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DEVELOPMENTOFTHEDRY POWDER INHALER: A REVIEW

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Abstract

A Dry Powder Inhaler (DPI) is a device that inhales dry powdered medication 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 formulation will allow a dry powder inhaler to achieve these objectives. The three main categories are nebulizer, pMDI, and DPI. DPIs, which administer medication to the lungs in the form of a dry powder, are an alternative to pMDI. To ensure that the patient receives the same dose each time at a varied airflow rate, API particles must be present in the size range of 1 to 10m.The use of pressurized metered dosage inhalers (MDIs) has been around for a while to treat lung conditions like asthma and chronic obstructive pulmonary disease. MDIs rely on the propellant, which makes up the majority of the MDI formulation, to atomize medication and excipients droplets, which should ideally deposit in the lungs. The methods of formulating for MDI drug delivery underwent significant improvements during the phase-out of chlorofluorocarbon propellants and the introduction of hydrofluoroalkane propellants, which are more environmentally friendly. There was also a greater understanding of the effects of formulation variables on product performance. This paper provides an overview of the difficulties involved in creating MDIs as solution or suspension products containing one or more medications, taking into account the physicochemical characteristics of various excipients and how their addition may affect the MDI's overall product performance.

Key Words: *Dry Powder Inhaler (DPI), COPD, Bronchitis, and Asthma.*

INTRODUCTION

Many illnesses are known to have an impact on the lungs, including asthma, chronic obstructive pulmonary disease, cystic fibrosis, idiopathic lung fibrosis, lung cancer, pneumonia, and tuberculosis. Due to the chronic nature of lung disorders, long-term treatment is necessary; as a result, systemic drug administration may cause side effects [1, 2]. Lung illnesses are treated using a variety of methods, such as chemical medicines, antibiotics, proteins, peptides, and genetic elements. But instead of fully curing ailments, many methods just alleviate their symptoms [2-4]. In order to effectively treat lung illnesses, researchers' top priority is to create innovative inhaler formulations. Since the active ingredient can be carried directly to the site of action in lower and upper respiratory tract disorders, inhaling medications has a number of benefits, including minimizing systemic side effects and improving treatment effectiveness. Additionally, the first-pass impact and a typical clinical response are biological barriers that can be bypassed by pulmonary drug administration. Another benefit is that the same therapeutic effect can be acquired at far lower doses than with oral administration, and there is no impact from any factors that could decrease patient compliance, such as pain or aversion to the medication. Formulations for inhalation can be used to deliver drug compounds varying in size from tiny molecules to massive peptide molecules. Physiological factors in the lungs, such as their huge surface area, highly permeable membrane structure, and low enzymatic activity, boost the efficiency of inhaler formulations even when inter-individual heterogeneity is noted [5–14].

Inhalation therapy is not a brand-new idea. In recent decades, inhalation therapy has become more significant. Asthma, chronic obstructive pulmonary disease (COPD), and allergic rhinitis are just a few examples of local nasal problems that can be treated with medications delivered by inhalation today. In some cases, the route of inhalation is also being looked into for the systemic distribution of pharmaceuticals. Inhalation therapy for local treatment primarily aims to lessen pulmonary symptoms, for instance by reducing and/or preventing airway inflammation and tightness. Corticosteroids, beta-sympathomimetic, muscarinic antagonists, and antibiotics are common examples of inhaled medications. These medications have significant advantages over their systemically delivered counterparts when inhaled. Importantly, by administering the medication directly to the target organ, the lung, high pulmonary drug concentrations can be attained. As a result, clinically equal or even superior inhaled dosages can be achieved compared to greater doses of systemically delivered medication. For delivering the good efficacy of API (Active Pharmaceutical Ingredient) using an appropriate medium, inhalation is finely disseminated in various dose forms. The inhalation dosage forms are relatively evenly distributed among the several categories in the pharmacopeial forum, as seen in figure 1.[15-23]

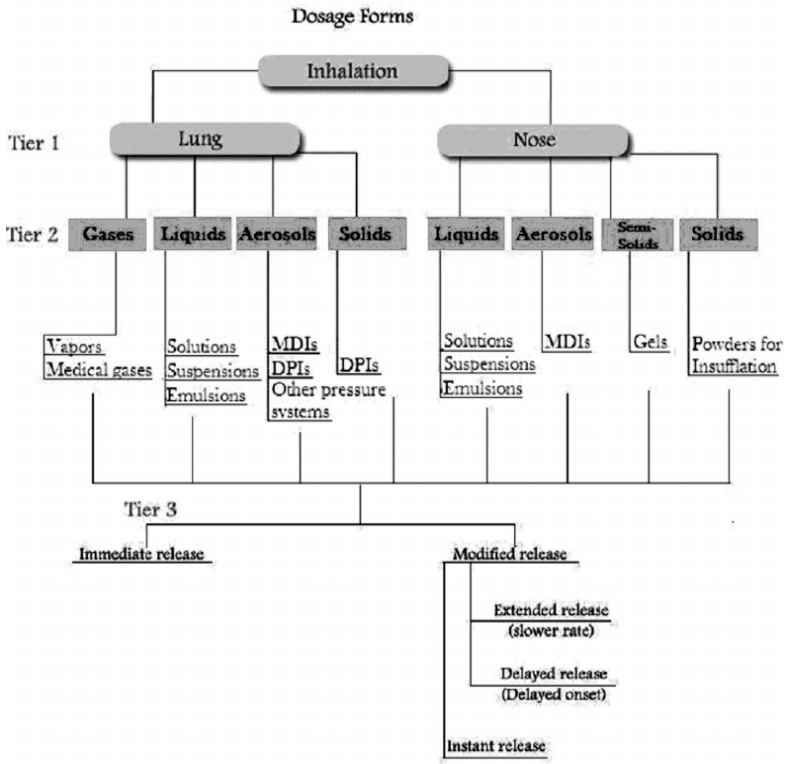

Fig. 1: Categories of inhalation dosage form

Dry Powder Inhaler:

