INTERNATIONAL JOURNAL IN PHARMACEUTICAL SCIENCES

Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Dry Powder Inhalers: A Critical Evaluation Of Their Effectiveness And Accessibility

Trupti Bhalekar*, Kalpana Sable, Jaya Mehetre, Kiran Dhamak

Department of Quality Assurance, PRES College of Pharmacy (Women's), Chincholi, Nashik-422102

ARTICLE INFO

Received: 11 July 2023
Accepted: 12 July 2023
Published: 22 July 2023
Keywords:
Pulmonary route, Dry powder inhaler, Carrier particle, Inhalation Device
DOI:
10.5281/zenodo.8173889

ABSTRACT

A Dry Powder Inhaler (DPI) is a device that inhales dry powdered medicine into the lungs. DPIs are frequently used to treat respiratory conditions like COPD, bronchitis, and asthma. In recent years, interest in DPI as an effective and ecologically friendly method of medication delivery to the lung has increased. Only an effective metering mechanism, a well-chosen device, and an appropriate powder composition will allow a dry powder inhaler to achieve these objectives. The three primary categories are nebulizer, pMDI, and DPI. DPIs, which provide medicine to the lungs in the form of a dry powder, are an alternative to pMDI. To ensure that the patient receives the same dosage each time at a varied airflow rate, API particles must be present in the size range of 1 to 10 m. Four different formulation procedures, including carrier-free, drug carrier, drug additive, and drug carrier additive, are used to create DPI. 'Twin Stage Impingner' completes the lung deposition research. The inward breath device, which is primarily divided based on measurements into single-unit and multi-dosage stores, is essential for achieving appropriate delivery of breathed in medication to the lung.

INTRODUCTION

Pulmonary drug delivery system

The pulmonary route of drug administration is becoming increasingly important in modern research because it allows researchers to concentrate on the delivery of drugs particularly to the lung for both localised and systemic therapy. The goal of the study is to investigate the technical, physiological, and therapeutic effectiveness features of the innovative pulmonary route of drug targeting and various drug delivery systems, including metered dosage inhalers (MDI), dry powder inhalers (DPI), nebulizers, etc. The study also focuses on the excipient compatibility, devices, methods of producing particle dosages, assessment, and improvements in the delivery of pulmonary drugs, as well as the processes of pulmonary drug administration. The conclusion drawn from the overall study is that various

***Corresponding Author:** Trupti Bhalekar
Address: *Department of Quality Assurance, PRES College of Pharmacy (Women's), Chincholi, Nashik-422102*
Email : trups_510@yahoo.co.in
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

pulmonary delivery systems have varied specificities for dose formulations and are useful tools for delivering medications to the target place [1]. For a very long time, pulmonary routes have been used to treat various respiratory disorders. Ancient inhalation therapies made use of plant leaves, resins, myrrh, and the vapours of aromatic plants. Nevertheless, these early medicines evolved into true pharmaceuticals around the beginning of the nineteenth century with the invention of liquid nebulizers.

Diabetes trial investigations began using nebulized swine insulin in 1925, and pulmonary administration of the newly discovered antibiotic penicillin was examined in 1945. In the middle of the 1950s, steroids were introduced for the treatment of asthma, and nebulizers were finding widespread usage.

The pressurised metered dosage inhaler (pMDI), which was first launched in 1956, has evolved into the mainstay of asthma therapy over the past five decades with the aid of developments in molecular design and medication discovery. Throughout the decade, a number of medications have been offered in forms that may be formed into drug dispersion for pulmonary administration to treat a variety of human illnesses. Such pulmonary drug delivery compositions are made to be inhaled by the patient, allowing the active medication included in the composition to reach the lung. It has been discovered that certain medications administered via the lungs quickly enter the bloodstream by way of the alveolar region. For the treatment of certain illness situations, the pulmonary route has several benefits over other administration routes, especially for the big protein molecules connected with the lung, which breakdown under gastrointestinal conditions and are cleared after the first pass. If deposited in the respiratory zone of the lungs, liver metabolism can be administered through the lungs. Devices used to administer medication via the pulmonary route are based on one of three platforms: dry powder, nebulizers, or pressurised metered dosage inhalers. Aerosol administration is a useful method for administering a medicinal chemical in the treatment of illness [1, 2, 3].

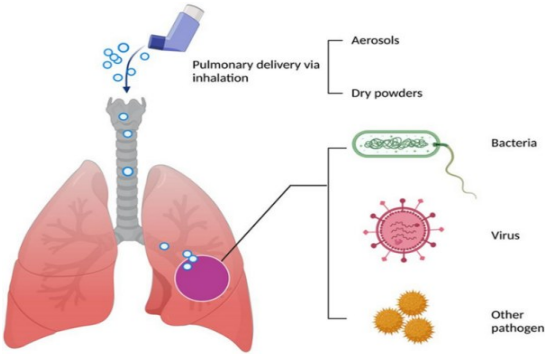

Figure 1: Schematic representation of pulmonary drug delivery system

Advantages of Pulmonary Drug Delivery System [1,4,5]

1. The pulmonary route is used to deliver big protein molecules that could otherwise be broken down in the gastrointestinal tract and removed through first pass metabolism.
2. As the remainder of the body is not exposed to medications, the adverse effects of pulmonary drug delivery systems are minimal.
3. Drugs administered via the pulmonary route have a rapid beginning of effect.
4. It is a non-intrusive method of medication delivery.
5. Additionally, pulmonary delivery has the possibility for a more effective and maybe more cost-effective prevention or treatment of respiratory and systemic illnesses.
6. The pulmonary drug delivery system is a no-needle method.
7. Drug dosage is reduced since it is immediately deposited in the lung.
8. The respiratory system has a substantial surface area that is very permeable, allowing drugs to be absorbed into the blood.

