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Review Article

EVALUATION STUDY OF DRY POWDER INHALERS: A CONCISE, SYSTEMATIC REVIEW

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A B S T R A C T

A dry powder inhaler (DPI) is a device that delivers medication to the lungs in the form of a dry powder, in different regions of the airways in prophylaxis/ treatment/ diagnosis of pulmonary and systemic disorders [1]. Interest in DPI as an efficient and environmentally friendly way of delivering drugs to the lung has accelerated in recent years [2]. Most of the Pharmaceutical companies are now prioritizing in the development of dry powder inhalers (DPIs) above pressurized formulations for the delivery of medications to treat various lungs diseases [3]. The efficacy of the drug and its treatment can be achieved from the new ideas on controlling the pharmacokinetics, pharmacodynamics, formulation, an efficient metering system, and a carefully selected device [4]. This study provides an in-depth analysis of the development in the methods to identify lung deposition study and in-vitro evaluation of dry powder inhalers.

INTRODUCTION

Pulmonary drug delivery system

Pulmonary drug delivery continues to demonstrate steady growth in the global market in the last several years, due to its unique properties such as a large absorptive area of up to $100m^2$; extremely thin 0.1-0.2µm absorptive mucosal membrane and good blood supply [5]. Pulmonary route have been used to treat various respiratory diseases for centuries. Ancient inhalation therapies included the use of leaves from plants, vapours from aromatic plants, balsams, and myrrh. Pulmonary route of drug has become an attractive target and of tremendous scientific and biomedical interest in the health care research area as the lung is capable of absorbing pharmaceuticals either for local deposition or for systemic delivery [6]. It is a needle free technique which has been developed in the recent past, to improve the Quality of pulmonary drug delivery system without affecting their integrity. Because of advancement in applications of pulmonary drug delivery it is useful for multiple diseases. So pulmonary drug delivery is best route of administration as compare to other routes [7]. Understanding the transport and deposition of inhaled aerosols is of fundamental importance to inhalation therapy. The efficacy of the drug and its treatment can be achieved from the new ideas on controlling the pharmacokinetics, pharmacodynamics, immunoginecity, and biorecognition.

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Devices used to deliver drug by pulmonary route area based on one of three platforms pressurized metered dose inhaler, nebulizer and dry powder.

Advantages of Pulmonary Drug Delivery System

- The large protein molecules which might be degrade in gastrointestinal tract and eliminated by first pass metabolism are given by pulmonary route which avoid the first pass metabolism.
- Pulmonary drug delivery System has negligible side effect as the rest of body is not exposed to drugs.
- Drugs given by pulmonary route gives quick onset of action.
- Pulmonary delivery also offers the potential for better and perhaps more economical treatment or prophylaxis of respiratory and systemic diseases.
- It is non-invasive drug delivery system.
- Pulmonary drug delivery system is needle free technique.
- Drug is directly deposited in the lung, so minimizes the dose requirement.
- Respiratory tract provide a large surface area which is highly permeable for absorption of drug into the blood.
- Reduction of dosage i.e. Drug content of one 4 mg tablet of salbutamol equals to 40 doses of meter doses [2,4,12].

History of Inhalation Therapy

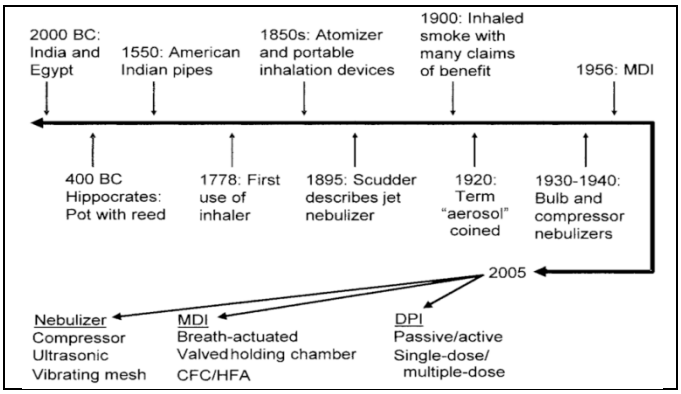


Figure 1 An abridged timeline of the history of aerosol therapy. MDI metered-dose inhaler. CFC chlorofluorocarbon. HFA hydro fluoroalkane. DPI dry powder inhaler [25].

