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Review article

Formulation and product development of dry powder inhaler: an overview

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ABSTRACT

This review focuses on the dry powder inhaler (DPI) formulation and development process. Most DPI formulations consist of micronized drug blended with larger carrier particles, which enhance flow, reduce aggregation, and aid in dispersion. A combination of intrinsic physicochemical properties, particle size, shape, surface area, and morphology affects the forces of interaction and aerodynamic properties, which in turn determine fluidization, dispersion, delivery to the lungs, and deposition in the peripheral airways. When a DPI is actuated, the formulation is fluidized and enters the patient's airways. Under the influence of inspiratory airflow, the drug particles separate from the carrier particles and are carried deep into the lungs. If the cohesive forces acting on the powder are too strong, the shear of the airflow may not be sufficient to separate the drug from the carrier particles, which results in low deposition efficiency. This review thus demonstrates that the successful delivery of dry powder aerosols to the lung requires careful consideration of the powder production process, formulation and inhaler device. The developments and improvements towards high dose powder pulmonary drug delivery are summarized and discussed here. It also throws light on the invention and improvement of novel inhaler devices as well as the further development of formulation principles and new powder engineering methods.

Keywords: Dry powder inhaler, Carrier particle, Aerodynamic diameter, formulation development trigger.

INTRODUCTION

Since ancient times pulmonary route has been used to treat various respiratory diseases. Ancient therapies include the use of leaves from plant, vapours from aromatic plants, balsam and myrrh. Although aerosols of various types have been in use since the middle of the 20th century, the use of pulmonary route for systemic delivery is recent. Targeting the delivery of drug into the lungs is one of the important aspects of local or systemic drug delivery systems. Development of pharmaceuticals for inhalation is basically a challenging job as it involves formulation and selection of device for aerosol dispersion. The lungs have lower buffering capacity than any other delivery sites which limits the range of excipients that could enhance the delivery outcomes. Nowadays, respiratory diseases such as asthma or COPD are mostly treated using pressurized metered dose inhalers (MDI). However, the use of chlorofluorocarbon (CFC) propellants in the manufacture of MDI is a matter of growing concern towards environmental hazards. As a solution to this problem, a range of alternatives devices, such as dry powder inhalers, which do not contain propellants are being evaluated and developed [1].

Advantages of Pulmonary Drug Delivery

Large surface area is available for absorption.

Avoidance of first pass hepatics metabolism.

Compared to other oral route smaller doses are required to achieve equivalent therapeutic effect.

Provides fast drug action.

Provides local action within the respiratory tract.

Reduction in systemic side-effects.

Reduces extracellular enzyme levels compared to GI tract due to the large alveolar surface area.

Disadvantages of Pulmonary Drug Delivery

In order to get effective drug deposition, aerodynamic filter present efficiently in lungs must be overcome.

Pulmonary airways having mucous lining clears the deposited particles towards the throat.

Only 10-40% of the drug leaving the inhalation device usually deposited in the lungs.

It has short-lived duration of activity because drugs are rapidly removed from the lungs or because of rapid drug metabolism.

Require frequent dosing [2].

Dry Powder Inhaler (DPI)

Inhaled drug delivery systems can be divided into 3 principal categories: pressurized metered- dose inhalers (pMDIs), dry powder inhaler (DPIs), and nebulizers, each class with its unique strengths and weaknesses. The pMDI is the most widely used device taking into account its global market share of about 80%. pMDI emit dose at high velocity which causes deposition mostly in the oropharynx, also it requires more careful coordination of actuation and inhalation. 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. Moreover, the use of chloflourocarbon (CFC) and hydroflouroalkane (HFA) as propellants in this drug delivery system has raised an environmental concern regarding ozone depletion. The development of DPIs has been encouraged to overcome disadvantages of pMDIs and to aid the delivery of macromolecules and products of biotechnology. Concurrently, DPIs proved successful in addressing other device and formulation-related shortcomings of the pMDI.

Dry powder inhalers contain the drug in a powder formulation, where drug particles (< 5 μm) are blended with a suitable large carrier (e.g. lactose) to improve flow properties and dose uniformity and drug powders are delivered deep into the lung via a device known as dry powder inhaler (DPI). Powder de-agglomeration and aeroionisation from these formulations are achieved by the patient's inspiratory airflow. When the patient activates the DPI and inhales, airflow through the device creates shear and turbulence; air is introduced into the powder bed and the static powder blend is fluidized and enters the patient's airways. There, the drug particles separate from the carrier particles and are carried deep into the lungs, while the larger carrier particles impact in the oropharynx and are cleared. Thus, deposition into the lungs is determined by the patient's variable inspiratory airflow.