Classification of Pulmonary Drug Delivery System [1, 6]

a) Nebulizers

Nebulizers have been used in medicine since the middle of the nineteenth century. In this technique, the medication is dissolved or suspended in a suitable solvent to produce aerosols. While certain medications are insoluble or unstable in solution, it is nevertheless feasible to construct suspensions known as heterogeneous systems. In a solution, the active component is dissolved in a solvent to form a homogenous phase. Nebulizers are incredibly adept at producing mists of very small droplets that have good lung deposition. The nebulizer platform uses air jet or ultrasonic technologies to atomize an aqueous-based medicinal solution. These are mostly used in hospital and outpatient care settings to provide dosages across several breaths to patients who are newborns, elderly, or severely ill. To stop microbial development, these formulations may include preservatives [1, 7, 26, 28].

Advantages of Nebulizer [1, 8, 30]

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

Disadvantages of Nebulizer [9, 30]

1. Equipment is expansive which is hard to transport.
2. Variability in execution between various nebulizers.
3. Need for 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.

b) Pressurized Metered Dose Inhaler (pMDI)

The first modern inhaler device, the Pressurised Metered Dose Inhaler (pMDI), received approval in 1956. A propellant is used to mix the medication in pMDI devices, which then cause the performed mixture to be ejected from the canister in precisely defined proportions. The actuator, metering valve, and container are the three main parts of a conventional MDI [7, 9,26,28,30].

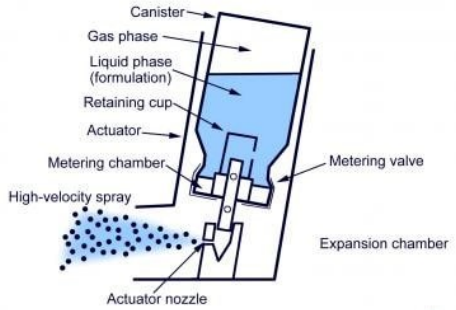

Figure 2: Schematic representation of Typical MDI

Advantages of pMDI [1, 8, 10, 30]

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

Disadvantages of pMDI [1, 8, 10, 30]

1. High velocity dose emission increases the likelihood of early oropharynx deposition. As a result of the minimal drug deposition in the lungs, the use of pMDI is restricted to the treatment of upper airway disorders. Only 10 to 15 percent of the dosage reaches the lungs.
2. They demand meticulous coordination between inhalation and actuation.
3. If the pMDI is not shaken when using suspensions, the drug content/dose might be troublesome.
4. has ozone-depleting propellant, such as chlorofluorocarbon (CFC), in it
5. Only specific medications that are stable in a propellant can be used in pMDI.

c) Dry Powder Inhaler (DPI)

A Dry Powder Inhaler (DPI) is a device that inhales dry powdered medicine into the lungs. Although DPIs have also been used to treat diabetes mellitus, their primary usage is to treat respiratory conditions such asthma, bronchitis, emphysema, and COPD. A different choice for

pMDI is DPIs.DPI is primarily divided into Active and Passive categories. The majority of DPIs are passively activated by breath. To function, they are dependent on the patient's inspiration. The patient merely takes a deep breath to access the medicine; there is no need to coordinate breathing with activation. There are two subcategories of passive DPI: pre metered (single or multidose), in which the dose is premeasured during manufacturing. Blister, capsule, etc. Device metered those pre-measures each dosage upon activation and contains the medicine in a reservoir within [9, 26, 28, 30, 24].

1. **Dry Powder Inhaler**

Over the past 10 to 15 years, dry powder inhalers (DPIs) have evolved dramatically. A Dry Powder Inhaler (DPI) is a device that inhales dry powdered medicine into the lungs. The dry powder platform consists of devices that turn medicine powder with a particle size of 1 to 5 m, or mixes with excipients, directly into aerosols. As a carrier for the active pharmaceutical ingredient (API), excipients are utilised in DPI. Lactose Monohydrate is the most popular carrier. To lower emissions of the ozone-depleting and greenhouse gases, hydrofluoroalkanes and chlorofluorocarbons, respectively, that are utilised as propellants, DPIs have been developed as alternatives to pMDI. Although DPIs have also been used to treat diabetes mellitus, they are most frequently used to treat respiratory illnesses such asthma, bronchitis, emphysema, and COPD [11,12,26,28,30].