Following types of inhalation devices are present

Inhaler technology is currently used to administer an extensive list of medications, including glucocorticoids, beta-agonists, anticholinergics, and certain antibiotics directly to the lungs. There are different kinds of devices available on the market useful for pulmonary administration. A wide variety of different inhalers is available and can be broadly diverged into three distinct classes:

Inhalation drug delivery system by- Metered dose inhalers
Inhalation drug delivery system by- Nebulizer
Inhalation drug delivery system by-Dry powder inhalers

Each class with its unique strengths and weaknesses. This classification is based on the physical states of dispersed-phase and continuous medium, and within each class further differentiation is based on metering, means of dispersion, or design [9].

Nebulizers: Since mid-nineteenth century nebulizers are utilized as a part of treatment Nebulizers are a type of inhaler device that aerosolizes a solution of medication using compressed gas, a mesh, or ultrasonic waves. The primary disadvantages of nebulizers are the length of time it takes to use them; external power requirement, their size and weight may limit portability. Presently, there are three main types of nebulizer devices: jet, mesh, and ultrasonic.

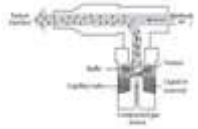


Figure 2 Components of a jet (a) and an ultrasonic (b) nebulisers [10].

Jet nebulizer: Jet nebulizers produce an aerosol by delivering a jet flow of compressed air or oxygen through a narrow opening, creating an area of negative pressure directly above a reservoir of medication.

Mesh nebulizer: Mesh nebulizers are portable, battery operated devices that produce a liquid aerosol by forcing a solution of medication through a mesh or plate with multiple apertures. This avoids the requirement of a compressed air source or an internal baffling system. Furthermore, these devices typically generate aerosols with a high fine particle fraction (FPF) compared to conventional jet or ultrasonic nebulizers, thus improving their ability to deliver drugs to the lower respiratory tract.

Ultrasonic nebulizer: Ultrasonic nebulizers convert electrical energy into high-frequency ultrasonic waves using a power unit. The high-frequency ultrasonic waves then stimulate the mechanical vibration of a piezoelectric element in the transducer. This transmits the high-frequency vibrations to the surface of the liquid reservoir to create an aerosol [11].

Pressurized metered dose inhalers: The Pressurised MDIs (pMDI) was the first type of inhaler device to be marketed for the treatment of airway disease (1956) .They are compact, portable, relatively inexpensive, and contain at least 200 metered doses per canister that are immediately ready for the use. It is the most cost-effective type of inhaler device and the and quickly gained widespread acceptance [8]. The propellant is a liquefied compressed gas that can maintain a constant vapour pressure, which is essential for proper device functionality as it allows for a consistent suspension pressure regardless of the volume remaining in the canister. They consist of a micronized form of the drug in a propellant under pressure with surfactants to prevent clumping of drug crystals [12]. The principal components of a typical MDI are the container, the metering valve and the actuator.

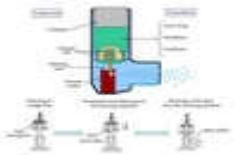


Figure 3 Components of a pressurised metered-dose inhaler. Lower panels illustrate the process of aerosol generation. From [10].

Breath-actuated pMDIs: Breath-actuated (BA) pMDIs are alternatives to conventional press-and-breath pMDIs are a newer generation of inhaler technology designed specifically to address the issue of poor actuation-inhalation coordination and thus improve patient compliance and confidence.

Dry Powder Inhaler (DPI): Modern dry powder inhalers were first introduced in 1970, were developed to provide an alternate solution to MDIs in the management of airway disease. Dry powder inhaler are the delivery devices containing pharmacologically active drug particles (<5 µm) in powdered formulation, blended with suitable carrier that have been milled to produce micronized particles in the respirable range. Most commonly used carrier is Lactose Monohydrate [13]. DPIs are a promising option for certain patient populations and may help to overcome several limitations that are associated with other types of inhalation delivery devices such as accuracy and reproducibility of the dose delivered, compliance and adherence issues, or environmental aspects [14].