DevelopmentoftheDPI:

Pressurized metered-dose inhalers (pMDIs), DPIs, and nebulizers are the three main types of inhaled medication delivery devices. Each category has its own advantages and disadvantages. Within each class, further distinction is based on metering, mechanisms of dispersion, or design. This classification is based on the physical states of dispersed-phase and continuous media. Nebulizers differ significantly from pMDIs and DPIs in that the medication is suspended or dissolved in a polar liquid, typically water. Nebulizers are frequently used in hospital and ambulatory care settings rather than for the management of chronic diseases since they are larger and less convenient and disseminate the aerosol continuously for a long time. A nonpolar volatile propellant or a dry powder mix (DPI) that becomes fluidized when the patient inhales is used in pMDI and DPIs, which are bolus medication delivery devices. Many clinical trials that have been evaluated by Barry and O'Callaghan [24] and more recently by Dolovich et al.[25] have thoroughly examined the clinical performance of the various types of inhalation devices.These authors came to the conclusion that none of the devices are therapeutically superior, and that other considerations, like cost, convenience, and availability, should be used to make device choices. The pMDI was the first modern inhaler device, initially certified in 1956.[26] The pMDI continues to be the most popular device, with an approximate 80% market share worldwide.[27] The need for alternatives to pMDIs, a desire to reduce the emission of ozone-depleting and greenhouse gases (hydrofluoroalkanes and chlorofluorocarbons, respectively) and a desire to improve the delivery of macromolecules and biotechnological products are the driving forces behind the development of DPIs. Additionally, DPIs were effective in correcting the pMDI's other device and formulation-related flaws. DPIs are more effective, stable, and user-friendly systems. A pMDI emits the dose at a rapid rate and under pressure, which increases the likelihood of early deposition in the oropharynx.[28,29] pMDIs need to carefully coordinate the actuation and breathing processes. Giraud and Roche reported that improper usage of

pMDIs is still a common issue, despite improvements to their design (such as the use of spacers)[30]. They discovered that a significant number of patients treated with corticosteroid pMDIs had worsened asthma control due to improper coordination of actuation and inhalation.DPIs don't need much, if any, coordination between actuation and inhalation because they are actuated by the patient's inspiratory airflow [31]. Better lung delivery has frequently been obtained as a result than with comparable pMDIs.[32] DPIs are also favoured in terms of processing and stability because they are often created as one-phase, solid-particle mixes.[33] 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 that contain propellant and cosolvents may be able to extract organic chemicals from the parts of the device.[34] The primary benefits and drawbacks of the DPI (in comparison to the pMDI) are listed in Table 1. Excellent evaluations are available if you want additional information on how aerosol delivery systems have changed.[35,36] Interest in and development of DPIs have been further stoked by the creation of a number of new DPI devices, which have been reviewed elsewhere [33],[37-39], and the commercial success of the bronchodilator-corticosteroid combination drug Advair (GlaxoSmithKline, Research Triangle Park, North Carolina).[40]

POLYMERIC DRY POWDER INHALERS:

In the creation of DPIs, polymers are widely used [41] (Table 1) in order to achieve continuous drug release and protection against enzymatic degradation of active compounds. The main goal of the development of polymeric DPIs was to alter the characteristics of water-soluble formulations' fast drug release. Due of their low toxicity, biocompatible polymers like polyvinyl alcohol (PVA) and poly (lactic-co-glycolic acid) (PLGA) are frequently utilized as sustained drug release agents [42–44]. Other polymers used to make polymeric dry powder inhalers include polylactide (PLA), poly-caprolactone (PCL), hydroxyl propyl methyl cellulose (HPMC), chitosan, gelatin, hyaluronic acid (HA), and locust bean gum (LBG) [45]. To achieve the desired drug concentration in the target location, a greater amount of polymer must be inhaled for a longer period of time, which may cause pulmonary inflammation and/or fibrosis [46,47]. To overcome this problem, natural polymers are increasingly being used instead of synthetic polymers [48-50]. Moreover, powder drug formulations based on nanoparticles are more stable than those based on liposomes and protect the active substance from airway defense mechanisms, such as mucociliary clearance and phagocytosis [51]. However, toxicity associated with inhalable nanoparticles remains a concern that needs to be addressed. Andrade et al. used thin-film hydration and freeze-drying techniques to produce and evaluate insulincontaining self-assembled polymeric micelles as DPIs. The Andersen Cascade Impactor was used at a flow rate of 28.3 L/min and 4 L of airpass condition to evaluate in vitro aerosolization and deposition properties of these particles. Using a rotahaler, the study reported FPF higher than 44% and MMAD less than 5.1 µm [52]. Rezazadeh et al. produced paclitaxel containing polymeric micelles as DPI using spray drying technique. In this study, systemic side effects are expected to be alleviated by local application. Tocopheryl succinate and polyethylene glycol were used to produce polymeric micelles. Aerodynamic parameters of obtained DPI were evaluated using Andersen Cascade Impactor with Spinhaler® device. MMAD, FPF and emitted dose (%) were <4 µm, 60.1±10.23% and 89.8±4%, respectively [53].

