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REVIEW ARTICLE

A Review on Dry-powder Inhaler

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ABSTRACT

In recent years, the pulmonary drug delivery system is found to be preferred route of administration for various drugs. It has been divided into three classes: Nebulizers, pressurized metered-dose inhalers, and dry-powder inhaler (DPI). This article focuses on the DPI formulation, principle of working, DPI devices, and evaluation parameters. DPI formulations consist of micronized drug blended with larger carrier particles, which enhance flow, reduce aggregation, and aid in dispersion. DPIs are commonly used to treat respiratory diseases such as asthma, bronchitis, and chronic obstructive pulmonary disease. DPI is formulated using four types of formulation strategies such as carrier-free, drug carrier, drug additive, and drug-carrier additive. The particle size of active pharmaceutical ingredients must be present in size range about 1–5 µm which also guarantee that the patient gets the same dose every time at different airflow rate. A DPI is a device that delivers medication to the lungs in the form of a dry powder. DPI devices can be categorized as capsule-based, blister based, canister/cartridge-based, and other types.

Keywords: Aerodynamic particle size distribution, blending, carrier, content uniformity, delivered dose uniformity, dry-powder inhaler

INTRODUCTION

Classification of inhaled drug delivery system[1-5]

Inhaled drug delivery systems are commonly used to treat respiratory diseases such as asthma, bronchitis, and chronic obstructive pulmonary disease (COPD). This classification of inhaled drug delivery system is based on the physical states of dispersed-phase and continuous medium. Nebulizers are distinctly different from both pressurized metered-dose inhalers (pMDIs) and dry-powder inhalers (DPIs), in that the drug is dissolved or suspended in a polar liquid, usually water. pMDIs and DPIs are bolus drug delivery devices that contain solid drug, suspended, or dissolved in a nonpolar volatile propellant or in a dry powder mix that is fluidized when the patient inhales.

Inhaled drug delivery systems can be divided into three principal categories:

- pMDIs,
- DPI,
- Nebulizers.

Nebulizers[2,5]

In this system, aerosols are generated from solution or suspension of the drug in an appropriate

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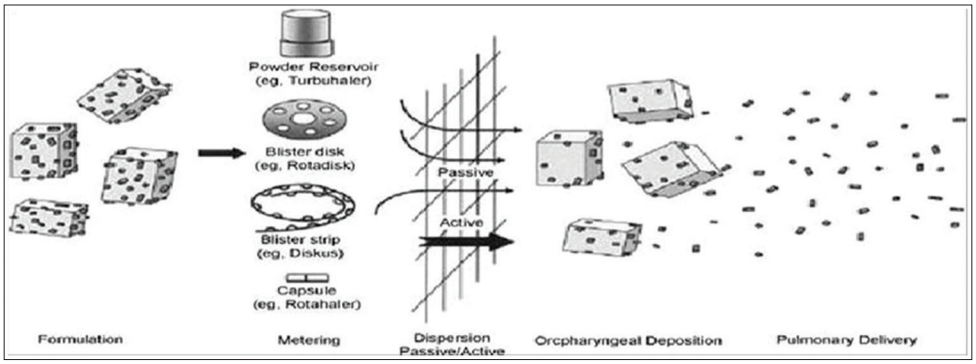

Figure 1: principle of working of dry-powder inhaler

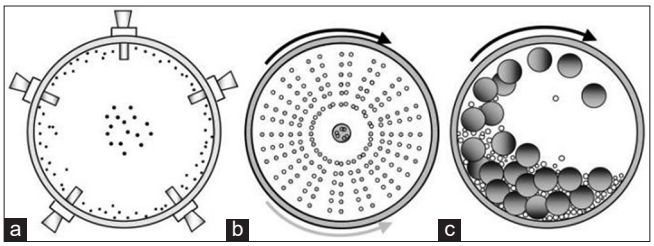

Figure 2: Micronization. Cross-sections of three mills commonly used to create micron-size particles. (a) Jet mill, (b) Pin mill, (c) Ball mill

solvent. These are utilized mostly in hospital and ambulatory care settings for delivering doses over multiple breaths, and to infants, elderly and critically ill patients. These formulations may contain preservatives to reduce microbial growth [Figures 1 and 2].

***Advantages of nebulizer*[2,5]**

1. High measurements of the drug can be utilized
2. Multiple medications can be utilized as a part of a single system
3. Requires less coordination of patient
4. Easy formulation handling.

