Journal of Medical Pharmaceutical And Allied Sciences

www.jmpas.com
ISSN NO. 2320 - 7418

RESEARCH ARTICLE

FORMULATION AND PRODUCT DEVLOPMENT OF DRY POWDER INHALER: AN OVERVIEW

Thorat Santosh R.*[1], Meshram Sarika M.[2]

[1]Lupin Research Park, hinjewadi, pune, India

[2]Tata Consultancy Services, hinjewadi, pune India.

Correspondence
Santosh R Thorat Lupin Research park, pune, India.
Email Id: santoshthorat345@gmail.com

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

Received
5 May 2015
Reviewed
27 May 2015
Accepted
18 June 2015

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.

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:

1. Large surface area is available for absorption.
2. Avoidance of first pass hepatics metabolism.
3. Compared to other oral route smaller doses are required to achieve equivalent therapeutic effect.
4. Provides fast drug action.
5. Provides local action within the respiratory tract.
6. Reduction in systemic side-effects.
7. Reduces extracellular enzyme levels compared to GI tract due to the large alveolar surface area.

Disadvantages of Pulmonary Drug Delivery:

1. In order to get effective drug deposition, aerodynamic filter present efficiently in lungs must be overcome.
2. Pulmonary airways having mucous lining clears the deposited particles towards the throat.
3. Only 10-40% of the drug leaving the inhalation device usually deposited in the lungs.
4. It has short-lived duration of activity because drugs are rapidly removed from the lungs or because of rapid drug metabolism.
5. Require frequent dosing.

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 (2).

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.

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 (3).

Advantages:

1. Enviromental sustainability
2. Propellant free design
3. No coordination required.
4. Less potential for formulation problems.
5. Less potential for extractable from device components.
6. Formulation stability.

Disadvantages:

1. Deposition efficiency depends on patients inspiratory airflow.
2. Greater potential problems in dose uniformity.
3. Less protection from environmental effects.
4. More expensive than pressurized metered dose inhalers.
5. 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).

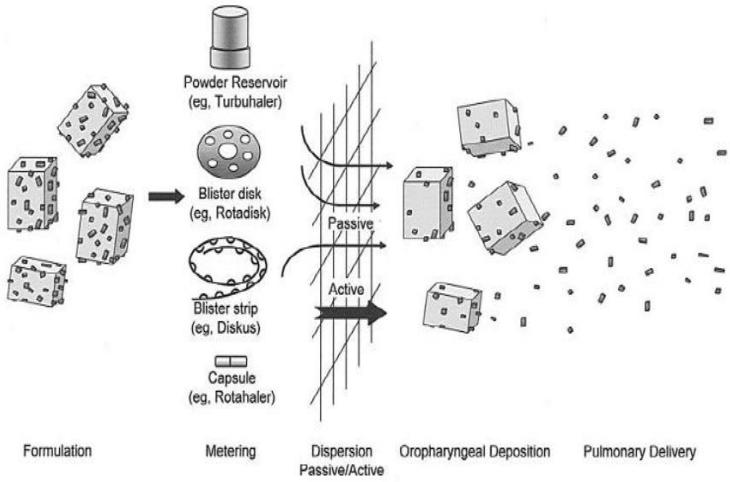

Fig 1. Principle of DPI

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 (6).

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) (6).

Advantages of lactose as a carrier:

1. Well-investigated toxicity profile,
2. Physical and chemical stability,
3. Compatibility with the drug substance,

4. Broad availability,
5. Low cost.

Techniques of DPI formulation:

The particle size distribution affects the deposition of drug in the respiratory tract. However, before drug can be delivered to the lungs, drug particles must leave the DPI and separate from each other and from other components in the formulation. Thus, a DPI formulation must undergo flow, fluidization, and deaggregation. However, micronsize particles, particularly those resulting from high-energy operations such as jet milling, have high surface areas and surface energies, which result in poor flow and a high tendency to aggregate.

A) Controlled crystallization or precipitation:

Crystallization, or precipitataion, is the process by which particles are produced from solution of the material in a suitable solvent. The formation of a stable, crystalline material is normally the target of this final step. In the production of materials for use in DPI products, however, the particle size of the crystallized product is normally too large. Subsequent reduction in particle size is then necessary and can significantly alter the physical nature of the material.