Polymeric dry powder inhalers can be produced in many different ways. For instance, Farhangi et al. developed ciprofloxacin-loaded polymeric nanomicelles by spray drying process using chitosan-lipid conjugates. Produced formulations had significantly higher antibacterial effect compared to free ciprofloxacin. Volume mean diameter and FPF of the formulation were 1.7 µm and 60%, respectively [54]. As can be seen from the examples given, it is possible to obtain DPI with different aerodynamic properties by changing the production parameters.

Table 1. Examples of polymeric DPIs along with key results

System Type	Drug	Result	Reference
Polymeric DPIs	Budesonide	FPF: 52.8 ± 1.0%, MMAD: 2.21–5.75 µm Plasma concentration of deslorelin in the large-porous DPI analysis was 120-fold higher compared to untreated deslorelin.	[55]
Large porous polymeric DPIs	Deslorelin	Plasma concentration of deslorelin in the large-porous DPI analysis was 2.5-fold higher compared to small conventional DPI.	[56]
Large porous polymeric DPIs	Doxorubicin	Diameter: 14.1 ± 2.1 µm, MMAD: 3.6 ± 0.4 µm	[57]
Cyclodextrin containing large porous polymeric DPIs	Insulin	Density: 0.144 ± 0.007 g/mL, MMAD: ~10 µm	[58]

Novel Drug Delivery System for DPI:

- **Lipid Vesicles**

❖ Liposomes: Liposomes are typically self-enclosed small spherical arrangement composed of a single bilayer lipid membrane (unilamellar liposomes) or several bilayer lipid membranes (multilamellar liposomes) with a size range

of 50 to 1000 nm. They have various functions ranging from drug delivery to food carrier [59]. They help improve the solubility, bioavailability, in vitro and in vivo stability, targeted delivery, and sustained release and, moreover, have ability to enhance the intracellular uptake of drug components and bio distribution pattern with protecting the encapsulated agent from the destructive action of the external environment [60]. Literature showed that numerous inhaled liposomal products are in various stages of clinical trials [61]. Site-specificity, biodegradability, biocompatibility, good safety profile, and potential to enclose both hydrophobic and hydrophilic particles are the prime reasons to choose liposomes in pharmaceutical industries [62]. Liposomes are widely scrutinized as vehicle for the dry powder inhalation delivery of various drugs for treatment of several diseases and pathological conditions. They can be easily aerosolized and provide prolonged retention of carriers and drugs in the respiratory track [63]. Liposomesseem mostly suitable for delivery of drugs to the lungs as they can be prepared from substances endogenous to the lung as elements of lung surfactant. Lung surfactant is a complex mixture, of which about 85% is phospholipid, generally dipalmitoyl phosphatidylcholine (DPPC), with phosphatidylglycerol as the next most widespread phospholipid. Surfactant is also composed of cholesterol and two groups of nonserum proteins which are believed to be important in the adsorption, spreading, and reutilization of surfactant. The mechanisms for the clearance and reutilization of lung surfactant are likely to be of major importance in determining the fate of liposomes deposited in the alveoli. The rate and extent of pulmonary uptake of liposomes are a function of their composition; significantly faster rates occur when liposomes contain phosphatidylglycerol [64]. In most cases, no considerable undesirable side effects were observed after the application of neutral or slightly negatively charged liposomes, though cationic liposomes were found to be toxic to human cells and potentially can introduce genetic aberrations. Besides, adverse side effects of cationic liposomes considerably increased with an increase of positive charge of the particles. Still, because cationic liposomes normally are used for the formation of almost neutral complexes with negatively charged nucleic acids, such modification of cationic carriers usually prevents adverse effects on the cells [65].

❖ Proliposomes: Proliposomes are described as dry, freeflowing microparticles with a dispersed system which can easily form a liposomal vesicle when in contact with water or biological fluids. Simply, powdered drugs are prepared by the adsorption of phospholipids and drug moiety onto the microporous matrix of carrier particles [66]. Compared with conventional liposomes, proliposomes display more advantages in stability, drug release, and solubility [67]. Therefore, proliposomes would be a potential medium to enhance oral absorption of hydrophobic drugs. The primary mechanism allowing proliposomes to improve oral absorption might be partially explained by the presence of bile salts, which can interact with phospholipids in the gastrointestinal tract to construct mixed micelles for medium to augment the solubility of hydrophobic drugs [68].

❖ Lipospheres: Lipospheres are also typically selfenclosed small spherical arrangement composed of water dispersible solid microparticles of particle size between 0.2 and 100 μm in diameter and a solid hydrophobic fat core stabilized by one monolayer of phospholipid molecules embedded in their surface. Due to their solid lipid matrix, controlled release from these carriers is achievable which is essential to provide the drug over a prolonged period of time with improved bioavailability and physicochemical stability [69]. Cyclosporine A (CsA) lipospheres based DPI was formulated using dipalmitoylphosphatidylcholine (DPPC) and dipalmitoylphosphatidylglycerol (DPPG) (75 : 25) phospholipids by spray drying method. Aerosol dispersion patternwas determined using a next generation impactor (NGI) with a HandiHaler device at 60 L/min using #3 HPMC capsules. The percentage of fine particle fraction (FPF), mass median aerodynamic diameter (MMAD), and geometric standard deviation (GSD) was found to be 52.99 ± 4.12%, 2.79 ± 0.47 μm, and 1.85 ± 0.05, respectively. In summary, compared to drug alone prepared co-SD CsA, DPPC/DPPG lipospheres displayed better physicochemical properties and aerosol dispersion with very low residual water content [63]. Singh et al. investigated the rifampicin loaded phospholipid lipospheres containing sulfphobutyl ether, β-cyclodextrin, and Vit. C formulated using spray drying technique. Prepared amorphous lipospheres showed spherical morphology with the size range of 1–5 μm. Aerosol dispersion pattern was concluded using Andersen cascade impactor (ACI) with device operating at 28.3 L/min using #3 HPMC capsules. The FPF and emitted dose (ED) were found to be 52.99 ± 4.12% and 85.40 ± 1.04%, respectively. Moreover, prepared lipospheres exhibited approximately ∼2-fold improvement in antimycobacterial activity over MTB H37Rv strain compared to drug alone. Improvement in antimycobacterial activity may be attributed to the cyclodextrin-cholesterol matrix structure [70].