General Requirements of DPI

DPIs have to meet the following requirements.

i. **Particle Size of API -** Inhalable Active Compound is required. It must exist in particles that range in size from 1 to 10µm in order to be able to enter the lungs. If the technique parameters are adequate, micronization, controlled precipitation from a suitable solvent, or spray drying can be used to produce such microfine particles. [14, 30]

ii. **Drug content uniformity -** In a single-dose system, it's crucial that each capsule or blister contain the same quantity of powder and medication, and in a multi-dose system, the reservoir must consistently release the same quantity of powder and medication [13,14,30].

iii. **Content uniformity at different airflows -** The patient's breathing pattern affects how much medication is delivered through a DPI. This suggests that the dosage must be released in the same way whether breathing is low or high. Therefore, it is crucial for a DPI to maintain content consistency across various airflows [13, 30].

iv. **Stability of powder against humidity and temperature -** The lactose must be safeguarded from particle size expansion since the lactose particle size distribution is crucial to the action of a DPI. An undesirable mixture of temperature and relative humidity is the primary factor for particle size increase. Stability depends on maintaining proper temperature and relative humidity levels when storing items in the appropriate container. [13, 30]

Advantages of Dry Powder Inhaler

Given that the search for alternatives to pMDIs is what drove the development of DPIs, the following are some benefits of DPI over pMDI:

- **Require little or no coordination of actuation and inhalation.**

The misuse of pMDIs continues to be a major problem. It was discovered that a significant majority of patients using corticosteroid pMDIs had reduced asthma control due to improper synchronisation of actuation and inhalation. While DPIs need little to no synchronisation of actuation and inhalation, they are triggered by the patient's inspiratory airflow. Better lung delivery as a result of this has frequently been achieved than with similar pMDIs. [10, 30].

- **Formulation Stability**

DPIs are preferred as stable formulations since they are often made as one-phase, solid particle blends. Due to their lower energy state and lower rate of chemical deterioration, dry particles are less likely to react with contact surfaces. However, pMDI formulations, which contain propellant and co-solvents, may be able to extract organic chemicals from the parts of the device.

- **Propellant-free design** Propellers like hydrofluoroalkanes and chlorofluorocarbons, which deplete the ozone layer and contribute to global warming, are found in pMDI. In order to save the ozone layer from being destroyed, the production of CFC propellants was prohibited as of January 1st, 1996. Therefore, DPI, which does not include propellant, was used to replace pMDI. DPIs are thus formulations that are favourable to the environment [5, 10, 30].
- **Flowability**

For the right amount of powder to produce a DPI, this attribute must be adequate. Since practically all active compounds have low flowability, the carrier must provide the excellent flow [13, 30].

- **Other advantages of DPI are as follows [10, 5,15,28,30]**
  1. high carrying capacity for medication doses. DPIs can deliver a variety of dosages with a single, brief inhalation, ranging from less than 10 mg to more than 20 mg.
  2. Due to minimal oropharyngeal deposition, minimal device retention, and minimal exhaled loss, there is little additional pulmonary drug loss.
  3. DPI experiences less adverse effects because the rest of the body is not exposed to the medication while it is deposited in the lungs.
  4. Less possibility of extraction from gadget parts.

Formulation Strategies for Dry Powder Inhaler

The effectiveness of DPI mostly depends on the powder's flow characteristics, which are primarily influenced by strong interparticle forces that cause the cohesive bulk powder to agglomerate. The van der Waals force, electrostatic force, and capillary force are the three different interparticle forces. When the particles are sufficiently near to one another (0.2–1.0 nm) and tiny (20µm or less), the van der Waals force may be observed. The van der Waals force can be dramatically altered by surface roughness, geometrical structure, and particle deformation. When particles with different work functions are brought into contact, electrostatic force can result from the potential difference. The powder becomes sticky as a result of the Coulomb attraction. In order to construct liquid bridges between the particles in close contact, fluid condenses in the spaces between them, creating capillary force. Electrostatic force, which decreases with expanding moisture, is sacrificed for high capillary force [1, 24, 30].

Following are some formulation techniques for DPI to tackle these challenges:

a. Carrier Free

The active therapeutic agent in a carrier-free method might take the shape of a single chemical, a composite made of many compounds, or encapsulated particles. There are several manufacturing methods, including spray drying, supercritical fluid, crystallisation, and milling. As a result of their inability to create ideal particle shapes, narrow particle size distributions, low surface energies, and avoidance of amorphous material, crystallisation and milling were determined to be inappropriate for the preparation of pulmonary medicines. The aerodynamic particle size of the medication for inhalation must be smaller than 5µm [1, 30].

b. Drug Carrier

For dry powder inhalers, it is challenging to distribute 1 g to 1 mg of medication dosages into

the tiny blisters. Additionally, because the ideal particles are between 1 and 5 m, it is difficult to entrain powder by inhalation. To improve their flow and to boost the volume of each dosage, the drug molecules are combined with bigger particles. These carrier particles' geometric sizes might range from 50 to 100 m. If properly prepared, coarse particles in a bed of tiny particles can act as an additional agitator or turbulence promoter to aid in the fluidization of fine particles. Additionally, a combination that has been bulked up is considerably simpler to administer in dosages that include extremely little quantities of active substance. This approach has some drawbacks, including the fact that carriers frequently deposit in the mouth with several drug particles clinging to them, which results in less medicine reaching the lungs. Poor separation of drug particles from the carrier particles' surfaces also leads to ineffective delivery [1,30].

Figure 3: Different types of Dry Powder Inhaler [1]

c. Drug Additive

The fluidization properties of medication fine powders can also be improved by the inclusion of tiny particles. Enlarging the separation distance will significantly lessen the adhesive force, which in turn improves the fluidization behaviour of tiny particles and also improves the flow property of drugs since van der Waals attraction is mostly dependent on particle-particle distance. Submicron silica (0.5–3 wt%), alumina (29 nm), and aerosol 200 (12 nm) were utilised as additives [1, 30].

d. Drug Carrier Additive

To improve medication distribution, an extra particle type could be used in the formulation. This filler might act as a physical spacer by taking up residence at high-energy spots like clefts in the carrier surface or it could take the form of a tiny particle with the same composition as the carrier. The usage of fine lactose in a lactose carrier system is the most prevalent illustration of this kind of system. The separation of drug particles from the carrier particle has enhanced as a result of an increase in the lactose fine fraction [1, 30].