Figure 4 Different dry powder inhalers [17].

Many factors affect the device performance. Some of the factors include such as

- Mouth piece configuration,
- Grid structure and mouthpiece length,

- Impaction angle of the powder with devices
- Air inlet size [15]

Majority of DPI's are passive breath- actuated devices. Once loaded the patient puts mouth piece of inhaler into their mouth and take a deep inhalation holding the amount of dose delivered is less than few tens of milligrams in a single push. Larger powder may cause cough [16].

Trends in dry powder inhalation technology

- Changes in the performance of the DPI can be achieved either through changes in the design of the device by changes in the powder formulation, the forces governing the particle-particle interactions in the agglomerates and the forces playing a role in the de-agglomeration process.
- Supercritical fluid technology is applied to improve the surface properties of the drug substance. Large porous particles have reduced inter-particulate forces because of their low density, the irregular surface structure and/or reduced surface free energy. Moreover, these particles are claimed to have improved aerodynamic behaviour in the airways, whereas phagocytosis of the deposited particles in the alveoli is reduced. In another approach, smaller porous particles (3-5mm) have been used to improve de-agglomeration and lung deposition.
- Changes in device technologies are few new developments really aim at an increase of the de-agglomeration forces generated during the inhalation.
- Air classifier Technology has been recently used in the devices to prevent agglomeration in devices. In this technology multiple classifier chambers are placed in a parallel arrangement, which further increases the dose that can be aerosolized [24].

Ideal characteristics for DPI devices
Characteristics of ideal DPI systems will include most or all of the following attributes

- Simple and comfortable to use
- Compact and economical to produce
- Highly reproducible fine-particle dosing.
- Multidose system
- Overdose protection
- Minimal extrapulmonary loss of drug, with low oropharyngeal deposition, low device retention and low exhaled loss.
- Indicate number of doses delivered and/or remaining
- Physically and chemically stable powder
- Powder protected external environment and can be used in all climates and protected from moist exhaled air [18].

Advantages of dry powder inhalers

Typical advantages of dry powder inhalers are

- Formulation stability
- Less potential for extractables from device components
- Environmental sustainability
- Propellant- free design
- Less need for patient coordination

Disadvantages of dry powder inhalers

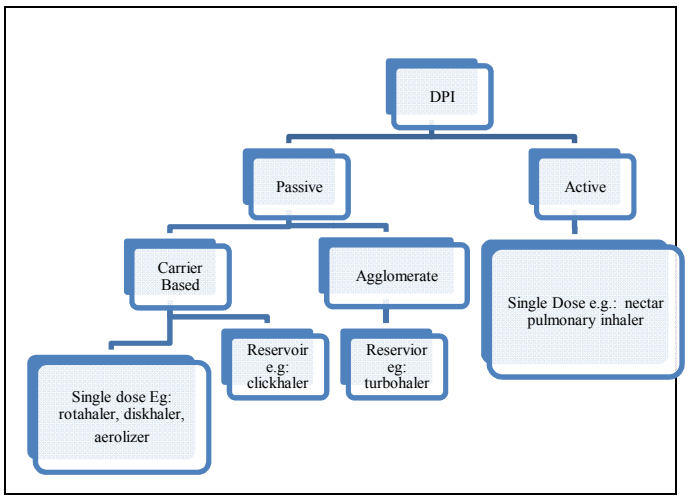
Typical disadvantages of dry powder inhalers are

- Less protection from environmental effects and patient abuse
- More expensive than pressurized metered dose inhalers
- Not available world wide
- Development and manufacture more complex/expensive
- Dependency on patient's inspiratory flow rate and profile
- Device resistance and other design issues
- Greater potential problems in dose uniformity [22]