❖ Lipid-Coated Particles: Liposomes, proliposomes, and lipospheres have been the platform of choice for pulmonary drug delivery applications over the past decade. However, extensive investigation has revealed their restrictions as drug delivery carriers. They have limitations. For instance, phospholipid may sometimes undergo oxidation and hydrolysis like reaction, short half-life, and poor mechanical stability due to leakage and fusion of the formulation [71]. To overcome these limitations, a hybrid class of lipid-coated particles has received good attention in recent years. Lipid coating offers better stability and higher encapsulation efficiency than liposomes. The existence of a low lipid coating level permits the preparation of powders with few excipients, thereby delivering more drug to the lungs. Additionally, the hydrophobic nature of neutral lipids (cholesterol) decreases the absorption of the ubiquitous vapor, leading to lessening the aggregation and the adhesion of particles. Tobramycin lipid-coated particles were prepared using mixtures of cholesterol and phospholipids (75 : 25) by spray drying technique. Developed lipid-coated particles showed small, smooth surface properties and good flowability with a mean size of about 1-2 mm. Aerosol dispersion pattern was

determined using a multistage liquid impinger (MSLI) with a Cyclohaler device at 100 L/min for 2.4 s using #3 HPMC capsules containing 15 mg of tobramycin lipid-coated particles. The FPF of prepared lipid-coated particles was found to be 68% with approximately ~1.5-fold improvement in FPF compared to uncoated micronized tobramycin particles. Developed lipid-coated tobramycin DPI formulations required very low amount of excipient and produce better lung deposition. These formulations are mostly useful for drugs that are active at relatively high doses, for example, antibiotics, since they allow the delivery of a high concentration of antibiotic directly to the site of action while minimizing systemic exposure [72].

Nanoparticulate System:

Nanoparticles are solid, colloidal particles comprising macromolecular materials that differ in size from 10 nm to 1000 nm in which the drug moiety is dissolved, encapsulated, and entrapped and/or to which the drug moiety is adsorbed, embedded, or attached, which can be administered in fluid form with a liquid carrier. A wide variety of delivery systems includes nanoparticles, polymeric nanoparticles, polymeric micelles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanocapsules, nanospheres, nanoemulsion, and many more. They have the capacity to modulate both the pharmacokinetic and pharmacodynamic properties of drugs, thereby improving their therapeutic index. Nanoparticles help modify the biodistribution, in vivo stability, bioavailability, and penetration through biological barriers. Moreover, they also provide controlled and targeted drug release [73-75]. Inhalable nanoparticles are advantageous for the objective of improving the solubility, dissolution profiles, and pharmacokinetic profile and reducing premature mucociliary clearance of hydrophobic drugs [76]. The size, shape, and composition of nanoparticles are key features which determine their percentage retention and targeting properties [77]. Inhaled nanoparticles could be easily exhaled during administration due to their small diameter ($\ll 1\ \mu$m) and low inertia. Nanonization often conveys an enormous increase in Gibb's free energy due to the increase in surface area. Moreover, these particles have tendency to grow due to Ostwald ripening and can suffer from uninhibited agglomeration [78–81]. This issue has been resolved by transforming nanoparticles into inhalable microaggregates via numerous techniques like spray drying and spray freeze drying or with leucine, mannitol, and PVA as matrix components [82,83]. Spray freeze dried microaggregates exhibited superior aerosolization performance compared to those produced by spray drying and this was credited to the porous structure and low density of the particles [84-86].

Microparticulate System:

The expression "microparticle" in drug delivery is usually designated to a particle with one or several micrometers in dimension. Based upon the method of preparation, the drug is entrapped, encapsulated, or simply dissolved to the microparticle template. Microparticle matrix contains many materials like polymers, ceramics, metals, and glass. This system is believed and accepted as a steady means to deliver the drugs to the target site with specificity [87]. Various delivery approaches involve microparticles, microspheres, solid lipid microparticles, polymeric microparticles [88,89], surface coated microparticles [90], and so forth. In clinical practices, microparticles appreciably influence retention in the lungs and targeting properties of therapeutic agent, apart from the fact that active targeting microparticles also offer numerous advantages like masking, facilitation of handling, controlled dissolution profile, and protection [91].