Formulation

Three processes are primarily involved in DPI formulation;

a. API Production

Particle size is a crucial requirement of API for DPI. Drug particles should be no larger than 5 m. It should fall between 2 and 5 m. Typically, throughout the bulk drug manufacturing process, the drug particle size is not adequately regulated. To reach an aerodynamic particle size for the drug, the drug's particle size must be decreased in a separate unit operation. There are several methods for reducing particle size, including grinding, spray drying, and supercritical fluid extraction. There are many other types of mills that are used to reduce drug size, but only a select handful of them are suitable for DPI to reduce size in the range of 2-5 m, including fluid-energy mills like the jet mill, high-peripheral-speed mills like the pin-mill, and the ball mill. High-velocity particle-particle collisions in the jet mill reduce particle size. The milling chamber is filled with unmilled particles. Through nozzles, high-pressure nitrogen is fed to the solid particles, which then accelerate them to sonic speeds. The particles slam together and break. Larger particles are subjected to greater centrifugal forces as they fly around the mill and are pushed to the outside edge of the chamber. The centre discharge stream is how small particles leave the mill [9, 27, 30].

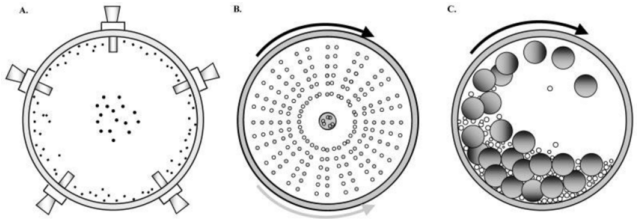

Figure 4: Cross-sections of 3 mills commonly used to create micron-size particles. A: Jet mill. B: Pin mill. C: Ball mill [9, 16]

A pin mill employs mechanical force to grind material by collisions between particles and solids, which can result in particles as small as one micron in diameter. It has a rotating rotor and a stationary stator plate, both of which are supplied with a number of concentrically attached pins. Centrifugal force is used to feed powder into the milling chamber and move it through the milling chamber. The finished milled product is gathered at the bottom. The ball mill is a cylindrical device that rotates while being filled with balls and a substance to be ground into powder. The medication is dissolved in water or a solvent and sprayed into a heated expansion chamber as a fine mist during spray-drying. Small amounts of medication are left behind as the droplets dry, and these particles gather at the chamber's bottom [16, 27, 30].

b. Formulation of API with or without carriers.

The carrier component of DPI improves the powder's flow characteristics as well as the aerosol performance of cohesive medicines and fine lactose. The blending method combines the medication and carrier after each has been brought to the desired state separately. Poor dosage homogeneity may be the result of insufficient mixing. In many instances, insufficient mixing cannot be corrected by merely lengthening the blending period. The homogeneity of the mix is affected by the blender type, rotation speed, capacity, and fill level. Depending on the forces that exist between the various particles, different powders may need different blending requirements. Geometric dilutions are required as preblending procedures for low concentration (drug-carrier ratio) blends [16]. The coarse carrier particles have high energy active sites on their surface, which causes the drug particles to cling strongly to them (Particle size > 20 m). The majority of the active sites on coarse carrier particles are saturated by the expansion of fine carrier particles (Fines 10 m), to which the micronized medication is subsequently bound. As a result, the drug sticks to passive sites, or sites requiring less energy, and makes it easier for the micronized medication to break down during inhalation, increasing the respirable fraction [9, 16, 27, 30].

c. Integration of the formulation into device

The combined mixture is then put into reservoirs, blisters containing several doses, or capsules for use with an inhaler. The automated filling procedure is dependent on the metering system's characteristics [16].

Principle of dry powder inhaler design [24]

Most DPIs contain micronized drug mixed with larger carrier particles, which prevents aggregation and helps flow property. The dispersion of a dry powder aerosol is directed from a static powder bed. To generate the aerosol, the particles must be moved. Movement can be brought about by several mechanisms viz.; Passive and Active. 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. 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 (Fig. 1.5). Deposition of drug into the lungs is determined by the patient's variable inspiratory airflow. Inadequate drug carrier separation leads to

low deposition of drug into the lung which affects the efficiency of DPI [9, 18, 30].