Overview of the DPI's Family

In particular, dry powder inhaler devices are mainly classified by the number of doses the device can carry, the patient contribution to aerosolize the powder, or by the mechanism of powder dispersion. By the number of doses, DPIs can be classified as:

1. Single unit dose
2. Multi –unit dose
3. Multi –dose reservoir



Classification of DPIs

1. In a single-unit dose device, the drug is formulated as a micronized drug powder and carrier system and supplied in individual gelatin capsules, before each administration, the patient has to load the device with one capsule for a single dose delivery. Single dose device is further classified into single unit dose, single use disposable.
2. Multi-unit dose DPIs, use factory-metered and sealed doses packaged so that the device can hold multiple doses at the same time without having to be reloaded.
3. Multi-dose reservoir DPIs store the powder in bulk and have a built-in mechanism to meter individual doses upon actuation. Issues such devices are the environmental humidity into the reservoir or the dependence of the dose and the moisture uptake from patient exhalation.

Based on the mechanism for powder aerosolization, DPIs can be classified as passively- or actively-actuated devices. The first passive DPIs in the market were the Rotahaler and the Spinhaler, which are single-dose devices. In the rotahaler, a capsule with the powder dose is loaded in the device. Active

(power assisted) DPI devices are designed with an internal energy source to aerosolize the powder bed in the DPI, so that dose administration is no longer dependent on the patient inspiratory flow rate. In active devices, the powder is dispersed by vibration, gas discharge, or an impeller. When the patient inhales, an electrical impulse is sent to the blister, stimulating the piezoelectric polymer which is incorporated in each sealed blister to vibrate ejecting the powder into a flow stream [19].

Lung deposition study

The deposition of inhaled particles in the human respiratory tract depends fundamentally on the particle properties and the way the patients breathe at the time of delivery. The vital size characteristic for deposition is called aerodynamic diameter, it is determined by the actual size of the particle, its shape, and its density. A small amount of particles in the aerodynamic size range of approximately 3.5-6µm can penetrate to some extent at moderate inspiratory flow rates beyond the central airways into the peripheral region of the lung, while particles less than 3.5µm and greater than approximately 0.5µm will largely bypass the bronchial airways during inhalation and penetrate almost entirely to the deep lung.

Table 1 Summary of the methods used to identify the lung deposition of inhaled products [21].

1. Pharmacokinetic (using plasma or urine samples)
- Relative lung deposition (drugs with an extensive first pass, charcoal block, absorption lag times)
- Total systemic delivery
2. Gamma Scintigraphy
- Two dimensional
- SPECT
- PET
3. Clinical studies
- Spirometry (crossover or parallel design)
- Bronchoprovocation for lung disposition
- Multiple dosing for extra-pulmonary effects
4. In vitro

Determination of the in vitro particle size distribution, fine particle (respirable) dose, emitted dose
Pharmacokinetic methods:

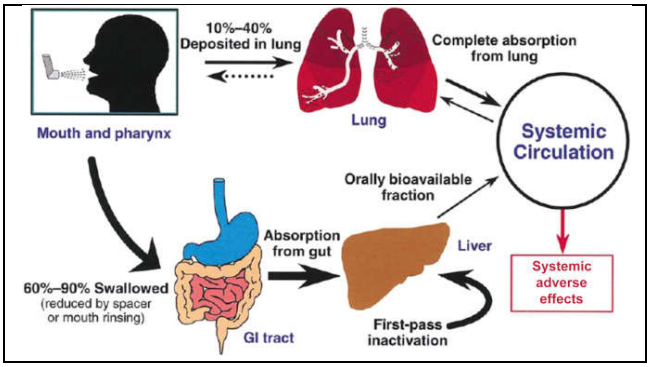


Figure 5 Pharmacokinetic description of an inhaled dose [20].

Various pharmacokinetic methods have been described for assessing drug deposition in the lungs, based on the quantification of drug in plasma or urine. Pharmacokinetic methods are indirect measurements because they utilize measurements from serum or urine to identify the amount of drug delivered to the systemic circulation via the lungs and gastrointestinal tract thus procedures to differentiate between these two routes of absorption are required.

