DRY POWDER INHALERS (DPI): A REVIEW

Patel Chirag J*, Satyanand Tyagi2, Patel Pinkesh1, Patel Jaimin1

1Department of pharmaceutics, Maharishi Arvind Institute of Pharmacy, Jaipur, Rajasthan, India- 302020.

2President, Tyagi Pharmacy Association & Scientific Writer (Pharmacy), Chattarpur, New Delhi, India-110074.

ABSTRACT

Now a day’s pulmonary drug delivery remains the preferred route for administration of various drugs. The search for alternatives to metered-dose inhalers (MDIs) has accelerated recently in a bid to find effective products that do not use chlorofluorocarbon propellants. A wide range of Dry powder inhalers (DPIs) devices are currently available on the market to deliver drugs into lungs with a view to maximize drug delivery with low variability. DPIs are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Some DPI used lactose as bulking agent and to aid in powder uptake from the device during inhalation. DPIs in general are easier to use than the MDI and cause fewer irritant effects. Unlike the MDI few patients develop a poor inhalation technique with continued use of DPIs.
1. **INTRODUCTION**:

Growing attention has been given to the potential of a pulmonary route as an non-invasive administration for systemic delivery of therapeutic agents (mainly peptides and proteins) due to the fact that the lungs could provide a large absorptive surface area (up to 100 m²) but extremely thin (0.1μm – 0.2μm) absorptive mucosal membrane and good blood supply. Pulmonary drug delivery is an important research area which impacts the treatment of illnesses including asthma, chronic obstructive pulmonary disease and various other diseases [1].

Advantages and disadvantages of pulmonary drug delivery system:

**Advantages [1, 2]**

1) Allows for a reduction in systemic side-effects.

2) Provides local action within the respiratory tract.

3) Provides reduced dose.

4) It can be employed as an alternative route to drug interaction when two or more medications are used concurrently.

5) Provides rapid drug action.

6) Offers the potential for pulmonary administration of systemically active materials.

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

8) Reduces evasion of first pass hepatic metabolism by absorbed drug.

**Disadvantages [3, 4]**

1. The duration of activity is often short-lived due to the rapid removal of drug from the lungs or due to drug metabolism.

2. Necessitates frequent dosing.
The aerosolization or inhalation of medicaments by humans has been used since late the 1950s and since 1956, the pressurized metered dose inhaler become the most commonly used device to deliver inhaled asthma drugs [5]; however, with the advancement of science and technology, pulmonary delivery of drugs has become the route of choice after the introduction of the DPI in 1967 [6]. Inhalation therapy, or pulmonary drug delivery, via MDIs, DPIs or nebulisers, is the preferred method of treating patients with asthma [7]. The clinical features of nebulisers, MDIs and DPIs have recently been compared and pulmonary drug delivery is increasingly becoming a target for systemic drug delivery as a result of its inherent convenience, ability to administer drugs with poor oral availability, and the large surface area of lungs and long residence times associated with peripheral lung deposition [8].

Technical challenges have resulted in a greater variety in design and function of DPIs relative to MDIs. Current designs include pre-metered and device-metered DPIs, both of which can be driven by patient inspiration alone or with power-assistance of some type. Pre-metered DPIs contain previously measured doses or dose fractions in some type of units (e.g., single or multiple presentations in blisters, capsules, or other cavities) that are subsequently inserted into the device during manufacture or by the patient before use. Thereafter, the dose may be inhaled directly from the pre-metered unit or it may be transferred to a chamber before being inhaled by the patient. Device-metered DPIs have an internal reservoir containing sufficient formulation for multiple doses that are metered by the device itself during actuation by the patient. The wide array of DPI designs, many with characteristics unique to the design, will present challenges in developing information in support of an application. Regardless of the DPI design, the most crucial attributes are the reproducibility of the dose and particle size distribution. Maintaining these qualities through the expiration dating period and ensuring the functionality of the device through its lifetime under patient-use conditions will probably present the most formidable challenge [6, 9, 10]. An ideal DPI should be a device (Figure: 1), which is simple to use, cost effective, convenient to carry, sufficient moisture protection, accurate and uniform dose delivery, deliver optimal drug particle size and high fine particle fraction (FPF) and low flow rate dependency [11, 12]. DPIs represent the most rapidly expanding field in pulmonary drug delivery in recent years, largely as a result of the perceived limitations in MDIs and nebulizers. Unlike MDIs, DPIs avoid problems inherent in the use of propellant gases and the need for coordination of inhalation and actuation [13].

