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Review Article

How can we bring high drug doses to the lung?

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ABSTRACT

In the last decades, dry powder inhalation has become a very attractive option for pulmonary drug delivery to treat lung diseases like cystic fibroses and lung infections. In contrast to the traditional pulmonary application of drugs for asthma and chronic obstructive pulmonary disease, these therapies require higher lung doses to be administered. The developments and improvements toward high dose powder pulmonary drug delivery are summarized and discussed in this chapter. These include the invention and improvement of novel inhaler devices as well as the further development of formulation principles and new powder engineering methods. The implementation of these strategies is subsequently described for some prototypes and formulations in research and development stage as well as for already marketed dry powder products. Finally, possible adverse effects that can occur after inhalation of high powder doses are shortly addressed.

1. Introduction: why pulmonary drug delivery?

The main benefit of pulmonary drug administration is the delivery directly to the location of the disease, while minimizing systemic exposure and toxicity [1]. Pulmonary delivery is characterized by a rapid clinical response and the ability to bypass therapeutic barriers such as poor gastrointestinal absorption and first-pass metabolism in the liver [2]. It can achieve a similar or superior therapeutic effect at a fraction of the systemic dose. For example, an oral dose of 2–4 mg salbutamol is therapeutically equivalent to 100–200 μg by inhalation [2]. This is particularly important when considering aminoglycoside antibiotics for the treatment of *Pseudomonas aeruginosa* infections of the lung. Only low sputum aminoglycoside concentrations are achieved by the administration of relatively high intravenous doses, which carry the potential for systemic toxicity, whereas high sputum concentrations can be achieved by inhalation without the risk of systemic toxicity [3]. Inhaled medications have been available for many years for the treatment of lung diseases like asthma and chronic obstructive pulmonary disease (COPD). Devices and formulations were designed for the administration of relatively low doses ranging from 6 to 500 μg [4]. In recent years, the treatment for other diseases like cystic fibroses and lung infections, as well as systemic diseases by pulmonary administration, has become more attractive. However, these therapies in general require higher doses to be effectively administered to the lung.

2. Devices for pulmonary drug delivery

Systems for pulmonary delivery include pressurized metered dose inhalers (pMDI), soft mist inhalers, nebulizer and dry powder inhalers (DPI). With respect to delivered dose, pMDIs and the Respimat® soft mist inhaler were designed for the delivery of highly potent drugs for the treatment of asthma and COPD, but face several factors that limit high dose delivery. Due to a poor delivery efficiency (mean lung deposition of 12%), a small metering valve of 25–100 μl [5] and limited increase in concentration [6], only small delivered doses of less than a milligram per puff can be achieved with pMDIs [7]. The Respimat® soft mist inhaler improved delivery efficiency to about 40%, but high dose delivery is still limited by a small metering chamber of only 15 μl [8]. Thus, pulmonary delivery of high drug doses has been realized by nebulization of liquid formulations. This form of administration has some drawbacks, such as restricted portability of jet and ultrasonic nebulizers due to the required power source, as well as a noisy compressor for jet nebulizers. These drawbacks were improved for portable battery-powered vibrating mesh nebulizers. The administration is nevertheless time-consuming and regular cleaning and disinfection of the systems are required [9]. This is particularly apparent for cystic fibrosis (CF) patients, where the time burden is immense when applying several aerosol therapies. It may take up to three

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hours per day for the administration of drugs followed by the cleaning and sanitizing of the aerosol equipment [7].

DPIs have the capacity to deliver higher payloads of drug to the lung. The first DPI (Aerohaler) was used in 1964 for the inhalation of 100,000 units of crystalline penicillin G sodium dust (approximately 60 mg) three times a day to treat patients with various infections of the respiratory tract [10]. In 1971 the Spinhaler® was developed [11] and approved for the delivery of 20 mg of the anti-asthmatic drug cromolyn sodium [12]. However, early DPI devices featured poor delivery efficiencies (only 4–17% lung delivery for cromolyn sodium) and the dosing performance depended on the patient's inspiratory flow rate [13,14]. In order to be effectively delivered to the alveolar region, particles must have an aerodynamic size between 1 and 5 μm [2]. Particles in this size range are extremely adhesive and cohesive. To improve powder fluidization and aid in de-aggregation, the micronized drug is either formulated with controlled agglomeration (soft pellets) or, most often, blended with larger carrier particles [15] in a drug-carrier ratio of usually 1:67.5 [16,17]. The high percentage of carrier particles and the poor delivery efficiency limit the maximum lung dose, which can be delivered in one actuation, to just a few milligrams [6]. For administration of an appropriate lung dose of the antiviral drug zanamivir, for example, the patient needs to inhale two blisters containing 5 mg zanamivir formulated with 20 mg lactose-monohydrate twice a day [18]. Additionally, the large variations in lung deposition which depend on the inspiratory flow rate restrict the standard blending technology to drugs with a relatively large therapeutic index [19]. There has been continuous development of DPIs in order to overcome these limitations. A specific de-agglomeration zone was introduced for enhanced fine drug particle separation by turbulences and multi-dose DPIs were designed [4]. The Novolizer® and the AirMax™ devices use tangential air flow which forms a cyclone in the device for optimized powder dispersion [20]. This approach improves lung delivery [21], but still shows variable performance at different flow rates [22,23]. In contrast, drug delivery with the Taifun® device, which incorporates a vortex chamber, is relatively independent of the inhalation flow [24]. Constant drug deposition at different flow rates is also shown with the Turbospin® device, where the inspiratory air is drawn through aerodynamically designed slits of the capsule chamber, putting it into a vortical motion. This causes shaking and twisting of the capsule for efficient powder release [25,26]. DPIs that include an active mechanism for powder dispersion are less dependent on the patient's inspiratory flow, which is particularly important when considering systemic drug delivery. The Exubera® and the Aspirair™ devices are aimed for systemic delivery and use compressed air for powder aerosolization [27–29]. Nevertheless, all of the devices described above are designed for the delivery of small doses. DPI with drugs like anticholinergics, beta-2-agonists or glucocorticoids to treat asthma and COPD contain between 6 and 500 μg drug per dose [4]. An apomorphine hydrochloride formulation at 400–800 μg for the treatment of male erectile dysfunction was recently developed using the Aspirair™ device [29]. The Exubera® device was designed for the delivery of 1 or 3 mg of a dry powder insulin formulation to treat diabetes [27,28].