Estimation of delivery can be achieved by comparing area-under-the-curve data or urinary drug excretion (to infinity) for inhaled products. To associate the effective lung dose, methods which differentiate between drug delivered to the systemic circulation via the oral and pulmonary routes are needed.

To separate systemic delivery via the gastrointestinal and pulmonary routes, oral charcoal to block all gastrointestinal absorption or sampling during the lag time of the absorption phase has been used. The 'charcoal block' method, used to quantified the amount of drug deposited in the lungs can be quantified for a limited range of drugs following the blocking of gastrointestinal absorption by a swallowed charcoal slurry. The concentrations of drug in either the urine or in plasma during the first 30 or 60 min after inhalation may also constitute an index of lung deposition for some drugs, since the contribution of swallowed drug to systemic levels is negligible during these time periods. The major limitations of pharmacokinetic methods are highly drug specific and also do not provide any data about the pattern of regional deposition within the lungs themselves [21].

Imaging Techniques

The radionuclide imaging methods of gamma scintigraphy, single photon emission computed tomography (SPECT) and positron emission tomography (PET) enable whole lung deposition to be quantified and regional lung deposition to be assessed. These parameters will determine the amount of drug deposited in the lungs from inhalers, and also determine directly the clinical efficacy of drugs given by inhalation.

Gamma Scintigraphy

Gamma scintigraphy was first used during diagnostic testing, and its use was extended to pharmaceuticals in the 1970s. Gamma scintigraphy is the most practical and widespread of these methods and can accurately quantify the amount of drug delivered to the lungs for any inhaled drug product.

Two-dimensional gamma scintigraphy has been the most commonly used method to determine the lung deposition following inhalations. Using this method, if two inhalation products deliver the same amount of drug and have similar whole lung and regional deposition patterns then their clinical effect within the airways should be the same. This method allows extensive characterization of the particle size distribution emitted from an inhaler. Scintigraphy methods involve changes to the original formulation to incorporate the radiolabel. However, for dry powder inhalers the multistage liquid impinger has been recommended. Following inhalation, the lungs and oropharynx are imaged in two dimensions by a large radiation detector connected to a data processing system in which images are stored as a matrix of picture elements (pixels).

Lung deposition patterns are assessed by dividing the lung fields into a series of zones representing primarily deposition in large, medium and small diameter airways.

Three-dimensional imaging techniques: The three-dimensional imaging techniques such as SPECT and PET offer the potential advantage of being able to relate deposition patterns within the lungs more precisely to airways of different sizes than is possible in gamma scintigraphy.

SPECT (single photon emission computed tomography)

This method is as similar to two - dimensional gamma scintigraphy except that the gamma camera rotates through 360. This allows a full three-dimensional reconstruction of the lungs but takes much longer so the radiation dose has to be higher. Furthermore, the technique is difficult to apply to multidose inhaled products. By using this method it is possible to create a three dimensional penetration index which provides more sensitivity than two dimensional imaging.

PET (Positron emission tomography)

PET imaging has a further potential benefit, in that it is possible to chemically incorporate a radiolabel directly into the structure of the drug molecule. The ones recently used are positron emitters such as 11C or 18F. Disadvantages of this new method are that the positron emitters used so far have short half-lives and the method is very expensive [20].

General Guidelines for In Vitro Testing of DPIs

Appearance and Colour: The appearance of the contents of the container (i.e., formulation) and the appearance of components of the container closure system should comply with their respective descriptions as an indication of the drug product integrity. For example, if any color is present with the formulation then a quantitative test with relevant acceptance criteria should be established for the drug product.

Delivered Dosage Uniformity (DDU): Dosage Unit Sampling Apparatus (DUSA) for desired testing device are used to perform Delivered Dose Uniformity test. The total quantity of drug emitted from the device, thereby accessible to the user is termed as the delivered dose. Not more than two actuations per determination should be used for DDU. The amount of drug substance discharged should be expressed both as the actual weight and as a percent of the label claim from the actuator. Delivered dose uniformity is a critical quality attribute (CQA) in determining the safety, quality and efficacy of inhaled drug products. For dry powder inhalers DSUA is a bigger version of MDIs sampling apparatus, which is available for use with flow rates up to 100 l/min for sampling.