B) Micronization:

Micronization involves high energy particle-size reduction technique that can convert coarse-diameter particles into particles less than 5mm in diameter. Different types of equipment can micronize particles, for example, jet or fluid enrgy mills and ball mills. All techniques involve applying a force on the particle, typically in the form of a collision, either particle-particle or particle-equipment. The force acts as imperfections in the crystal surface, initiating crack propagation through the particle. As the size of the particle decreases, the number of imperfection decreases, thereby masking the task of reducing particle size more difficult.

C) Blending:

It serves as a commonly used method for improving the flowability, fillability, and dispersability of small cohesive particles wherein the drug is blended with excipients particles, most commonly lactose, of considerable larger size. The objective of the mixing process is to produce an ordered powder in which the small particles attach themselves to the surface of larger “carrier” particles. For high volume production, the process generally involves a high shear mixer. The final product performance of a powder blend in DPI is ultimately depends on the individual drug and

carrier properties as well as on the process by which they are blended. The consistent behaviour of carrier particles from batch to batch can be ensured by means of secondary processing.

The finished blend has a tendency to segregate due to the separation of the particle from the carrier or carrier of different sizes during the steps involved in transport and storage. Hence these steps are required to monitor closely. Segregation can be minimized by the careful selection of formulation and process equipment.

D) Pelletization:

The process involves deliberate agglomeration of the fine drug material into less cohesive, larger units. Pelletization is usually achieved by vibratory sieving or any process that tumbles powder. The resultant pellets must be used in a system capable of deaggregating to an appropriate particle size for aerosol drug delivery (7).

ADVANCES IN FORMULATION OF DPI:

Research into dry powder formulations has been an area of growth in recent years. Various techniques are used to made advances in dry powders formulation for inhalation involves either, micronization via jet milling, precipitation, or spray drying using various excipients, such as lipids and polymers, or carrier systems like lactose.

A) Lactose carrier systems:

To overcome the problem of poor flow of cohesive powders, pulmospheres are the new type of aerosol formulation is the large porous hollow particles. They have low particle densities, excellent dispersibility and can be used in both MDI and DPI delivery systems. These particles can be prepared using polymeric or non-polymeric excipients, by solvent evaporation and spray-drying techniques. Pulmospheres are made of phosphatidylcholine, the primary component of human lung surfactant. The large size of pulmospheres allows them to remain in the alveolar region longer than their nonporous counterparts by avoiding phagocytic clearance (8).

B) Biodegradable polymers:

Biodegradable polymer microspheres are currently being studied as sustained release pulmonary drug carriers. Polymers such as polylacticacid and poly glycolic acid have been investigated for pulmonary drug delivery. Although a limited amount of research has been published in this area, the sustained-release profiles achieved with corticosteroids appear promising (9).

C) Liposomes and Nanoparticles:

Liposomes, as a pulmonary drug delivery vehicle, have been studied for years and used as a means of delivering phospholipids to the alveolar surface for treatment of neonatal respiratory distress syndrome. More recently, they have been investigated as a vehicle for sustained-release therapy in the treatment of lung disease, gene therapy and as a method of delivering therapeutic agents to the alveolar surface for the treatment of systemic diseases (10).

D) Active Delivery System:

The technology of dry powder inhalers has developed to use energy as a key element in the process of particle de-agglomeration. Storage of mechanical energy in systems based on springs or compressed-air chambers was one of the alternatives found in some devices. Exubera® (Nektar Therapeutics, USA), for example, uses an air chamber that is actuated by the patient through a kind of manual pump. The effectiveness of this device, which was designed for aerosolizing insulin, was tested and showed similar results with airflows ranging from 5 to 56 L/minute (11).