In spite of the still existing limitations for the delivery of larger doses, Crowther-Labiris et al. [3] administered a lactose-blended micronized gentamicin dry powder formulation using the Clickhaler® device (nominal dose of 160 mg gentamicin) to ten chronically *P. aeruginosa* infected patients. These patients had to take 32 inhalations to achieve a cumulative lung dose of 60 mg gentamicin. A new device designed for the delivery of high powder doses is the Twincer®. It is used for the application of antibiotics and sugar glass formulations containing, for example, therapeutic proteins. With this device, de Boer et al. [30] demonstrated that powder doses up to 25 mg of pure drug can effectively be de-agglomerated, which possibly could be further optimized to a dose of 50 mg. Depending on the size of the classifier chamber, fine particle fractions between 40% and 60% were achieved for 8 mg colistin sulfomethate. The powder formulation is stored in a blister strip, which can be opened by pulling the cover foil sticking out of the inhaler. During inhalation, the air passes through the powder channel and entrains the powder, which is then divided into two circular classifiers until it is discharged via holes into the mouthpiece. This new aerosolization principle distinguishes the single-dose-device from classical capsule based devices. Furthermore, the Twincer® was designed as a low cost disposable inhaler, which makes it also appealing for medications that have to be given only once (e.g., vaccines) [30]. Another interesting novel dry powder inhaler for the delivery of high dose (25–250 mg) cohesive powders was described by Young et al. [31,32]. The inhaler aerosolizes powder by using pressurized canisters filled with nitrogen gas at a pressure of 6–14 bar. The powder is contained in a sealed disposable vial. An FPF of approximately 40% related to delivered dose could be achieved with a loading dose of 120 mg. A downside of this inhaler could be the large amount of pressurized gas required, which also requires a long time period to exhaust. For delivered dose studies using 12 bar nitrogen canisters, the device was actuated for a 10 s period [32]. A similar approach by using a standard propellant canister is described by Winkler et al. [33]. In this multi-dose inhaler, the powder is dispersed by utilizing liquid propellant into the cavities of a blister strip containing the metered doses. This concept considers a breath actuation, a cavity opening and a transport mechanism. A dose of up to 16 mg of fine particle is reported in combination with that device. Recently the Novartis Podhaler® (T-326 Inhaler), which evolved from the Turbospin® device, was approved to address the needs of high-payload delivery of engineered tobramycin particles of around 50 mg. It was designed to have a low airflow resistance (0.08 cm $H_2O^{1/2}$/LPM) to allow patients to generate high airflow rates. A size 2 capsule is inserted into the device and pierced twice at the bottom by a staple. Similar to the Turbospin® device, the vortical air flow causes the capsule to spin while powder is shaken out of the two pierced holes and aerosolized [34]. *In vitro* particle depositions were found to be largely independent of the inhalation maneuver [35]. Although single-dose capsule based inhalers were the first DPI devices on the market, this technology still has a great popularity and its use for high dose delivery has been demonstrated.

3. Powder formulation methods

New powder formulation methods are equally important as sophisticated devices for an efficient delivery of high dose DPI products. Owing to their small size, micron-sized particles are extremely adhesive and cohesive. To enhance powder flowability and dispersibility, the main formulation method is blending with large (30–90 μm) lactose carrier particles [17]. These lactose blends consist mainly of excipients and therefore hinder a delivery of high drug doses. Nevertheless, improved lung delivery efficiency can be a first step toward the delivery of higher lung doses. Strategies to improve lung delivery from lactose blends are summarized in the following. For these formulations, two oppositional requirements must be fulfilled. On the one hand, adhesion between carrier and drug must be sufficient for the blend to be stable enough to allow handlings such as filling. On the other hand, it needs to be weak enough to enable the release of the drug after inhalation when the carrier particles remain in the inhaler device or deposit in the oropharynx due to their large size. Drug detachment from the carrier during aerosolization is therefore crucial for efficient lung delivery [36]. To prevent incomplete de-agglomeration and improve lung delivery, different methods have been applied to

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