Aerodynamic Particle Size Distribution (ASPD): The equipment such as multistage cascade impactor, vacuum source, valve used to characterize the APSD of the DPI product. Appropriate minimum number of products (e.g.5) should be tested individually and the determination for each unit should be performed with the minimum number of actuations justified by the sensitivity of the analytical procedure used to quantitate the deposited drug. The amount of drug deposited on the critical stages of the cascade impactor should be sufficient for reliable assay, but not so excessive as to bias the results by masking individual actuation variability. Testing should be carried out under the same optimized conditions of air flow rate as is used in the DDU test. Acceptance criteria should be proposed based on the amount of drug deposited on various stages of the equipment. In most cases, three or four groupings should be sufficient to characterize the APSD adequately.

Sieve analysis: By weighing the material received on each sieve the particle size distribution can be calculated. To known particle size distribution sieves can be calibrated with reference materials. Sieves works well for coarse as well as granulated lactose. Fine powders may often lock the holes present in the sieves. Therefore for finer lactose grades air-jet sieving works better but it has a disadvantage that only one sieve screen at a time can be operated. For the measurement of particle size of lactose various sieve analysis techniques are present. Sieving could be done by using nest of standard sieves shaken on a sieve shaker or with air-jet sieving.

Laser diffraction: it is stated that laser diffraction involves. The measurement of, "a representative sample, dispersed at an adequate concentration in a suitable liquid or gas". The light of the laser beam is diffracted in different directions and the scatter pattern is recorded by detectors. The scatter pattern is strongly related to the particle size and the size distribution of the particles. The result of laser diffraction techniques is often expressed as a volume distribution

Moisture Content: 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, dose content uniformity. Although this test may not be directly related in terms of performance of inhalation aerosols, it provides assurance of consistency concerning the manufacture of the drug product such as formulation, filling, crimping, and sealing.

Net Content: This method used to determine the weather sufficient product has been placed into each container. The other method is a destructive method and consists of weighing a full container and then dispersing the contents. Other modifications consists of opening the container and removing as much as the product as possible. These tests are not indicated in determining the actual net content of each container as related to the amount that can actually be dispensed.

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. Furthermore, proper testing should be done to show that the drug product doesn't support the microorganism's growth and that microbial quality is maintained throughout the expiration period.

Spray Pattern: Comparison of spray pattern obtained from different batches of material or through the use of different valves should be used. The method of comparison is based on the impingement of the spray on a piece of paper that has been treated with a dye-talc mixture. Depending on the nature type of powder, oil soluble or water soluble dye is used.

Extractables/Leachable: This method determined whether any of the extractables or leachable presents in the formulation at the end of the shelf life of the product. The leachable profile should also be determined for compendial plastics and rubber container closure components. Identification should be seek for compounds that appear as leachable and also safety assessments should be conducted in accordance with sufficient established safety thresholds. Depending on the levels and types of compounds detected, consideration should be given to

including a test and limits for leachable in the drug product specification [22].

CONCLUSION

According to World Health Organization (WHO), nearly 240 Million people worldwide are affected by the chronic obstructive pulmonary disease (COPD), and approximately 300Million people worldwide are affected by asthma. Some of the essential performance characteristics regarding dry powder inhalers are associated with dose-delivery, fine particle fraction content and performances at varying airflows. These characteristics may vary with respect to, creating the need for fine tuning of the device or powder formulation, or both combined for achieving optimal performance. The requirement is particularly high in micro-dosing dry powder inhalers, which in turn is paving opportunities for medical device manufacturers in terms of innovations and advancements [23]. The Regulatory authorities regard gamma scintigraphy and pharmacokinetic methods as useful supporting data. The appropriate use of lung deposition data instead of clinical efficacy data in regulatory packages should lead to significant time saving in the drug development process, and hence a faster development programmes for inhaled asthma products.

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