***Disadvantages of nebulizer*[2,5]**

1. Equipment is expansive which is hard to transport
2. Variability in execution between various nebulizers
3. Need for an external power source
4. Nebulizers are not typically used for chronic disease management because they are larger and less convenient, and the aerosol is delivered continuously.

pMDI[2,5]

pMDI is the device in which medication is mixed into the canister with a propellant, and the performed mixture is expelled in precisely measured amounts on the actuation of the device. The principal components of a typical metered-dose inhaler (MDI) are the container, the metering valve, and the actuator.[6-12]

***Advantages of pMDI*[2,5]**

1. Easy to handle
2. Compact and convenient
3. High reliability
4. Accurate metering performance
5. Low cost.

***Disadvantages of pMDI*[2,5]**

1. It emits the dose at high velocity, which makes a premature deposition in the oropharynx more probable. Thus, use of pMDI limited to the treatment of the upper airway conditions due to low drug deposition in the lungs. Only 10–15% of dose is reached to the lung
2. They require careful coordination of actuation and inhalation
3. Drug content/dose is problematic if pMDI not shaken in the case of suspensions
4. It contains propellant such as chlorofluorocarbon (CFC) which depletes the ozone layer
5. pMDI is limited to certain drugs that are stable in a propellant.

DPI[2,5]

A DPI is a device that delivers medication to the lungs in the form of a dry powder [Table 1]. DPIs

Table 1: The main classes of DPIs, based on their intrinsic resistance and pressure drop across the device

Types of DPIs	Pressure drop across the device	Required inspiratory flow (L/min)	Example
Low resistance DPIs	<5 Mbar 1/2 L/min^{-1}	>90	Aerolizer, Breezhaler
Medium resistance DPIs	5–10 Mbar 1/2 L/min^{-1}	50–60	Turbohaler, Accuhaler/Diskus, Ellipta, Novolizer, Genuair
High resistance DPIs	>10 Mbar 1/2 L/min^{-1}	<50	Easyhaler, Twisthaler

DPI: Dry-powder inhaler

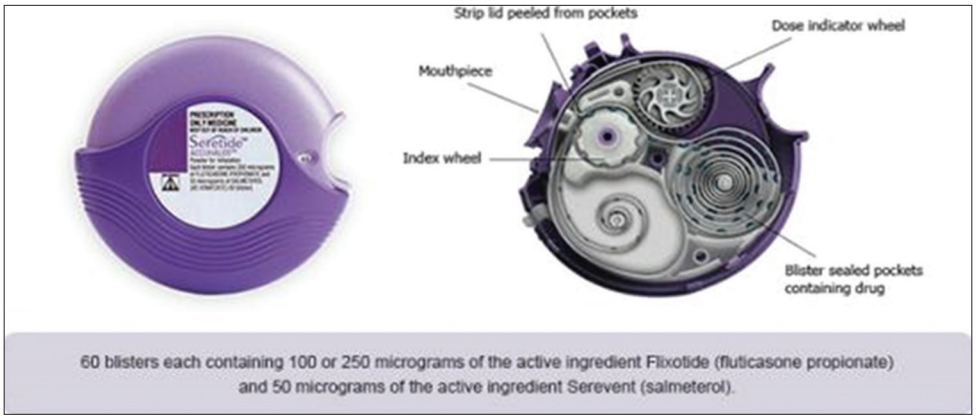

Figure 3: Blister-based device

Figure 4: System for testing the dose uniformity of dry-powder inhalers

Figure 5: Next generation impactor

are normally used to treat respiratory illnesses, such as asthma, bronchitis, emphysema, and COPD, although DPIs have additionally been utilized as a part of the treatment of diabetes mellitus. DPIs are a different option for pMDI [Figures 3-6].

Advantages of DPI[1,2,3,4,5,13,14]

1. Require little or no coordination of actuation and inhalation

Inaccurate utilization of pMDIs is still a predominant issue. It was found that poor coordination of

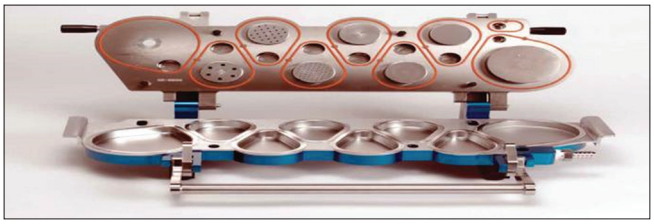

Figure 6: Next generation impactor (Open view)

actuation and inhalation caused decreased asthma control in a substantial proportion of patients treated with corticosteroid pMDIs. Whereas DPIs are activated by the patient's inspiratory airflow, they require little or no coordination of actuation and inhalation. This has frequently resulted in better lung delivery than was achieved with comparable pMDIs.