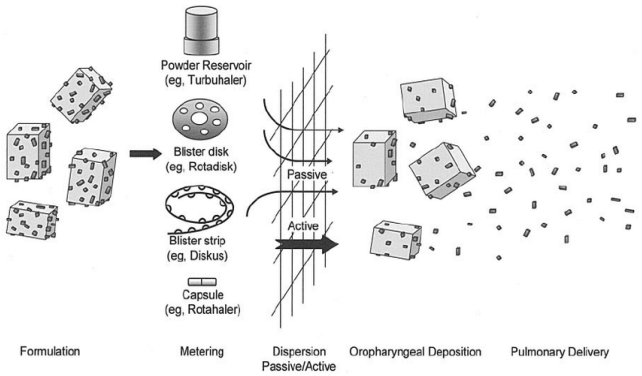

Figure 5: Principle of dry powder inhaler design [18]

For DPIs, many dispersion processes have been reported. Even though the majority of DPIs are breath activated and rely on inhalation to produce aerosol, a number of power-assisted devices (pneumatic, impact force, and vibratory) have been developed or are now in the works. These tools are being taken into consideration for systemically active medication delivery with constrained therapeutic windows. It is significant to highlight that these "active" inhalers have different advantages and disadvantages than passive inhalers and are not subject to the same restrictions. Furthermore, it has been claimed that great delivery efficiency and repeatability may be attained if shear and turbulence were to be standardised using a dispersion mechanism that is independent of the patient's breath. Therefore, a delivery method using an active inhaler may be formulation independent. Active-dispersion DPIs are not commercially available [18].

Lung Deposition Study

Fundamentally, the qualities of the inhaled particles and the patients' breathing patterns at the moment of administration determine how the particles deposit in the human respiratory system. Aerodynamic diameter, a crucial size parameter for deposition, is influenced by the particle's actual size, shape, and density. While particles smaller than 3.5µm and larger than about 0.5µm will largely bypass the bronchial airways during inhalation and penetrate almost entirely to the deep lung, a small amount of particles in the aerodynamic size range of approximately 3.5-6µm can penetrate to some extent beyond the central airways into the peripheral region of the lung.

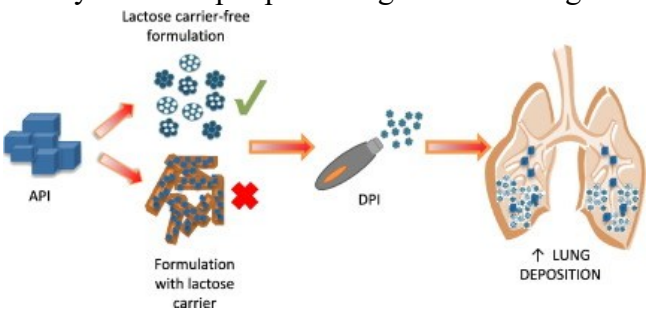

Figure 6: Particle deposition Characteristic of DPI's [29]

The inertia of larger particles, which is determined by their inertial mass, causes them to influence the upper airways. Higher inhalation flow rates make this impaction worse, and oropharyngeal deposition shows extremely high levels of inter- and intrasubject variability [17] even at regulated inhalation flow. The following five processes control particle deposition in lung airways:

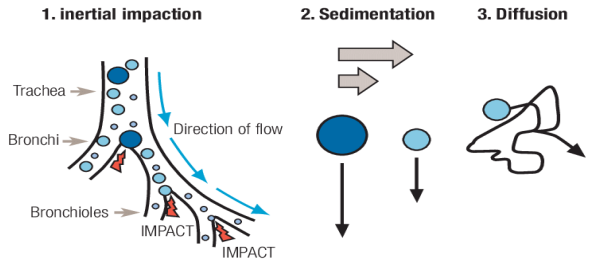

Figure 7: Three particle deposition mechanisms occurring within the respiratory tract

Aerosol characteristics, ventilatory parameters, and morphologies of the respiratory tract are three factors that might have an impact on these processes.

a. **Inertial impaction:** Inertial deposition of a particle onto an airway surface is how it is described. The big conducting airways' airway bifurcations are mostly where it occurs. High flow rates and rapid variations in the airflow's direction may be found here [29].

b. **Gravitational sedimentation:** It happens in tiny conducting airways with low air velocity and for particles smaller than 5 µm [4].
c. **Diffusion:** It happens in tiny airways and alveoli when there is very little airflow, for particles smaller than 0.5 micrometres, and when such particles are prone to Brownian motion [7, 17].
d. **Interception:** Only aggregates and fibres (such as asbestos) are significant. Even though the centre of mass of such particles may stay on a fluid streamline, deposition may nonetheless happen when the particle comes into touch with an airway wall [7].
e. **Electrostatic attraction:** The expansion of attractive forces to airway surfaces caused by the electrostatic charges enhances deposition, particularly for newly produced particles [17].

❖ **Lung Deposition Study by Twin Stage Impingner**

A measurement of the drug deposition during inhalation is the deposition of the emitted dosage.

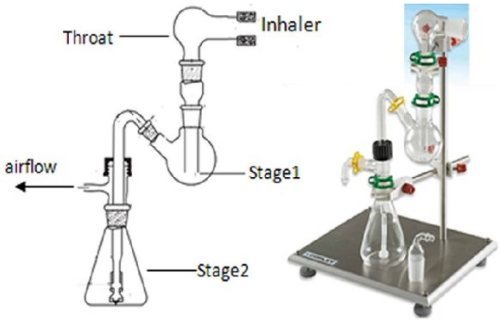

Figure 8: Schematic representation of Twin stage Impingner Apparatus

The impinger is made up of two glass flasks that connect to one another, and samples are gathered into a suitable liquid for examination. The assembly has a stage with an operational cut-off diameter of 6.4µm and is made to function at 60 L/min [19].