Full Text Available On www.ijupbs.com
DPIs are subject to strict pharmaceutical and manufacturing standards by regulatory bodies, the most challenging of which is the demonstration of device reliability in terms of delivered dose uniformity [14].

Figure 1: Dry Powder Inhalers

DISTINCTIONS OF DPIs FROM CONVENTIONAL DRUG PRODUCTS/MDIs

DPIs are complex drug products that differ in many aspects from more conventional drug products as well as from MDIs. The unique characteristics of DPIs should be considered during development, particularly with respect to formulation, manufacturing, container and closure system or device, and both in-process and final controls. Several key distinctions of DPIs are listed below:

1. The device with all of its parts, including any protective packaging (e.g., overwrap), and the formulation together constitute the drug product. Unlike most other drug products, the dosing and performance and therefore the clinical efficacy of a DPI may be directly dependent on the design of the device.

2. The portion of the formulation that is delivered by inhalation to the patient consists of the neat drug substance controlled to a suitable particle size distribution (e.g., micronized, spray-dried) or the drug substance contained within a matrix of excipients.
3. Energy is required for dispersion and aerosolization of the formulation and the drug substance. Whereas MDIs use energy stored in a liquefied gas propellant under pressure for aerosolization and dispersion, DPIs may rely on several energy sources, including energy from patient inspiration, from compressed gas, or from a motor-driven impeller.

4. MDIs administer doses of the drug substance formulation to the patient without contamination of the remaining formulation under normal use conditions; this is not necessarily the case with DPIs. In particular, device-metered DPIs can be susceptible to contamination (e.g., moisture, microbial) of the remaining doses. Contamination aspects under both in-use and abuse conditions should be considered during development of the drug product.

In DPIs, interactions may occur between the drug substance, carrier(s), and components of the container and closure system that significantly affect the safety and effectiveness of the drug product. For example, gravitational, fluid dynamic, and other interactive forces, such as electrostatic, van der Waals, and capillary forces, together are responsible for different fluidization behaviors exhibited by different powders in an inhaler. Electrostatic charge interactions influence the overall efficiency of a DPI, since such forces are considered to be significant for attraction and adhesion between the drug substance particles, excipients particles, and device surface. Additionally, particle size distribution, particle morphology, and moisture content can greatly influence the bulk properties of the formulation and the product performance [15, 16].

**DEVELOPMENT OF AN IDEAL DPI**

The device should be easy to use, inexpensive and portable. The device must provide an environment where the drug can maintain its physicochemical stability and produce reproducible drug dosing. The device should be designed to deliver high fine particle fraction (FPF) of drugs from the formulations [17]. However, devices with higher resistance need a higher inspiratory force by the patients to achieve the desired air flow. This could be difficult for patients with severe asthma and for children and infants. Therefore, a balance between these two factors is necessary to achieve the desired therapeutic effect from DPI formulations.
For an ideal DPI a number of characteristics are important for device reliability, clinical efficacy and patient acceptance. These include:

1. A device which is simple to use, convenient to carry, contains multiple doses, protects the drug from moisture and has a indicator (audiovisual) of doses remaining
2. Dose delivery which is accurate and uniform over a wide range of inspiratory flow rates
3. Consistent dose delivery throughout the life of the inhaler and consistency of dose when compared to other similar inhalers
4. Optimal particle size of drug for deep lung delivery
5. Suitability for a wide range of drugs and doses
6. Minimum adhesion between drug formulation and devices
7. Product stability in the device
8. Cost-effectiveness
9. Feedback mechanism to inform the patient of dose administration [7, 14, 18].

No DPIs achieve all of these ideal characteristics; however, considerable research is being conducted to improve their performance characteristics where necessary. Some of these ideal characteristics are more important than others and will require different levels of improvement and/or innovation. Furthermore, others are influenced by the need for patient education in the proper use and storage of their DPI [19].