Solid Dispersions:

Solid dispersions are one of the known approaches to improve drug solubility and release profile of poorly water-soluble drugs. It is a molecular mixture of drug in hydrophilic polymer wherein the drug physicochemical characteristics are regulated by the polymer properties [92]. Here, the drug dissolution profile may be enhanced by reducing the drug particle size to nearly a molecular level and by transforming the drug crystalline state to create a complete or partially amorphous state, both of which may improve drug solubility and bioavailability [93]. Commonly used polymers in formulation of solid dispersions are cyclodextrin, hydroxy propyl methylcellulose, hydroxy propyl cellulose, ethyl cellulose, silica, povidone, starch, and polyethylene glycols [94]. Solid dispersions act as a flexible platform for novel drug delivery systems. Itraconazole (ITZ) SD based DPI was formulated using polymeric surfactant, that is, TPGS and hydrophilic agent, and mannitol by spray drying method. Prepared ITZ-SD-DPI compared with ITZ-SD-DPI without TPGS and bulk ITZ. ITZ-SD produced an improved dissolution rate and greater saturation solubility than bulk ITZ. The use of a polymeric surfactant (TPGS) was helpful in terms of solubility and dissolution profile but it also reduced FPF ($47 \pm 2\%$ to $37.2 \pm 0.4\%$). Additionally, device and capsule retention of ITZ-SD-DPI was significantly reduced when TPSG was used into the formulations. This may be due to lubricant effect of TPGS which improved device and capsule emptying by reducing the surface interaction and greater particle cohesion. Mannitol solid dispersions with optimized quantity polymeric surfactant may provide an effective platform for poorly soluble active ingredients DPI [95]. Cyclosporine A (CsA) amorphous solid dispersion was prepared by using wet-milling technique (WM/CsA) and jet milled with coarse lactose (Respitose SV003) to obtain desired aerodynamic particle size. WM/CsA-DPI exhibits the better dissolution profile as compared to pure CsA. Aerosol dispersion was examined using ACI with Jethaler device operating at a flow rate of 28.3 L/min. ACI analysis recommended good dispersion and deposition in the respiratory organs with the FPF and ED of 54 and 96%, respectively. Moreover, intratracheal administration of WM/CsA (100 μg CsA) in experimental animals led to 85 and 71% reduction of granulocyte recruitment in lung tissues and bronchoalveolar lavage fluids. In comparison to a commercially available CsA oral formulation, WM/CsA showed 102 - fold reduction in AUC and Cmax values of plasma CsA at toxic concentration (10 mg/kg). WM/CsADPI would be

effective dosage form for clinical treatment of airway inflammations with minimal systemic side effects [96]. Δ9 - Tetrahydrocannabinol solid dispersion was formulated using insulin in a mixture of tertiary butanol and water by spray freeze drying technique. Prepared formulation contains highly porous particles with specific surface area of 90 m2 /g. In vitro deposition of the powder formulations was determined with MSLI at flow rate of 60 L/min for 3 sec. FPF was found to be 50% for prepared formulation [97].

Thin Film Freezing:

The particle engineering process, thin film freezing (TFF), has ability to produce low density pharmaceutical powders with a porous, matrix structure. In TFH, the particle morphology can be controlled by influencing the fluid dynamics and heat transfer characteristics upon spreading and freezing of liquid droplets on solid surfaces. When stabilizing excipients with high glass transition temperatures, for instance, PVP or HPMC, are incorporated in the formulation, the pharmaceutical powders can be turned into amorphous ones. These low density TFF developed powders have also been shown to be highly respirable when aerosolized with a marketed inhaler [98,99]. Microstructured crystalline voriconazole (VRC) and nanostructured amorphous TFF-VRC particles [PVP K25 (1 : 3)] were formulated using thin film freezing technique. The prepared microstructured crystalline VRC and nanostructured amorphous VRC particles showed particle size of 0.45 μm and 0.05 μm, respectively. Powder dispersion was examined using NGI with single dose capsule based HandiHaler device operating at a flow rate of 60 L/min. NGI analysis showed better dispersion and deposition pattern for microstructured crystalline VRC (% FPF 37.80) compared to nanostructured amorphous VRC (% FPF: 32.40) particles. Microstructured crystalline VRC particles also showed approximately ~2-fold improvement in % FPF in comparison to micronized VRC with InhaLac 70 (2% w/w). Moreover, in single dose 24 h pharmacokinetic studies (10 mg/kg) microstructured crystalline VRC particles showed 2.06- fold improvement in AUC(0–24 h) of plasma compared to nanostructured amorphous VRC particles [98]. Similarly, an amorphous dry powder of tacrolimus (TAC) was prepared using thin film freezing technique. Aerosol dispersion of TFFprocessed powder was performed using Miat monodose inhaler device. TFF-processed TAC dry powder showed FPF and MMAD of 83.30% and 2.26 μm respectively. Although being of relatively large geometric size, the TFF-processed dry powder was capable of attaining deep lung due to its low density, highly porous, and brittle characteristics compared to a crystalline micronized TAC powder produced by milling technique. Additionally, in single dose 24 h pharmacokinetic study, TFF-processed powder showed better pulmonary bioavailability with prolonged retention time compared to a crystalline micronized TAC [99].

DPI Device:

The inhalation device is important in accomplishing satisfactory delivery of inhaled drug to lung. Effective delivery of drugs into the deep lung relies on integration of powder formulation and device performance. The device should design to deliver high Fine Particle Fraction (FPF) of drugs from the formulation. Deviceswith higher resistance require a higher inspiratory force by the patients to accomplish the desired air flow. This could be difficult for patients with severe asthma, COPD and for children and infants. Therefore a balance between these two factors is necessary to achieve the desired therapeutic impact from DPI formulation[100-102]. The primary inhaler parts are same for all type of devices on the market and many in development. Dry Powder Inhaler device consists of; powder formulation, dose measuring system, powder deagglomeration principle and mouthpiece.