❖ **Next Generation Impactor**

A high-performance cascade impactor called the Next Generation ImpactorTM, or NGITM, divides aerosol particles into size fractions for testing dry-powder and metered-dose inhalers as well as other inhaled medication delivery systems including nebulizers and nasal sprays. Together with a group of 15 pharmaceutical firms, MSP developed the NGI, which has excellent aerodynamic performance, minimal interstage losses, and user-friendly features. International acceptance of the NGI in both the USP and the EP. It has detachable collection cups, O-ring-free connections, and a micro-orifice collector that may be used in most formulations in place of a final filter. Because of these features, the NGI is an easy-to-use, effective workstation that can do 10 to 20 inhaler determinations every day with a single impactor, using less capital equipment and leading to a cleaner, more effective laboratory [20].

Features [20]

- For the majority of formulations, a final micro-orifice collector that may be used in place of a final filter and seven impaction stages are included.
- Stage cut sizes from 15 L/min to 100 L/min are known, and the entire range may be used with the same parts.
- Additionally calibrated, specifically for nebulizers, at 15 L/min.
- At least five of the seven stages have D50 values between 0.54 and 6.12µm at all design flow rates.
- O-ring-free input connections, a hinged detachable cover, and a pair of removable collecting cups.
- electrically conductive and resistant to corrosion
- USP Induction Port Made of 316 Stainless Steel
- For the whole range of 30 L/min to 100 L/min, use one pre-separator.

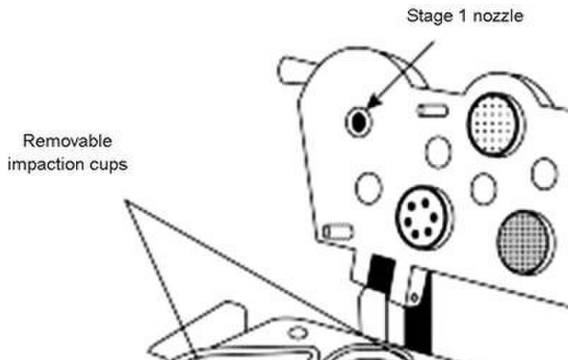

Figure 9: Schematic representation of Next Generation Impactor [20]

- **Aerodynamic Diameter and Dynamic Shape Factor**

The most crucial design factor in a DPI formulation is particle size. The determination of particle size and dispersion was done using geometrical elements or physicochemical characteristics. Aerodynamic diameter is the one of these that has the biggest impact on lung delivery and, eventually, therapeutic benefit [9]. Since it identifies with particle dynamic behaviour and primarily defines mechanisms of aerosol deposition, aerodynamic diameter is the most appropriate way to evaluate aerosol particle size. Both gravity settling and inertial impaction depend on aerodynamic diameter. The diameter of an analogous volume sphere with unit density Deq and the same terminal settling velocity as the real particle defines the aerodynamic diameter, Dae. The link between these dimensions is described by the following formula for particles bigger than 1µm [9, 21].

$$D_{ae} = D_{eq}\sqrt{\left(\frac{\rho_p}{\rho_o X}\right)}$$

Where,

Dae - Aerodynamic Diameter

Deq - Unit density of equivalent volume sphere.

ρP and ρo - Particle and unit densities

X- The dynamic shape factor.

Pharmaceutical powders are occasionally spherical, and form components serve as dimensionless indicators of sphericity departure. The ratio of the actual resistance force felt by the falling non-spherical particle to the resistance force felt by a sphere with the same volume is the dynamic form variable. To enter peripheral airways, a particle's aerodynamic diameter should be between one and five millimetres. Particles bigger than 5µm often settle in the throat or oral cavity, where they can be readily removed. Particles smaller than 0.5 m, however, may not deposit at all because of their sluggish Brownian motion and slow rate of settlement. Additionally, they are wasteful since only 0.1% of the mass carried into the lungs by a 5 mm sphere is delivered by a 0.5 mm sphere.

By reducing particle size, decreasing particle density, or increasing the dynamic shape factor, the aerodynamic diameter can be reduced.

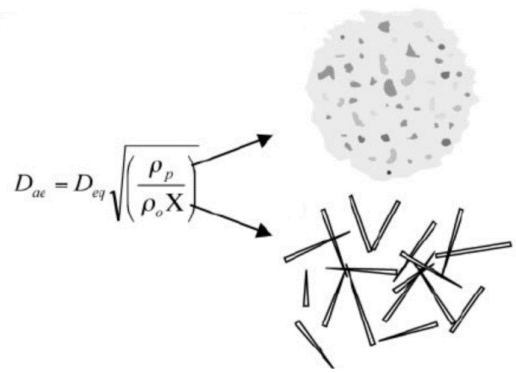

Figure 10: Strategies for altering the aerodynamic diameter

When figuring up the Dry Powder Inhaler's particle size distribution, side effects should also be taken into account. When bigger size particles are utilised, upper throat deposition occurs; however, smaller particles deposit more frequently in the alveoli, which may have a negative impact on the alveolar region's systemic circulation.

DPI Device

Effective drug delivery into the deep lung depends on the integration of powder formulation and device performance. The device should be designed to deliver high Fine Particle Fraction (FPF) of drugs from the formulation. Devices with higher resistance require a higher inspiratory force

from the patient to achieve the desired air flow. Patients with severe COPD, asthma, or newborns and children may find this challenging. To obtain the intended therapeutic impact from DPI formulation, a compromise between these two elements is therefore required. [22, 29, 30] All types of devices on the market and several others that are in development have the same basic inhaler components. Device for using dry powder inhalers includes a mouthpiece, dosage measurement system, powder deagglomeration mechanism, and powder formulation.