Dry Powder Inhaler Devices:

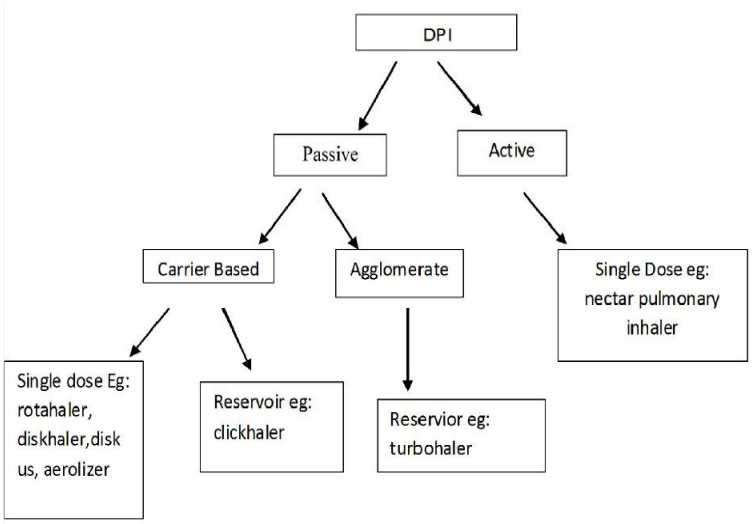

Fig 2. Types of DPI

The inhalation device is important in achieving adequate delivery of inhaled drug to lungs. The device should be easy to use, in expensive 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. However, devices with higher resistance need a higher inspiratory force by the patients to achieve the desired air flow (12).

Dry powder inhaler devices are classified by dose type into single-unit dose, multi-dose reservoirs, and multi-unit dose.

1. Single-unit dose device:

In a single-unit dose device, the drug is formulated as a micronized drug powder and carrier system and supplied in individual capsules, which are then inserted into the inhaler for a single dose and removed and discarded after use. The capsule body containing the dose falls into the device, while the cap is retained in the entry port for subsequent disposal. As the patient inhales, the portion of the capsule containing the drug experiences erratic motion in the airstream, causing dislodged particles to be entrained and subsequently inhaled. Particle deaggregation is mainly caused by turbulence promoted by the grid upstream of the mouthpiece.

Example: Rotahaler® (GlaxoSmithKline), Aerolizer® (Novartis), Handihaler® (Boehringer Ingelheim) etc.

Fig 3. Handihaler

2. Multi-dose devices:

There are two types of multi-dose devices, reservoir type devices and multi-unit dose devices. The multi-dose reservoir type device stores the formulation in bulk, and has a built in mechanism to meter individual doses from the bulk upon actuation. The multi-unit dose device uses factory metered and sealed doses packaged in a manner that the device can hold multiple doses without having to reload. Typically, the packaging consists of replaceable disks or cartridges, or strips of foil-polymer blister packaging that may or may not be reloadable. This pre-packaged does have the advantage of being protected from the environment until use, and ensuring adequate control of dose uniformity. Multi-dose DPIs have been developed, either as multi-unit dose or as multi-dose reservoir devices.

A. Multi-unit dose devices:

In this type of devices individual doses packaged in blister packs on a disk cassette. Following piercing, inspiratory flow through the packaging depression containing the drug induces dispersion of the powder. The aerosol stream is mixed with a bypass flow entering through holes in the mouthpiece that, gives rise to turbulence and promotes deagglomeration.

Example: M®(Boehringer Ingelheim), Diskhaler® (GlaxoSmithKline), Diskus® (GlaxoSmithKline) etc.

Fig 4. Diskus

B. Multi-dose reservoir devices:

It contains multiple doses of small pellets of micronized drug that disintegrate into their primary particles during metering and inhalation. One dose can be dispensed into the dosing xchamber by a simple back-and-forth twisting action on the base of the reservoir. Scrapers actively force drug into conical holes which cause the pellets to disintegrate. Fluidization of the powder is done by shear force as air enters the inhaler. Particle deagglomeration occurs by turbulence. The advantages of the reservoir systems are their relative ease and low cost of manufacture and the ease of including a large number of doses within the device.

Example: Turbuhaler® (AstraZeneca) etc.

Fig 5. Turbuhaler

Novel Dry Powder Inhalers Devices:

The dependence on high inspiratory flow rates for the operation of the first dry powder inhalers led to the development of new technologies based on passive and active powder dispersion mechanisms.

Devices using passive mechanisms include Novolizer® (Meda, Sweden) and Airmax® (Yamanouchi, Netherlands). The air classifier technology has been described as the most efficient passive powder dispersion mechanism currently used in dry powder inhalers. In this case, multiple supply channels generate a tangential airflow that results in a cyclone within the device during inhalation. A similar mechanism is used in the Airmax®.