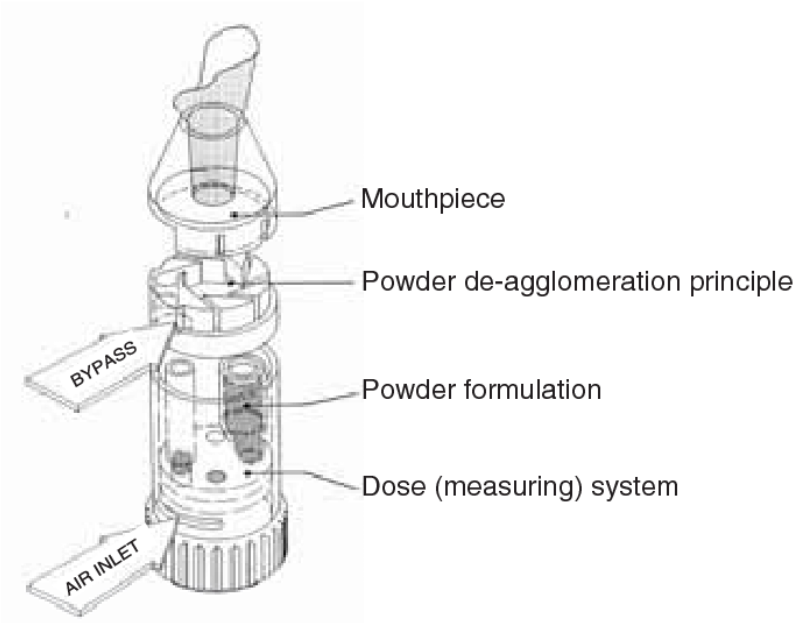

Fig2. Primary functional design elements of dry powder inhaler powder inhal

Ideal Characteristics for DPI Device: [103,104]

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.

Metered Dose Inhaler: (MDI)

The metered dose inhaler (MDI) to treat respiratory diseases was introduced many years ago. Due to the recently proposed ban on chlorofluorocarbon (Freon) production, the survival of the conventional MDI is uncertain. It is therefore incumbent on asthma caretakers to familiarize themselves with newer versions of the inhaler.

FORMULATION:

There are two types of MDI Formulation. Suspension Formulation and Solution Formulation. In suspension formulation, micronized drugs are dispersed in a propellant or combination of propellants. And in solution formulation drug is dissolved in the propellant or a combination of propellant and co-solvent. A suspension formulation is the most common dosage form when used together with hydrofluroalkane propellant.

SUSPENSION FORMULATION:

In suspension formulation, Micronized drug is suspended in the propellant, or a combination of the propellant drug must be insoluble in the propellant [105].

Advantages:

1. Formulation has good chemical stability.
2. No additional excipient needs to add which may be toxic.

Disadvantage:

1. The density difference between the propellant and drug affects dose uniformity.
2. Flocculation happens due to dissimilarity in hydrophilicity and hydrophobicity.

SOLUTION FORMULATION:

The drug is dissolved in HFA Propellant and appropriate co-solvent. Ethanol is added to produce the solution. This is two-phase system gas and liquid [105]. Compared with suspension formulation solution MDI provides the benefit of the homogeneous formulation.

Advantage:

1. Homogeneous and uniform drug delivery.
2. No particle growth and aggregation.

Disadvantages:

1. Adequate solubility is required in the vehicle.
2. Possible reduction in chemical stability.

BASIC MDI FORMULATION COMPONENT:

The fundamental components of pMDI are drug formulation, metering valve, propellant, actuator, and container. All play important role in the formulation of the aerosol plume and determining the amount of drug delivered to the lung.

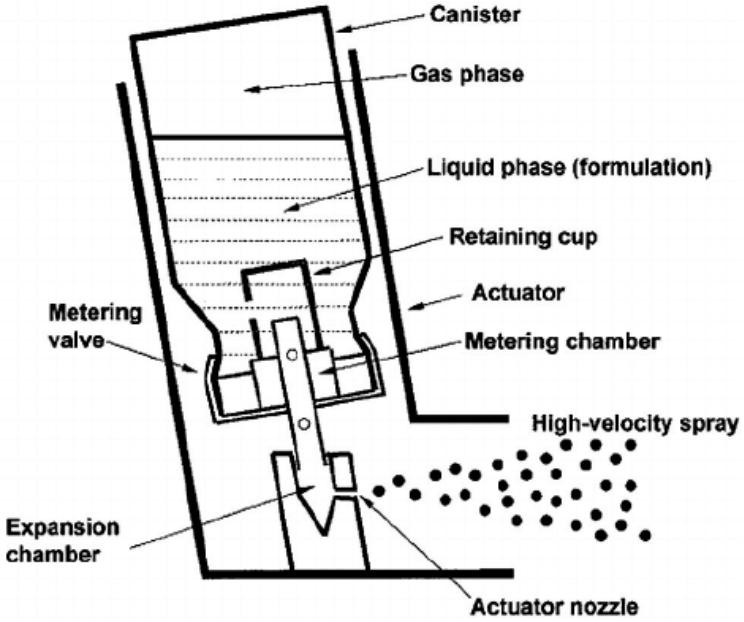

Figure No. 3: Basic MDI Formulation Component

Ideal properties:

1. Material used for the canister must be adaptable with the formulation.
2. It should have lightweight.
3. It should be break-resistant.
4. It must protect concentrate from sunlight.