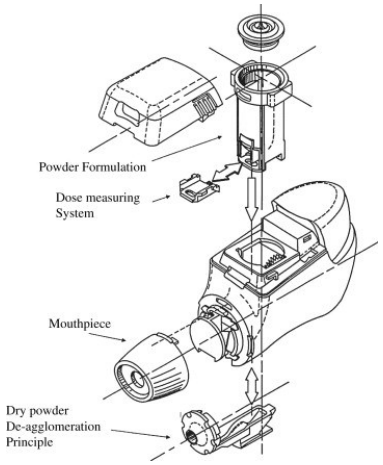

Figure 11: Primary functional design elements of dry powder inhaler [22]

❖ **Ideal Characteristics for DPI Device [23,29]**

1. Device should be easy to use.
2. Convenient to convey.
3. Contain multiple doses.
4. Protect the drug from moisture.
5. Indicate the dosages remaining i.e. audiovisual.
6. Accurate and uniform delivery of doses over extensive range of inspiratory flow rate.
7. Consistent dose delivery for the duration of the life of the inhaler.
8. Optimal particle size of drug for deep drug lung delivery
9. Suitability for a extensive range of drugs and doses.
10. Minimum adhesion between drug formulation and devices.
11. Product stability in the device.
12. Cost effectiveness.

❖ **Classification of DPI Device [1, 15, 24]**

Devices for dry powder inhalation are primarily categorised by dosage type into

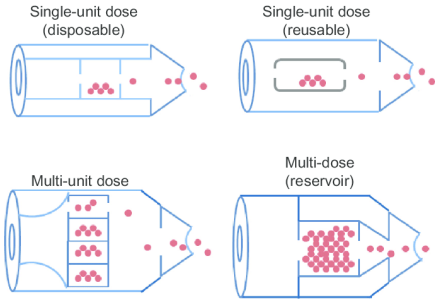

Figure 12: Illustration of four dose design for dry powder inhalers. A: Single Unit Dose, B: Single use disposable C: Multi unit dose, D: Multi dose reservoir

A. Single-unit dose

In a single-unit dose device, the medication is prepared as a micronized drug powder and carrier system and supplied in individual gelatin capsules. These capsules are then embedded into the device for a single dose and expelled and discarded after. Capsules containing dry powder for inhalation are used for single unit doses. After usage, these capsules are changed. Powder for inhalation is placed in the dosage cavity of a single-use disposable device.

B. Multi dose reservoir.

Multi dosage reservoir can also be categorised as multi-unit dose reservoir. The factory-metered, sealed doses used in the multi-unit dosage device are packed such that the device may store several doses without needing to be reloaded. Typically, the packaging consists of reloadable or replaceable discs, cartridges, or strips of foil-polymer blister packing. The advantage of this pre-packaged product is that it is shielded from the environment until usage and ensures adequate control of dosage consistency. If the device is a multi-dose reservoir, the formulation is stored in bulk and individual

doses are metered from the bulk when the device is activated. One of these products' principal drawbacks is moisture infiltration into the reservoir from patient exhale or humidity in the surrounding environment during the course of the product's lifespan, which results in a reduction in the flow rate of powder for inhalation.

DPI Devices are also classified into;

a. **Passive DPI Device -** These breath-activated devices rely on the patient's inspiration to supply enough air flow for entrainment and de-aggregation of the formulation. The actuation was often timed to coincide with the patient's inhalation, eliminating the coordination problems that are typically considered to be the main problem with pMDIs.
b. **Active DPI Device -** The aerosol is produced by active-dispersion devices using an energy source separate from the patient's effort. The advantage of this approach is that it lessens reliance on the patient's pressure generation and coordination abilities. Children and patients who are unable to generate enough pressure or flow rate on their own are encouraged to use this. Active DPIs, on the other hand, frequently exhibit complexity, which raises the price of the device and complicates obtaining regulatory clearance. Additionally, active inhalers would experience the same difficulty with breath coordination as pMDIs. Compressed air, batteries, or energy-storing spring mechanisms are examples of active methods for dispersion.

CONCLUSION

In conclusion, the evaluation of dry powder inhalers (DPIs) highlights their effectiveness and accessibility in treating respiratory diseases. DPIs offer advantages over traditional devices, including ease of use, portability, and improved drug delivery. Their dry powder formulation ensures stability and eliminates the need for propellants, making them environmentally friendly. DPIs effectively deliver medication directly to the lungs, ensuring efficient absorption and rapid action. They manage respiratory conditions like asthma and COPD well, with precise dosage control and consistent drug delivery enhancing treatment outcomes and patient compliance. DPIs are accessible to diverse patients, suitable for different ages and abilities. They eliminate coordination challenges faced by other devices, benefiting elderly and pediatric patients. However, proper education, training, and regular maintenance are necessary. Efforts should be made to address cost barriers and ensure global availability through collaboration among pharmaceutical companies, healthcare providers, and regulatory authorities, thereby benefiting patients worldwide.