Devices using active mechanisms include Exubera® (Nektar Therapeutics, USA), it involves storage of mechanical energy in

systems based on springs or compressed-air chambers was one of the alternatives found in some devices.

Characterisation of DPI (13,14,15):

Appearance and Colour: 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 any color is present with the formulation (either present from initial stage or form due to degradative processes occurring during shelf life), then a quantitative test with relevant acceptance criteria should be established for the drug product.

Particle size analysis: Many methods have been developed for the particle size measurement. Sieve analysis and laser diffraction are used for the particle size analysis for lactose used in inhalation products. Laser diffraction is a fastest growing technique that describes almost the full profile while sieve analysis gives only a limited amount of data. Sieve analysis is often used in combination with laser diffraction to guarantee the absence of coarse particles in the lactose.

Sieve analysis: 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. By weighing the material received on each sieve the particle size distribution can be calculated.

Laser diffraction: In the United States Pharmacopeia (USP) General Chapter <429> it is stated that laser diffraction involves the measurement of "a representative sample, dispersed at an adequate concentration in a suitable liquid or gas". For the measurement the powder is passing a laser beam. 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. The full profile is often evaluated and the particle size is often specified as a three point specification containing d10, d50 and d90 value. Also the amount of fines % below 5, 10 or 15 μm could be part of the specification. These parameters are often linked to product performance. For inhalation lactose the most common laser equipments used are supplied by Sympatec and Malvern.

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.

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_3) and upstream (P_2) of the flow control valve is maintained at ≤ 0.5 to ensure critical flow after the initial rise to stable sampling conditions. This control valve is also used to adjust the flow rate to provide a 4-kPa 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.

The cascade impactor should ideally operate at the final, fixed flow rate that is governed by the inhaler resistance for as long as is practical, as this type of particle size analysis equipment is designed to operate at a constant flow rate. In practice, a compromise is achieved by allowing the system to sample a total of 4.0 L from the DPI, which is intended to be a sufficient volume to permit the bolus to penetrate to the distal region of the impactor, thereby effecting a

complete size fractionation from which the aerosol APSD can be determined. This volume compares with the internal volumes of 1.155 and 2.025 L for the Andersen eight-stage non-viable cascade impactor (ACI) and next-generation pharmaceutical impactor (NGI), respectively, including the pre-separator.

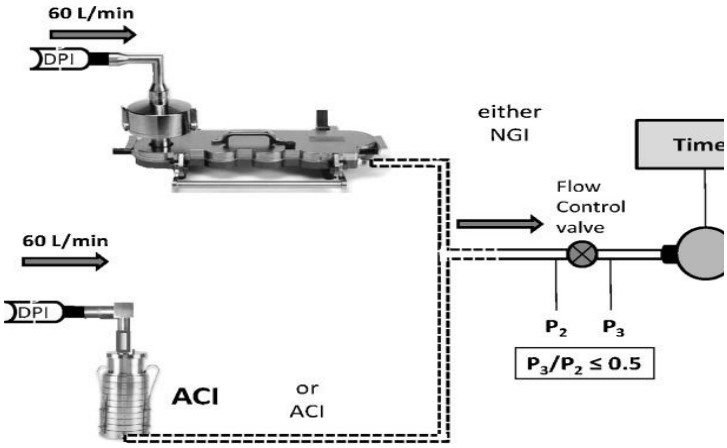

Fig 6. Determination of APSD by ACI or NGI.

Marketed Product of DPI (16):