2. Formulation stability
   Since DPIs are typically formulated as one-phase, solid particle blends, so they are preferred as stable formulation. Dry powders are at a lower energy state, which reduces the rate of chemical degradation and the likelihood of reaction with contact surfaces.
3. Propellant-free design
   pMDI contains propellants such as CFCs and hydrofluoroalkanes which are ozone-depleting and greenhouse gases, respectively. Production

of CFC propellants was banned from January 1, 1996, to stop the depletion of ozone layer. Hence, pMDI was replaced by DPI which does not contain propellant. Hence, DPI's are environmental friendly formulation.

4. Other advantages of DPI

- High drug dose carrying capacities. DPIs can deliver a range of doses from <10 mg to more than 20 mg through one short inhalation
- Minimal extra pulmonary loss of drug due to low oropharyngeal deposition, low device retention, and low exhaled loss
- As the drug is deposited in lungs, DPI's having fewer side effects as the rest of the body is not exposed to drug
- Less potential for extractable from device components.

Disadvantages of DPI[1,3,4,14]

1. More expensive than pMDIs
2. Development and manufacture more complex/ expensive
3. Dependency on patients' inspiratory flow rate and profile
4. Device resistance and other design issues
5. Potential for dose uniformity problems.

GENERAL REQUIREMENTS OF DPI[2,5]

1. Particle size of active pharmaceutical ingredients (API)

Active compound must be inhalable. To able to pass into the lungs, it must be present in particles of size about 1–5 μm. Such microfine particles can be obtained by micronization, controlled precipitation from suitable solvent, or by spray drying if the procedure conditions are suitable.

2. Drug content uniformity

To guarantee that the patient gets the same dose every time, it is important that each capsule or blister in a single-dose system contains the same amount of powder and medication while in a multi-dose system; the reservoir must release the same amount of powder and drug every time.

3. Content uniformity at different airflows

Drug delivery from a DPI depends on the patient's breathing pattern. This implies that the dose has to be released in exactly the same way at low breathing and a high breathing rate. Content uniformity at different airflows is, therefore, extremely important for a DPI.

4. Stability of powder against humidity and temperature

Because the particle size distribution of lactose is extremely important for the action of a DPI, the lactose must be protected against particle size growth. The main property responsible for particle size growth is an undesired combination of temperature and relative humidity. Controlling the temperature and relative humidity, followed by storage in the correct packaging, are important for stability.

5. Flowability

This property needs to be sufficient to obtain a DPI with the correct amount of powder. Because almost all active ingredients have poor flowability, the good flow has to be supplied by the carrier.

PRINCIPLE OF WORKING OF DPI[1,2,3,5,15]

Most DPIs contain micronized drugs mixed with larger carrier particles, which prevents aggregation and helps flow property. Movement of particles can be brought about by several mechanisms, namely, passive and active.[16] Passive inhalers employ the patient's inspiratory flow. 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.[17] There, the drug particles separate from the carrier particles and are carried deep into the lungs, while the larger carrier particles impact in the oropharyngeal surface and are cleared.[18-22]

WHY DPIs ARE PREFERRED OVER MDIs[23]

- MDIs have disadvantages both in terms of use and effectiveness
- MDIs contain propellants like CFCs that are harmful to the environment
- The use of pressurized MDIs results in high oropharyngeal deposition, and a low amount of drug is delivered to the lungs

- MDIs require shaking before use to mix the drug and propellant, failure to do so will lead to inefficient drug delivery
- The absence of dose counters in these devices also causes a problem as it gets difficult to track the dose taken or remaining.

DPIs are a better alternative to MDIs as they have many advantages over them

- These devices are propellant-free and contain micronized drugs alone or in combination with a suitable excipient preferably lactose monohydrate
- The need for patient coordination with respect to actuation and inhalation is eliminated as DPIs are breath-activated
- This helps in effectively delivering therapeutic agents to the lungs and lower oropharyngeal deposition as compared to MDIs
- Most of the DPI devices have dose counters that help in detecting the number of doses remaining
- As the DPI formulation contains only a solid dosage from there is less potential for extractable from components of device
- The DPI devices are user-friendly and more convenient to use, and hence, are preferred by patients over MDIs.