REFERENCES

1. Challenges and goals for next generation therapies, By Hak-Kim Chan, Paul M. Young, Daniela Traini, MatthewCoates. [www.pharmtech.findpharma.com/pharmtech /Do sage+Forms/Dry-powder-inhalers-challenges-andgoals-for-Articlestandard/Article/detail/418244, Dry powder inhalers]
2. Dry Powder Inhaler. http://en.wikipedia.org/wiki/Dry_Powder_In hal er]
3. Daniher D.I, Zhu J.Review Dry powder Platform for pulmonary drug delivery. Particuology., 2008, 6: 225- 238.
4. A Review by Prof. Naushad Khan Ghilzai, Midwestern University. [ILwww.drugdel.com/Pulm_review.pdf, Pulmonary Drug Delivery]
5. Dr. Morton D, Prof. Stanlforth J. Systemic Pulmonary Delivery: Success through Integrated Formulation and Device Development; ON drug Delivery, Pulmonary

delivery: innovative technologies breathing new life into inhalable therapeutics,2008, 12-13.

6. Shaikh S, Nazim S, Khan T, Shaikh A, Zameeruddin M, Quazi A. Recent Advances In Pulmonary Drug Delivery System: A Review; International Journal of Applied Pharmaceutics 2010, 2(4): 27-31.
7. Prime D, Atkins P. J, Slater A, Sunby B. Review of Dry Powder inhalers; Advance Drug Delivery Reviews., 1997, 26: 51-58.
8. Respirable Microparticles Of Aminoglycoside Antibiotics For Pulmonary Administration by Chiara Parlati.
9. Factors to Consider in Developing a Dry Powder Inhaler by David L. Gardner. [http://nanoparticles.org/pdf/Gardner.pdf]
10. Telko M. J, Embleton J. K. Dry Powdr Inhaler Formulation; Respiratory Care.,2005, 50(9):1209- 1227.
11. Malcolmson R. J, Embleton J. K. Dry powder formulations for pulmonary delivery; Reviews research focus, December 1998, 1(9): 394-398.
12. Dry powder inhalers. [www.lactose.com]
13. Keller M, Walz R. M. Dry Powder For Inhalation, United State Patent Application Publication, Publication No.- US2011/0114092 A1, Publication Date- May 19, 2011.
14. Ashurst I, Malton A, Prime D, SumbyB. Latest advances in the development of dry powder inhalers, reviews-research focus., 2000, 3(7): 246- 256.
15. Alagusundaram M, Deepthi N, Angalaparameswari S. R. S, Mohamed Saleem T. S, Gnanaprakash K, Thiruvengadarajan V. S, Madhusudhana C. Dry Powder Inhalers - An Overview; International Journal Research Pharmaceutical Science., 2010, 1(1): 34-42.
16. Dry Powder Inhaler Formulation By John Staniforth ,Mike Tobyn, Robert Price, 6th February 2001.
17. Information Broucher Copley Scientific, Quality Solutions for Inhaler Testing. [www.copleyscientific.com]
18. Indian Pharmacopoeia, The Indian Pharmacopoeia Commission Ghaziabad, 2010, 2(3); 20-34: 1187- 1188.
19. Shah nutan, shah vishal. Dry Powder Inhalation: A Review, International Journal of Research & Review in Pharmacy & Applied Science., 2010, 2(3): 458-472.
20. Frijlink H W, De Boer AH. Review Dry Powder Inhalers for Pulmonary Delivery; Expert Opinion, Ashley Publication., 2004, 1(1): 67-86.
21. Newman S. P, Busse W. W. Review Evolution of dry powder inhaler design, formulation, and performance; Respiratory Medicine., 2002, 96: 293-304.
22. Nazrul Islam, Ellen Gldaki. Mini Review Dry Powder Inhalers (DPIs)- A review of device reliability and innovation; International Journal of Pharmaceutics., 2008, 360: 1-11.
23. Kapileshwar Swain, Mahesh Giri, RN Gupta, VK Arora. Dry powder inhaler a Review; Research journal of pharmaceutical, biological and chemical science,2012, 3(3): 1346-1356.
24. Cochrane MG, Bala MV, Downs KE, et al. Inhaled corticosteroids for asthma therapy. Patient compliance, devices and inhalation technique.,2000, 117: 542–50.
25. Bissera Pilicheva, Plamen Katsarov, Margarita Kassarova. Flowability Evaluation of Dry Powder Inhalation Formulations Intended for Nasal Delivery of Betahistine Dihydrochloride.SMU medical journal.,2015, 2: 77-90.

26. Taneja ruche, sachdeva vishal, etal.recent trend in dpi technology. International research journal of pharmacy.,2012, 3(11),27-34
27. Niti Yadav, Alka Lohani. Dry Powder Inhalers: A Review. Indo Global Journal of Pharmaceutical Sciences, 2013, 3(2): 142-155.
28. Roberto W, Dal Negro. Dry powder inhalers and the right things to remember: a concept review. Dal Negro Multidisciplinary Respiratory Medicine. ,2015, 10(13): 2-4.
29. SP. Sahane, AK. Nikhar, S. Bhaskarana, DR.
30. Mundhada. Dry Powder Inhaler: An Advance
31. Technique for Pulmonary Drug Delivery System.
32. International journal of pharmaceutical and chemical sciences.,2012,1(3): 1027-1034.

HOW TO CITE: Trupti Bhalekar*, Kalpana Sable, Jaya Mehetre, Kiran Dhamak, Dry Powder Inhalers: A Critical Evaluation Of Their Effectiveness And Accessibility, Int. J. in Pharm. Sci., 2023, Vol 1, Issue 7, 288-301. https://doi.org/10.5281/zenodo.8173889