Table 1: Marketed Product of DPI

Device	DPI type	Company	Delivery method	Drug(s)
Aspirair	Multi-dose	Vectura	Powder/Active	Apomorphine hydrochloride
Omnihaler	Single dose	Innoveta Biomeds Ltd	Powder/Active	/
Actispire	Single dose	Britania	Powder/Active	/
NEXT DPI	Multi-unit	Chiesi	Reservoir	/
DirectHaler	Multi-unit	Direct-Haler	Pre-metered	/
JAGO	Multi-dose	SkyPharma	Reservoir	Salbutamol sulphate
Airmax	Multi-dose	Norton Healthcare	Reservoir	Formoterol Budesonide
Turbospin	Single dose	PH&T	Capsule	/
AIR	Single dose	Alkermes	Capsule	/
MicroDose	Multi-unit	MicroDose/ 3M	Powder/ Electronic activated	Insulin
Cyclovent	Multi-dose	Pharmachemie	Reservoir	Morphine
Dispohaler	Multi-dose	AC Pharma	/	/
Conix One	Single dose	Cambridge Consultant	Foil seal	Vaccines
Microhaler	Single dose	Harris Pharmaceutical	Capsule	Sodium cromoglycate
Technohaler	Multi-unit	Innoveta Biomeds Ltd	Blister	/
Spiros	Multi-unit	Dura	Blister/Active	Albuterol sulphate
Bulkhaler	Multi-unit	Asta Madica	Reservoir	/
Miat-Haler	Multi-unit	MiatSpA	Reservoir	Formoterol Fluticasone propionate Budesonide
Prohaler	Multi-unit	Valois	Blister	/
Otsuka DPI		Otsuka Pharmaceutical	Compact cake	/
Acu-Breath	Multi-dose	Respirics	Powder	Fluticasone propionate
MF-DPI	Multi-unit	/	Reservoir	Mometasone furoate
Swinhaler	Multi-dose	Otsuka Pharmaceutical	Powder	Budesonide
Pfeiffer	Single dose	Pfeiffer GmbH	Active	/
Certihaler	Multi-dose	Novartis	Powder	Formoterol

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

diseases 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.

REFERENCES

1. Swain K., Giri M., Gupta R.N., Arora V.K., and Saha S, 2012. Dry Powder Inhaler a Review, 3 (3), 1346-1356.
2. Yadav N., Lohani A., 2013. Dry Powder Inhalers: A Review, Indo Global J Pharm. Sci., 3 (2), 142-155.
3. Dhand R., Inhalation Therapy with Metered-Dose Inhalers and Dry Powder Inhalers in Mechanically Ventilated Patients, 2005. Respiratory care, 50(10), 1331-1346.
4. Taneja R. Et al, Recent trends in DPI Technology, 2012. Int. J. Pharm, 3 (11), 27-34.
5. Sahane SP., Nikhar AK., Bhaskaran S. and Mundhada DR.; 2012. Dry powder inhaler: an advance technique for pulmonary drug delivery system, Int. J. Pharm. and chem. sci, 1 (3), 127-135.
6. Rahimpour Y., Hamishehkar H.; 2012. Lactose Engineering for Better Performance in Dry Powder Inhalers; Adv. Pharm. Bulletin, 2(2), 183-187.
7. Telko M. J. and Hickey A. J., Dry Powder Inhaler Formulation, Resp. care, 50 (9), 1209-1227.
8. Shaikh S., Nazim S., Khan T., Shaikh A., Zameeruddin M.; Recent advances in pulmonary drug delivery system: a review, Int J Appl. Pharm. , 2, 4, 2731, 27-32.
9. V. Ravichandiran, K. Masilamani, S. Satheshkumar, D. Joseprakash; Dry powder for inhalation, Int. J. of Pharm. Sci. Review and Research; Volume 10, Issue 2, September – October 2011; Article-017; 85-89
10. Mukta Paranjpe and Christel C. Müller-Goymann; Nanoparticle-Mediated Pulmonary Drug Delivery: A Review; Int. J. Mol. Sci. 2014, 15, 5855-5873.

11. Muchao FP, Silva Filho LV, 2010. Advances in inhalation therapy in paediatrics; J. de Pediatria 86 (5), 267-276.
12. Shah ND, Shah VV, Waghamare J.; Dry powder for inhalation (DPI); Int. J. Res. and Rev. in Pharm. and Applied Sci; 2(3), 458-472.
13. British pharmacopoeia. Preparations for inhalations: International edition, 1998, 2; 740-742.
14. Indian Pharmacopoeia Vol 2; The Indian Pharmacopoeia Commission, Ministory of Health and Family Walefare, Govt of India, Gaziabad; 2010; 726-740
15. Draft Guidelines for Industry; Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products; Chemistry Manufacturing and controls Documentation; Center for Drug Evaluation and Research (CDER); 1998.
16. Islam N, Gladki E., Advances in Dry powder inhaler; Int J Pharm; 04:044.