FORMULATION OF DPI[1,2,3,24,5]

Formulation of DPI mainly includes three steps:

1. API production
2. Formulation of API with or without carriers
3. Integration of the formulation into the device.

API preparation

The final steps of bulk drug manufacture are crystallization from solution, filtration, and drying. Typically, the drug particle size is not well controlled during these steps. To create particles in the respirable size range (<5 μm in diameter), the drug particle size must be reduced in separate unit operation. The first size-reduction technique the formulation scientist will typically turn to is milling. There are many different mills, but only a few are able to mill powder to the required particle size range of 2–5 μm.

The three main types of mills used in API manufacture are fluid-energy mills, such as the jet mill and high-peripheral-speed mills, such as the pin-mill and the ball mill.

Jet milling (or air-attrition milling) is the most useful technique; it reduces particle size through high-velocity particle-particle collisions. Unmilled particles are introduced into the milling chamber. High-pressure nitrogen is fed through nozzles and accelerates the solid particles to sonic velocities. The particles collide and fracture. While flying around the mill, larger particles are subjected to higher centrifugal forces and are forced to the outer perimeter of the chamber. Small particles exit the mill through the central discharge stream. Depending on the nitrogen pressure and powder feed rate, particles down to 1 μm in diameter can be produced.

A pin mill uses mechanical impact to grind material, both by particle-particle and particle-solid collisions. A pin mill is equipped with a series of concentrically mounted pins located on a spinning rotor and stationary stator plate. The powder is fed to the milling chamber and transported through the milling chamber by centrifugal force. The milled product is collected from the bottom. The pin mill can produce 1 μm particles but not as small as the jet mill. On the other hand, the pin mill's power consumption is lower than that of the jet mill.

The ball mill is essentially a rotating cylinder loaded with drug and "milling media" (i.e., balls that grind the drug between each other as they tumble inside the mill). The size and material of the milling media can be varied. Ball milling is very slow, and the process is poorly scalable, which is why tumbling ball mills are used only in the laboratory.

Other techniques for making micron-size particles involve direct particle formation from solution. Two noteworthy approaches for controlling particle size are spray drying and supercritical fluid crystallization. These techniques are distinctly different from milling, in that the particles are built up (i.e., particle size is increased), whereas particle size is decreased during milling. In spray drying, the drug is dissolved in water or solvent and sprayed as fine mist into a heated

expansion chamber. The droplets dry, leaving behind tiny particles of drug that is collected at the bottom of the chamber. Compared to milling, spray drying can produce more spherical particles; however, spray-dried particles are mostly amorphous.

Spray drying and supercritical fluid methods offer more flexibility and the possibility of morphology control in addition to size control, but they may often yield only amorphous material or an undesired polymorph.

Formulation of API with or without carriers

Drug and carrier(s) are combined in the blending process. Inadequate mixing can bring about poor dose uniformity. In many cases, inadequate mixing cannot be overcome just by expanding the blending time. Blender choice, rotation speed, capacity, and fill level are all parameters for optimization which affects the blend homogeneity. There are high energy active sites on the surface of the coarse carrier particles thereby prompting to a strong adherence of the drug particles to the coarse carriers (Particle size >20 μm). Expansion of fine carrier particles (Fines <10 μm) saturates the active sites of coarse carrier particles mostly to which, then, micronized drug is attached. Hence, drug adheres to passive sites, i.e., less energy sites and facilitates the disaggregation of the micronized drug during inhalation.

Integration of the formulation into device

After the formulation has been blended, it is filled into capsules, multi-dose blisters, or reservoirs for use with the inhaler device. The filling process is automated and depends on the nature of the metering system.

FORMULATION STRATEGIES FOR DPI[2,5]

The efficacy of DPI is mainly depends on flow property of powder which is mainly affected by strong interparticle forces which make the cohesive bulk powder agglomerate. To overcome these difficulties different types of formulation strategies for DPI are as follows:

1. Carrier free
2. Drug carrier
3. Drug additives
4. Drug-carrier additives.

Carrier free

In carrier-free strategy, active therapeutic ingredient is in the form of a single compound, multi-compound composite or encapsulated particles. There are various production techniques ranging from crystallization and milling, spray drying, and supercritical fluid. Crystallization and milling were found unsuitable for preparing pulmonary drugs because they cannot produce optimal particle shape, narrow particle size distribution, low surface energy, and avoidance of amorphous material. The inhalation drug particle must have aerodynamic particle size <5 μm.

