage system. The key components of the technology are the battery operated motor, the breath actuated switch, the impeller, the mouthpiece and the dosing chamber.

The motor spins the impeller, which whips the powdered drug into an aerosolized drug. Each powder storage cassette contains 30 metered doses and the energy necessary to aerosolize the drug comes from the battery-powered motor. The delivery of drug is breath actuated and the inhaler is designed to be used for 1500 doses before a replacement is needed.

Conclusions

The replacement of MDIs, in particular considering the convenience and versatility of these devices is far from being reached by DPIs. Until now DPIs have been developed for specific products, therefore they possess a reduced versatility in term of application of the same device to different drugs. However, they did introduce new concepts in pulmonary drug delivery, solving some disadvantages of the pressurized devices. They are in their infancy and the efforts of researchers are now impressive. The future will certainly see many other devices containing additional innovative

features for the effective respiratory delivery of drug. The goals still remain the delivery of precise and uniform drug doses and increasing the respirable fraction in relation to the dose emitted from the device. The most updated concept in this field of powder respiratory drug would probably be the production of a device in which the emptying of reservoir and the de-agglomeration of the powder will be separate from the respiratory act.

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