While most DPIs are breath-activated, relying on inhalation for aerosol generation, several power-assisted devices (pneumatic, impact force, and vibratory) have been developed or are currently under development. These devices are being considered for the delivery of systemically active drugs that have narrow therapeutic windows. It is important to note that these "active" inhalers are not subject to the same limitations as passive inhalers and have a different advantage/disadvantage profile [3].

Moreover, it has been suggested that if shear and turbulence could be standardized by using a dispersion mechanism that is independent of the patient's breath, high delivery efficiency and reproducibility might be achieved. Thus, an active inhaler might provide formulation- independent delivery.

Advantages

Enviromental sustainability

Propellant-free design

No coordination required.

Less potential for formulation problems.

Less potential for extractable from device components.

Formulation stability.

Disadvantages

Deposition efficiencydepends on patients inspiratory airflow.

Greater potential problems in dose uniformity.

Less protectionfrom environmental effects.

More expensivethan pressurized metered dose inhalers.

Development and manufacturing is more complex than pMDI.

Principle of DPI

DPIs can be divided mainly into two classes: passive and active devices. Passive devices rely upon the patient's inhalatory flow through the DPI to provide the energy needed for dispersion. When the patient activates the DPI and inhales, airflow through the device creates turbulence, inspired air is introduced into the powder blend and is fluidized and enters the patient's airways. Due to turbulence the drug particles separate from the carrier particles and deposited into the lungs as schematically given in fig 1, while the carrier particles impact in the oropharynx and cleared. Thus, deposition of drug is determined by the patient's inspiratory air-flow. Dose uniformity is a challenge in the performance of DPIs [4].

Formulation of DPI

Dry powder inhaler formulations consist of the active pharmaceutical ingredient alone or carrier powder mixed with drug. Particle size of drug should be micronized less than 5 μm. The micronisation of drug is done by various techniques such as milling, spray drying, and supercritical fluid extraction. The requirement to use micronized drug (less than 5 μm) particle achieve good aerodynamic properties of the dispersed powder. Various techniques are being established to improve formulation performance by development of tertiary excipients like magnesium stearate and leucine. It helps in improving the performance of formulation by interfering with inter-particle bonding. The use of leucine in the DPI formulation as a ternary additive has helped in improving the performance of the DPI formulations due to its antiadherent action.

Carrier in DPI

Carrier particles are used to improve drug particle flow ability, improving dosing accuracy, minimizing the dose variability and

making them easier to handle during manufacturing operations. The use of carrier particles tends to facilitate the easy emission of drug particles from capsules and devices, thereby increasing the inhalation efficiency. Design of the carrier particle is important for the development of DPIs. The required characteristics of carrier particles include physico-chemical stability, biocompatibility and biodegradability. Also it should be compatible with the drug substance and must be inert, available and economical. Lactose is the most common and frequently used carrier in DPI formulations and nowadays various inhalation grades of lactose with different physico- chemical properties are available in the market.

Lactose, in particular alpha-lactose monohydrate, is typically used as carrier in dry powder inhalers. However, there are several drawbacks of lactose and modified lactose as a carrier for dry powder inhalers, which creates an urgency to find suitable alternative carriers for better drug dispersibility in DPI. Alternative carriers like mannitol, glucose, sorbitol, maltitol, and xylitol are also used as potential carriers in DPI formulations. Mannitol seemed to be a promising carrier for DPIs because sorbitol, maltitol and xylitol sugars were not able to generate desirable FPF (Fine particle fraction) due to their hygroscopic nature. Carrier like crystallized mannitol (Pearlitol 110 C), spray-dried mannitol (Pearlitol 100 SD), crystallized maltitol (Maltisorb P90) and spray- dried lactose (Lactopress SD 250) [5].

Moisture Content: Water in the drug product should be strictly limited since it may have a significant effect on characteristics such as aerosolization of the particles, particle size distribution, crystallinity, dose content uniformity, microbial content, and stability. The Karl Fisher method has been accepted to a greater extent for the measurement of small amounts of water present in the inhalation powder which has important effect on capillary condensation, solid-state phase behaviour, solid- state properties, and solid-state stability of pharmaceutical particles in the solid-state.