Drug carrier

It is hard to dispense 1 μg–1 mg of doses of the drug into the small blisters for DPIs. Furthermore, it is challenging to entrain powder by inhalation because the desired particles are between 1 μm and 5 μm. Hence, the drug molecules are mixed with larger particles to make them flow better and also to increase the volume of each dose. The geometric size of these carrier particles can range from 50 μm to 100 μm, for example, lactose, mannitol, and glucose.

Disadvantages

Carriers generally deposit in the mouth along with many drug particles adhered to them, which leads to less drug reaching the lungs, resulting in poor delivery efficiency.

Drug and additives

The addition of fine particles can also enhance the fluidization quality of drug fine powders. Van der Waals attraction is mainly rely on the particle-particle distance so by enlarging the separation distance will substantially reduce the adhesive force and consequently improves the fluidization behavior of

fine particles and also enhances the flow property of drug. Additives such as submicron silica (0.5–3 wt. %), alumina (29 nm), and aerosol 200 (12 nm) were used.

Drug carrier additives

The additive may be a fine particle such as a fine particle of the same composition as the carrier. The most common example of this type of system is the use of fine lactose in a lactose carrier system, for example, alumina and submicron silica.

DPI DEVICES[2,25,4,23]

DPI device delivers medication to the lungs in the form of dry powder.

DPI is mainly classified into:

- Active
- Passive.

The majority of DPI's are passive breath-actuated devices.

Passive DPI can be subdivided into two categories;

1. Pre metered where the dose is pre-measured during manufacture, for example, blister and capsule
2. Metered in which the drug is contained in reservoir within the device which pre-measures every dose on actuation.

There is no need to coordinate breathing with the activation.

Active device uses an energy source, independent of patient effort to generate the aerosol.

The ideal DPIs device should be[26]

1. Effective: Such as, able to consent the inhalation of a sufficient fraction of drug with a particle size ≤6 μ, independently of the patient's inspiratory flow;
2. Reproducible: Such as, able to always consent the inhalation of the same drug amount, also in terms of its respirable fraction;
3. Precise: Such as, able to consent to know at any moment the amount (or the no. of doses) of the drug remaining in the device, and whether or not the inhalation was correctly performed: Thus, the need for providing DPIs of a "dose counter" and of a "double-dosing protection counter," to avoid a further inhalation if the patient is unaware or not sure of having taken the previous one;
4. Stable: Such as, able to protect the drug(s) contained from the effects of temperature and/or humidity changes;
5. Comfortable: Such as, easy to use in different circumstances (particularly in critical conditions);
6. Versatile: Such as, it should consent the use of other drugs by inhalation;
7. Environmental compatible: Such as, not containing chemical contaminants;
8. Affordable: Such as, of acceptable cost, and possibly rechargeable.

THE MAIN CLASSES OF DPIS, BASED ON THEIR INTRINSIC RESISTANCE, AND PRESSURE DROP ACROSS THE DEVICE[26,25]

Capsule-based devices[27,24]

These DPI devices generally consist of a chamber where capsule is placed. When the patient push the button, capsule is broken by external force by the action of installed twist or pins. The powder is released and inhaled by the patient.

Capsule-based devices listed below

- Aerolizer,
- Rotahaler,
- ARCUS,
- FlowCaps,
- DOTT DPI,
- Breeze haler,
- Aerohaler, and
- Podhaler Redihaler.

Blister-based device[27,24]

Blister-based devices normally have a ring of aluminum blisters inside the device. Each blister contains one dose of drug pre-dispensed. The device also has a dose counter as a dosing indication. Drug powder is released by piercing the blister before inhalation. The drug powder is carried away by the air stream created by the patient's inhalation.

Some of blister based inhaler devices are listed below:
Acu Breathe, Aspirair, Diskhaler, Diskus, Forspiro, Gyrohaler, and Microdose DPI.

Cartridge-based device[27,24]

These devices have a powder chamber to store drug powder. The device has special mechanism to release drugs on inhalation.
The following are some cartridge-based devices:
Xectovair, Ultrahaler, Spiromax, Swinghaler, PADD, Jethaler, VIP inhaler, and NEXThaler.
It has a button connected with a push lever connected with a bar that is linked with the powder chamber. It can be used multiple times.