**COMPOSITION OF DPI [7, 20, 21]**

The composition of the formulation of a DPI has a direct effect on the stability of the formulation as well as on the dosing performance of the product. A carrier may be used for a DPI, for example, as a bulking agent to enhance reproducible dose metering. The suitability of a carrier is dependent on its chemical and physical characteristics, which can have direct effect on the performance of the product (e.g., ease of entrainment of the formulation, energy input necessary for dispersion and aerosolization of the active ingredient from the carrier, Hygroscopicity of the formulation). Hygroscopicity can result in uptake of moisture by the formulation which may affect the particle size distribution of the emitted drug substance, the stability of the drug substance, the dose hold-up in the device, and hence the delivered dose. The application should include a statement of the quantitative composition of the drug product, specifying the name and amount of each active and excipients contained in a stated quantity of the formulation.
These amounts should be expressed in concentration (i.e., amount per unit weight), as well as amount per metered dose and emitted dose at the mouthpiece under defined test conditions (e.g., flow rate, duration). For device-metered DPIs, the target formulation fill weight should also be indicated. A production batch formula representative of the one to be employed in the manufacture of the drug product should be included. Any calculated excess for an ingredient should be designated as such, the percent excess shown, scientifically justified, and documented in the submission.

**Lactose Monohydrate:** It is a commonly used carrier excipient for DPIs. Lactose carrier particles with low surface roughness may more effectively redisperse drug particles in an inhaled stream. Similarly, different morphic and amorphous forms of lactose may adhere differently to the drug substance particles and produce varying aerosolization behavior. Because the compendia monograph does not address the control for particle morphology and amorphous content, it should be supplemented with appropriate acceptance criteria and tests for control of these parameters in the application. Moreover, other additional recommended parameters for lactose include particle size distribution, quantitative color and clarity, assay, impurities and degradants, solvents, water content, microbial limits (total aerobic count, total mold and yeast, absence of pathogens), pyrogens, and/or bacterial endotoxins test, and specific and quantitative protein content. Protein determination may be performed by an adequate combination of specific and/or general methods (e.g., ELISA, Western Blot, amino acid analysis, Kjeldahl, Lowry, spectrophotometric assay).

**EVALUATION:**

The following test parameters are recommended for DPI drug products. Appropriate acceptance criteria and validated test methods should be established for each test parameter.

1. **Appearance and Color [7, 22, 23]**

The appearance of the content of the container (formulation contained in dose unit for pre-metered and reservoir for device-metered) and the appearance of the device components should conform to their respective descriptions as an indication of the drug product integrity. If there is any color associated with the formulation (either present initially or from degradative processes occurring during shelf life), then a quantitative acceptance criterion should be established for the drug product formulation.
2. **Identification [14, 24]**

Specific identification tests are recommended to verify the identity of the drug substance in the drug product. Chromatographic retention time alone is not an adequate method to ensure the identity of the drug substance in the drug product. If the drug substance is chiral, then at least one of the methods used for identification should be specific for this property.

3. **Microbial Limits [7, 25]**

The microbial quality should be controlled by appropriate tests and acceptance criteria for total aerobic count, total yeast and mold count, and freedom from designated indicator pathogens. Acceptance criteria should be reflective of the data for the submitted batches (e.g., clinical, preclinical, biobatch, primary stability, production) but at a minimum should meet the acceptance criteria proposed in the Pharmacopeial Forum. Furthermore, appropriate testing should be done to show that the drug product does not support the growth of microorganisms and that microbial quality is maintained throughout the expiration period. The minimum sample size should be 10 grams or the full content of ten containers.

4. **Water or Moisture Content [5, 7, 14]**

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.

5. **Net Content (Fill) Weight (Device-metered) [19, 21, 26]**

The total net weight of all formulation components in the container should be determined. The net content weight of each of ten test containers should be in accordance with the release specification.

6. **Drug Content (Assay) [5, 21, 26]**

This test determines the amount of the drug substance in each individual dosage unit for pre-metered DPIs and in the reservoir for device-metered DPIs. The assay should be determined analytically with a stability indicating method. The acceptance criteria should be tight enough to ensure conformance in other related attributes (e.g., dose content uniformity).

7. **Impurities and Degradation Products [5, 7]**

The levels of degradation products and impurities should be determined by means of stability indicating methods. Acceptance criteria should be set for individual and total degradation products and impurities. For identification and qualification thresholds, refer to the appropriate guidance. Individual impurities or degradation products appearing at levels 0.10 percent or greater 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.