Drug Content (Assay): The drug concentration present in the formulation (in the entire container) should be determined analytically with a stability indicating method. The acceptance criteria should as high as possible to ensure conformance in other related aspects (e.g., dose content uniformity).

Impurities and Degradation Products: By means of stability indicating methods the levels of degradation products and impurities should be determined. Acceptance criteria should be set for individual and total degradation products and maximum impurities. For identification and qualification thresholds, refer to the appropriate guidance. If the individual impurities or degradation products appearing at levels 0.10 percent or greater it should be specified.

Specified impurities and degradation products are those, either identified or unidentified, that are individually listed and limited in the drug product specification.

Microbial Limits: The microbial quality should be controlled by suitable tests and acceptance criteria for total aerobic count, total yeast and mold count, and freedom from designated indicator pathogens.

Delivered Dose Uniformity

Both air flow rate and total volume of air drawn through the device should be thoroughly evaluated to obtain optimum test conditions. It is recommended that the volume of air drawn through the device be limited to two liters. Acceptance criteria and tests would apply to both device-metered DPIs and pre-metered DPIs (e.g., blisters, capsules). In the case of device- metered DPIs, the dose content uniformity should be established and monitored at the beginning, middle, and end of the labeled number of doses [6].

Aerodynamic Particle Size Distribution

The current pharmacopeial procedure for assessing the aerosol aerodynamic particle size distribution (APSD) from a dry powder inhaler (DPI) includes the aerosolization and release of the powder bolus containing the active pharmaceutical ingredient(s) (API(s)) from the inhaler. The aerosol generation process and release of the aerosol bolus from the inhaler is accomplished by coupling the mouthpiece of the DPI containing the API(s) in either bulk powder (reservoir) or single-dose format to the entrance of an induction port whose purpose is to provide a basic simulation of an adult oropharynx. A preseparator is commonly inserted between the induction port and the pre-assembled impactor for the purpose of capturing carrier-bound API particles that collectively may be an order of magnitude in size larger than the carrier-free, disaggregated micronized API particles that are typically inhaled to provide therapeutic benefit. The preseparator also serves to capture any API- containing particles (agglomerates *etc.*) that may be released particularly from reservoir-based DPIs, particles whose size exceeds the effective cut off diameter of the first stage of the cascade impactor. The complete system is connected to a vacuum pump *via* a flow controller containing a critical orifice that eliminates the impact of fluctuations caused by variations in pump performance. The capacity of the vacuum pump is chosen such that the ratio of pressures downstream (P) and upstream (P) of the flow pressure drop over the device. The word “critical” means that the flow has reached sonic velocity right at the controlling orifice. This condition therefore has nothing to do with the impactor, but it is merely a method of controlling the impactor flow rate in a reliable and reproducible manner. Other methods of controlling flow rely on human intervention (valves and flow

meters) or on electronic feedback control. These more electronic control methods could be subject to wear, drift over time, and electronic failures. Once the system has been assembled, actuation of the DPI takes place by initiation of flow propagating backwards from the vacuum pump, through the impactor, preseparator and induction port, and finally through the device itself. In the simplest methodology, the sampling duration can be set by a timer-operated solenoid valve that allows flow from the pump to enter the impactor system for a predetermined duration [7, 8].

CONCLUSION

DPI can be considered as an attractive drug delivery system, both for drug that are to be administered for local therapy in the lung, as well as for drugs that act systematically and for which the lung is only port of entry to the body. They have several advantages like propellant free nature, high patient compliance, high dose carrying capacity and drug stability. It has become subject of interest for the treatment of iseases like: asthma, chronic obstructive pulmonary disease (COPD). Currently, the inhalation performance of DPIs is being improved by changing formulation strategy, drug and carrier particle engineering. The future research in DPIs will thus aim to assimilate drug in a matrix particle to achieve specific pulmonary drug deposition and probably to achieve intracellular drug delivery especially, proteins, peptides, plasmids, DNA etc. The design of inhaler needs improvement to meet requirements of an ideal inhaler. A better understanding of the influencing properties of powder on the performance of DPI will help to address the challenges in the development of DPI formulation and inhaler devices for optimum therapeutic benefits.

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