EXCIPIENT[3,24,28,5,14]

DPI formulations, excipients function first and foremost as carrier particles. Usually, no more than a few milligrams of the drug need to be delivered, and excipients provide bulk, which improves handling, dispensing, and metering of the drug. Excipients also reduce drug cohesiveness by occupying the high-energy sites of the drug particles.
The excipient is selected from the group consisting of glucose, lactose fructose, sucrose, mannitol, xylitol, sorbitol, dextran, trehalose, starches, and cellulose and derivatives thereof.
Currently, lactose is the only excipient used in DPIs marketed in the United States. The reasons for this are as much historical as they are physicochemical/pharmaceutical in nature. Lactose had long been used as an excipient in oral dosage forms before being deployed in DPIs. It had an established safety and stability profile, manufacturing process with tight controls over purity and physical properties, and was available and inexpensive. Lactose is highly crystalline and has smooth surfaces and satisfactory flow properties desirable for a DPI carrier particle. Lactose is less hygroscopic than other sugars. Lactose is quite versatile; several manufacturers offer excipient-grade lactose of various sizes and morphologies. One drawback of lactose is that it is a reducing sugar, which makes it incompatible with drugs that have primary amine moieties.
Excipients can make up over 99% of the product by weight, making them crucial determinants of overall DPI performance. Despite the apparent lack of choices, the excipient must be carefully selected; physicochemical properties such as size and morphology profoundly affect the performance of the formulation.
It should also be noted that excipients are not always required; the Pulmicort (budesonide) Turbuhaler (AstraZeneca, Wilmington, Delaware) is an example of an excipient-free formulation.

LACTOSE[1,29,5,15]

- Lactose is often selected as carrier/excipients because of several advantageous properties like
- Improve the flow-ability of the powder during manufacturing and help handling
- Act as a bulking agent
- Aid in powder uptake from the device during inhalation and aerosolization
- Low reactivity and toxicity
- Low water content
- Low cost.

The lungs have lower buffering capacity than any other delivery sites which limits the range of excipients that could augment the delivery outcomes.

EVALUATION[30,4,24,31]

- Appearance and color
- Identification
- Assay
- Impurities and degradation product
- Delivered dose uniformity (DDU)
- Uniformity of dosage units
- Aerodynamic particle size distribution (APSD)
- Foreign particulate matter
- Microbial limit
- Water or moisture content
- Net content (Fill) weight
- Leachables (Stability).

Appearance and color

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.

DDU

Dosage unit sampling apparatus for the desired testing device is used to perform DDU 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. DDU is a critical quality attribute in determining the safety, quality, and efficacy of inhaled drug products. For DPIs DSUA is a bigger version of MDIs sampling apparatus, which is available for use with flow rates up to 100 l/min for sampling.

APSD

The aerodynamic size distribution of an aerosol cloud defines where the particles in that cloud are likely to deposit following inhalation. It is generally accepted, for example, that to be therapeutically effective the particles should be in the range of 1–5 μ to deposit in the lungs. The particle mass below 5 μ is normally described as the fine particle mass. Particles having an aerodynamic size in excess of 5 μ will generally impact the oropharynx and be swallowed whereas below 1 μ the possibility exists that the particles will remain entrained in the air stream and be exhaled.

The European Pharmacopoeia (Ph. Eur.) currently specifies one twin and three multistage impactors for the aerodynamic assessment of fine particles in both MDIs and DPIs:

- Ph. Eur. Apparatus A: Twin impinger (Glass)
- Ph. Eur. Apparatus C: Multi-stage liquid impinger (MSLI)
- Ph. Eur. Apparatus D: Andersen cascade impactor (ACI)
- Ph. Eur. Apparatus E: Next generation impactor (NGI).

The United States Pharmacopeia (USP) test chapter <601> specifies six impactors suitable for aerodynamic size distribution:

- USP Apparatus 1 for MDIs: ACI
- USP Apparatus 2 for DPIs: Marple-Miller impactor
- USP Apparatus 3 for DPIs: ACI + Preseparator
- USP Apparatus 4 for DPIs: MSLI
- USP Apparatus 5 for DPIs: NGI + Preseparator
- USP Apparatus 6 for MDIs: NGI.

At the current time, only three impactors appear in both Ph. Eur. and USP:

- MSLI
- ACI
- NGI.

In the case of USP, however, the use of the MSLI is restricted to DPIs only, which leaves just the ACI and NGI as suitable candidates for testing both DPIs and MDIs if both pharmacopeial standards are to be satisfied.

Moisture content

The Karl Fischer 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 behavior, 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

Several methods can be used to determine whether sufficient product has been placed into each container. The tared cans that have been placed onto the filling line are weighed again, and the difference in weight is equal to the net contents. The other method is a destructive method and consists of weighing a full container and then dispersing the contents. The contents are then weighed with provisions being made for the amount retained in the container. Other modifications consist 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.

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