Propellant:

One of the most crucial components of an MDI is its propellant. The propellant is described as liquefied gas with a vapour pressure greater than atmospheric pressure (14.7 Psia) at a temperature of 105ºF The Propellant is responsible for developing proper pressure within the container. It expels the product when the valve is opened. Propellants perform the essential function of expelling the material from the container by supplying the necessary pressure within the aerosol system. Mixtures of Propellants are often used to obtain necessary delivery and spray characteristics of aerosol. Propellants in MDIs typically make up more than 99 % of the delivered dose, so it is the properties of the propellant that dominate more than any other individual factor. Suitable propellants must pass a stringent set of criteria, they must:[106]

- Odourless, colourless, non-irritant, non-reactive and stable.
- Have a boiling point in the range -100 to +30°C
- Have a density of approximately 1.2 to 1.5 g cm−3 (approximately that of the drug to be suspended or dissolved)
- Have a vapour pressure of 40 to 80 psig have no toxicity to the patient
- Be non-flammable
- Be able to dissolve common additives. Active ingredients should be either fully soluble or fully insoluble.

There are general classes of the liquefied gas propellants depending upon their chemical nature.

1. **Fluorinated Hydrocarbons:** [107]
   They are also known as Chlorofluorocarbons (CFCs). They are the propellants of the choice for oral inhalation and nasal aerosols. The most important propellants include trichloromonofluoromethane (P-11), dichlorodifluoromethane (P-12) and dichlorotetrafluoroethane (P-114). Although CFCs are stable and non-toxic in the lower atmosphere, in the stratosphere, slow decomposition of CFCs by solar radiation results in the free chlorine content. Destruction of the ozone layer allows increased transmission of ultraviolet radiation to the earth's surface. For this reason they are being replaced by Non-CFCs.
2. **Hydrofluoroalkanes:**[108,109]
   These are also known as Non-chlorofluorocarbons (Non-CFCs) eg. HFA-134a, HFA-152a and HFA-227. These propellants do not contain chlorine and therefore have zero ozone depleting potential.
3. **Hydrocarbons:**
   Hydrocarbons like propane, butane, and isobutane, are used in topical pharmaceutical aerosols. They are preferred for use as propellants because of their environmental acceptance and low cost. However, they are flammable and explosive.
4. **Semiflurinated alkanes (SFA):** [110]

These are with flurocarbon and hydrocarbon segments. These are colourless non-aqueous liquids with low surface tension, high gas dissolving capacities, strong intramolecular bonds, and weak intermolecular interactions. E.g. Perflorobutyl pentane (F4H5), Perfluoro hexyl Hexane(F6H6), Perfluoro hexyloctane (F6H8).

Packaging Components:

Proper choice of packaging components is necessary as they affect the product performance. As given in MDI has three packaging components.

- **Containers (Canisters):** [111]
  Containers made up of as glass, stainless steel and aluminum have been used for pharmaceutical aerosols because of aesthetics and excellent compatibility with drugs. Aerosol containers must withstand pressures as high as 180 Psig at 130ºF. Mostly Aluminum type canisters used in pMDI formulation filling.

- **Metering Valves:** [112]
  The valve regulates the flow of active ingredients and Propellant from the container and determines the spray characteristics of aerosol. It must be manufactured from materials that are inert to the contents of aerosol. The function of the metering valve is to meter accurately and repetitively, small volumes of liquid containing the drug and to seal the pack against undue leakage of propellant vapour. The valve is a complex assembly of at least seven component parts, which are made of various materials. An integral part of these valves is the metering chamber, which is directly responsible for the delivery of the desired amount of therapeutic agent. The size of the metering chamber can be varied so that from 25µl to 75µl of product can be delivered per actuation. The chamber is sealed by the metering gasket and the stem gasket. In the actuated position, the stem gasket will allow the content of the metering chamber to be dispensed while the metering gasket will seal off any additional product from entering the chamber. Therefore, the chamber is always filled and ready to deliver the desired amount of therapeutic agent.

- **Actuator (Adaptor) and special devices:**[113,114]
  Actuator allows for easy opening and closing of the valve and is an integral part of MDI. The actuator (adaptor) is designed for oral inhalation. It incorporates the discharge orifice called spray nozzle and a socket to engage and form a seal with the metering valve stem. The expansion chamber is very important in influencing the physical characteristics of spray where active ingredients must be delivered in a proper particle size range. The actuator should restrain sideways motion of the container during actuation to minimize side stresses on the valve stem that may cause faulty metering or leakage between the valve stem and actuator. The actuator should provide adequate air ducting for inhalation to the mouthpiece at an acceptable low flow resistance.

- **Spacers:**
  Metered-dose inhalers are sometimes used with add-on devices referred to as holding chambers or spacers, which are tubes attached to the inhaler that act as a reservoir or holding chamber and reduce the speed at which the aerosol enters the mouth. They serve to hold the medication that is sprayed by the inhaler. This makes it easier to use the inhaler and helps ensure that more of the medication gets into the lungs instead of just into the mouth or the air. With proper use, a spacer can make an inhaler somewhat more effective in delivering medicine. Spacers can be especially helpful to adults and children who find a regular metered-dose inhaler hard to use. People who use corticosteroid inhalers should use a spacer to prevent getting the medicine in their mouth, where oral yeast infections and dysphonia can occur. The respiratory spacer devices eliminates the need for coordination of actuation and inspiration and reduces the primary droplet size by providing extra time for complete evaporation of propellant and reduces the velocity of the aerosol particles passing through the device.