8. **Dose Content Uniformity [5, 21, 27]**

The recommendations for acceptance criteria and tests for emitted dose content uniformity from the mouthpiece of DPIs under defined optimum test conditions are the same as for MDIs. 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.

The following acceptance criteria are recommended:

The amount of active ingredient per determination is not outside of 80–120 percent of label claim for more than one of nine determinations from three containers, none of the determinations is outside of 75–125 percent of the label claim, and means for each of the beginning, middle, and end determinations are not outside of 85–115 percent of label claim. If two or three of the nine determinations are outside of 80–120 percent of the label claim, none is outside of 75–125 percent of label claim, and the means for each of the beginning, middle, and end determinations are not outside of 85–115 percent of label claim, an additional six containers should be sampled at the beginning, middle and end of the canister (second tier). For the second tier of testing of a batch, the amount of active ingredient per determination is not outside of 80–120 percent of the label claim for more than 3 of all 27 determinations, none of the 27 determinations is outside of 75–125 percent of label claim, and the means for each of the beginning, middle, and end determinations are not outside of 85–115 percent of label claim.

9. **Particle Size Distribution of Emitted Dose [9, 23, 26]**

The emitted particle size distribution under defined test conditions should be determined by multistage cascade impaction to profile the aerodynamic diameters of the drug substance particles. The equipment and accessories should be selected so that the majority of the dose is introduced into the cascade impactor for fractionation. A complete profile of the dose including the finer particles (e.g., less than or equal to 2 μm) should be determined.
10. **Microscopic Evaluation [5, 7, 27]**

Before the advent of the impactor particle sizing methods, microscopic examination of the formulation was used to determine drug substance particle size. This method is relatively crude in measurement capability, is subjective, and does not provide a profile of the aerodynamic size of the delivered particles of drug substance. Furthermore, microscopy does not usually account for density of the particles and may not easily distinguish between, for example, two drug substances in a formulation. However, microscopic examination of the formulation has certain merits and, therefore, should be retained for release and stability purposes. For example, the examination provides information on the presence of large particles, changes in morphology of the drug substance particles, extent of agglomerates, crystal growth, and foreign particulate matter.

Appropriate acceptance criteria should be instituted for the appearance of the drug product formulation using a microscopic test approach. This test is useful for detection of large particles and agglomerates of the drug substance, can define morphology of drug substance and carrier particles, and can detect foreign particulate matter. The type, origin, and profile of foreign particulates, including fine particulates, should be controlled.

**LABELING [5, 14, 21, 28]**

To achieve consistency and uniformity in the content, product title, and format of DPI labeling, the following information pertinent to DPIs is recommended in the labeling.

1. **Product Title**

To standardize the nomenclature for oral DPIs, the established name of all such drug products should include the designation (Drug Substance) Inhalation Powder, and the metered dose. The name and strength should be followed by a phrase such as For oral inhalation only.

2. **Labels**

The label(s) should bear the following information:

1. Established name of the drug product
2. Metered-dose
3. Number of medication actuations per container or device
4. Net content (fill) weight (device-metered)
5. Usual dosage
6. Excipients (established names)
7. Route of administration
8. Recommended storage conditions including any warning statements regarding temperature, humidity, and light
9. Manufacturer's and/or distributor’s name and address
10. "Rx Only" or "L Only" statement
11. Lot number
12. Expiration date
13. Use period once the unit is removed from protective packaging (if applicable)
14. NDC number(s)
15. Dispensing instructions for pharmacist and additional statements for physician, if applicable
16. Reference to the patient’s instructions for use and additional instructional statements (e.g., loading instructions for pre-metered DPIs, inhalation instructions, instructions pertaining to protective caps, etc.)

DISCUSSION:
Most of the manufacturers and researchers are looking for novel efficient devices because in 2007, more than 20 new patent applications were filed for new designs of inhalers or parts of inhalers. Along with the device design, there is a great concern about the interaction between formulation and device that has to be accounted during designing a new device. DPI products may focus both on the inhaler device as well as the powder formulations for optimum therapeutic benefits. The delivery device may develop into a disposable device that will overcome the need for cleaning the device, concerns over product stability, and less expensive with improved patient compliance. Therefore, to realize the full potential of DPIs, at the lowest cost to both pharmaceutical companies and patients, innovation of new device with enhanced lung deposition and device reliability will play important roles in the future.

REFERENCES:


Full Text Available On www.ijupbs.com