QUALITY CONTROL TEST FOR METERED-DOSE INHALER:

Individual component testing:

- Propellant
- Metering Container
- Valve
- Surfactant
- Actuator

In-process control testing:

- Drug suspension concentration
- Drug suspension
- Filled canister
- Control of leakage rate
- Metering valve function
- Analytical testing applied to finished product.

- Identity
- Microbial limit test
- Spray pattern
- Water content

Drug product specification test for inhalation product:

- Leak test
- Number of doses delivered
- Content of active ingredient delivered per actuation
- Uniformity of delivered dose
- Drug content
- Spray pattern
- Vapour pressure
- Retention on Actuator
- Sterility
- Moisture content
- Preservative Content

Leak test:

The leak rate is most important in the stability study. The test is performed by randomly selecting 12 canisters of known weight which are kept in a water bath and maintained at 50°C. Then the canisters are checked after equilibrium for the presence of any leak in the form of air bubbles rising from the orifice or the valve crimp. The weight of these canisters was recorded as W1. Then the canisters are placed in overturned position for NLT 3 days and their weight is recorded as W2. The leakage rate is determined by a formula.

Number of doses delivered:

The content of MDI is discharged by actuating the valve at an interval of NLT 5 seconds and the number of doses discharged from the MDI is observed.

Content of active ingredient delivered per actuation:

The inhaler is discharged in the inverted position under the surface of diluents then pressurized. The content of the active ingredient delivered per actuation of the valve is determined by discharging the pressurized container through the stainless steel base plate that is kept in a100 ml beaker. In this beaker 60 ml diluent is added, the inhaler is shaken for 30 seconds before dose collection. Ten deliveries at the beginning, middle, and end of the calculated number of doses are discharged below the surface of diluent maintaining the pressurized container in the vertical plane and released the aerosol through the hole in the center of the base plate. [105]

Uniformity of delivered dose:

The delivered dose is the dose delivered from the inhaler to the patient. The main purpose of this test is to ensure dose uniformity within discharges from multiple containers of the batch. The Unit spray sampling apparatus USP is used. This test is designed to demonstrate the uniformity of medication per actuation expected with the label claim discharged from the mouthpiece of a sample. (105)

Drug content:

It gives the guarantee of uniformity of dose content in the drug product. The concentration of drug substance in the whole container is determined by using HPLC analytical method. The label of the container is removed by ethyl acetate and the container is placed in the refrigerator at -70°C for 5-10 minutes. After 10 minutes make a hole in the canister, then the canisters are cut and rinsed. Then the different dilutions are made and analyzed by the HPLC method.

Spray pattern:

The spray pattern test is useful for determining the performance of a specific formulationvalve combination and ensure therapeutic performance. The spray transfer through MDI has impinged onto a glass plate containing an activated silica gel dye mixture. The MDI is kept at a distance of 3cm from the plate. Then the spot is observed under UV light.

Vapor Pressure:

The Vapor pressure is determined by using a pressure gauge. The pressure difference indicates the presence of air in the headspace. A canister punctuating device is also widely used for exactly measuring the vapor pressure. The unit of vapor pressure is expressed in psig. [115]

Retention on actuator:
At the time of spraying from MDI, some amount of drug may get retained on the actuator. This indicates the waste drug which is not available for inhalation. Deliveries are fired through pMDI with an actuator attached to it in the sample collection tube adjusting air flow rate 28.3 L/min. Then the drug is extracted by adding diluent to the beaker and the actuator is separated, rinsed with diluent, and sonicate for 5 minutes. The solution collected is examined for the content of the drug. [116]

Sterility:
Sterility testing should be conducted according to an accepted pharmacopeia test.

Moisture content:
Chromatography and Karl Fischer method are most commonly used for the determination of moisture content. Karl Fischer is a most accurate technique for determining the moisture specifically for water content by using the Karl Fischer reagent. Karl Fischer reagent contains a basic solution of sulfur dioxide iodine and solvent as alcohol is most widely used.

Preservative content:
Preservative assay testing must be conducted.

Patient Education:
Patient training is most important for the proper use of aerosol devices because an error in the use of devices and in administering therapy was much more common when training was not given to a patient. Patient's poor knowledge regarding their disease and poor competency among dispensers are among the factor leading to improper use.

Conclusion:
DPIs are viewed as potential drug-delivery systems in the healthcare sector, but their application is constrained by difficulties in achieving a repeatable therapeutic and non-toxic effect. However, a significant rise in the use of inhalers has been noted due to the quick advancement of production technologies and testing techniques. One of the best techniques for achieving both local and quick systemic effects is still pulmonary administration. The scientific community is presently concentrating on enhancing the available formulations; including overcoming the related limitations, as DPIs are also the most stable formulations that can be supplied via inhalation. For the treatment of COPD, the inhalation is the best technique. The starting of inhalation in 1950 with smoke cigarettes containing the anticholinergic botanical, To treat severe asthma, use datura stramonium. Because of the destruction of the ozone layer, the Metered Dose Inhaler was created with CFC as its first propellant before introducing HFA. With the use of the metering valve, which may provide the precise dosage of medication to a patient with the help of the MDI's explicative operating mechanism, this device's many components will provide efficient efficacy in a measured manner. The filling process of the MDI was used in this article to effectively explain formulation features. There are some guidelines for evaluating the mdi that were reported in this by using the summary of inhaler testing or evaluation system.
powder inhaler
Primary functional design elements of dry
powder inhaler

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