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Dry Powder Inhalers: A Review

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ABSTRACT: In the recent years pulmonary drug delivery system is found to be preferred route of administration for various drugs. It has been divided into 3 classes: Nebulizers, pMDI, DPI.DPI are used as an alternative to pMDI because pMDI contains propellant (CFC) which has ozone depletion characteristics. DPI delivers medication in the form of dry powder to lungs. DPI is formulated either as a carrier based system or carrier free system. A wide range of dry powder inhaler devices are presently available in the market to deliver drugs with maximum drug delivery and low variability. This review focuses on the DPI formulation, factors affecting performance of DPI, and evaluation parameters. The development of DPI is governed by regulatory bodies. FDA and EMEA supported by pharmacopoeia are responsible for assessing safety and efficacy.

KEYWORDS: Laser Diffraction; Nebulizer; Pulmonary Route; Propellant.

INTRODUCTION

Since ancient times pulmonary route have been used to treat various respiratory diseases. Ancient therapies include the use of leaves from plant, vapors 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 [1]. 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 excipient that could enhance the delivery outcomes [2].

Advantage of Pulmonary Drug Delivery [3]

1. Large surface area is available for absorption.
2. Close proximity to blood flow.
3. Avoidance of first pass hepatics metabolism.
4. Compared to other oral route smaller doses are required to achieve equivalent therapeutic effect.
5. Provides rapid drug action.
6. It can be employed as an alternative route to drug interaction when two or more medications are used concurrently.
7. Provides local action within the respiratory tract.
8. Provides reduced dose.
9. Allows for a reduction in systemic side-effects.
10. Reduces extracellular enzyme levels compared to GI tract due to the large alveolar surface area.

Disadvantages of Pulmonary Drug Delivery [3]

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 (conventional) 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. Compel frequent dosing.

DEVELOPMENT OF INHALATION DEVICES

Development of inhalation devices have diverged into 3 distinct classes:

- Nebulizers
- Pressurized metered dose inhalers (pMDIs)
- Dry powder inhalers (DPI)

Nebulizers are systems in which the liquid formulations are disperse using compressed air or piezoelectric vibrations. The primary disadvantages of nebulizers are the length of time it takes to use them (typically at least several minutes to set up, inhale and clean), external power requirement, their size and weight may limit portability. In contrast pMDIs inaugurated in the 1950's prevail over the market for many years; it uses a pressurized gas propellant to aerosolized the dose. Because pMDI is pressurized it emit dose at high velocity which makes premature deposition in the oropharynx most likely. Thus it requires more careful coordination of actuation and inhalation. However this delivery system is now under increasing threat because of environmental concern regarding ozone depleating chloflourocarbon (CFC) as propellent.

The US Food and Drug Administration (FDA) has regulated that in the US after 2008 no CFC MDIs will be sold. In need of an alternative propellent, CFC have been replaced by HFA (hydroflouro alkane) , although the transition have not proven seamless , challenges arose with respect to reformulation issues, redesigning valves and actuators and conducting clinical trials.4 The elastomeric components in currently available metering valves are generally incompatible with HFA propellants, and some surfactants (oligolactic acids, acyl amide acids, and monofunctionalized polyethylene glycols) used in CFC formulations are not soluble in HFAs.. GlaxoSmithKline have developed formulations by using HFA-134a alone as particulate suspensions without any surfactant eg: salbutamol, salmeterol, and fluticasone propionate. Sophisticated measures had to be employed to prevent the adhesion of drug particles to canister walls, which could cause unacceptable dose variations [4-5].

As an alternative to pMDI, dry powder inhalers (DPIs) have been developed, which do not contain propellant but it have their own advantages and limitations [5].

DPIs are devices through which a drug powder formulation of an active drug is delivered for local and systemic effect via pulmonary route.

In DPIs, the drug particles (<5µm) are blended with the suitable large carrier (e.g. Lactose), to improve the flow properties and dose uniformity and the dry powders are delivered to the lung through a device known as Dry Powder Inhalers. Powder deagglomeration and aeroionization of the formulation occurs via patients own effort. In order to achieve this, a high turbulence is needed to break the large agglomerates to the smaller, fine and inhalable particles [6-8].
Dry powder devices which operate at low inspiratory flow rate e.g: Diskhaler, turbohaler, are clinically desirable for childrens and adults with decreased lung function either because of age or disease.

Characteristics of ideal DPI systems will include most or all of the following attributes [9]

1. Simple and comfortable to use.
2. It should be compact and economical.
3. Highly reproducible fine particle dosing.
4. Reproducible emitted doses.
5. Powder should be physically and chemically stable.
6. Minimal extra-pulmonary loss of drying.
   - Low oropharyngeal deposition.
   - Low device retention.
   - Low exhaled loss.
7. Multidose system.

8. Powder protected from external environment and usable in all environments.
9. Overdose protection.
10. Indicating the no. of doses delivered or remaining.

No DPIs achieved all of these characteristics; however considerable research is being conducted to improve their performance characteristics wherever necessary.

Advantages of DPI

Propellant-free , Less need for patient coordination, Less potential for formulation problems, Less potential for extractable from device components, Formulation stability

Disadvantages of DPI

Dependency on patient's inspiratory flow rate and profile, Device resistance and other design issues, Greater potential problems in dose uniformity, Less protection from environmental effects and patient abuse, More expensive than pressurized metered dose inhalers, Not available worldwide.

The formulation of DPI can be classified into three categories:

- API production.
- Formulation of API with or without carrier.
- Integration of formulation into device.

Inhaled drug combinations are generally considered a unique medication whose in vitro performance and in vivo efficacy must be demonstrated. All DPIs have 4 basic features Fig.2:

1. A dose metering mechanism.
2. An aerosolization mechanism.
3. A deaggregation mechanism.
4. An adaptor to direct the aerosol into patient mouth.

To introduce the drug particle into the lungs, they must be < 5µm in aerodynamic diameter. This is achieved by milling the powder prior to formulation. An important consequence of fine particle requirement for the inhalation arises from the fact that powder flow properties are dependent on the particle size distribution; fine particles generally flows less well than coarse ones. The final formulation must flow sufficiently well either to be dispersed from the bulk reservoir to give an adequately responsible dose or be capable of being handled well on automatic filling machine to produce the unit dose form for use in device. Small particles are also notoriously difficult to disperse must therefore be formulated to have appropriate properties such as reasonable flow ability and high dispersibility. 3 major processes are involved in delivery of drug particles from the carrier, their dispersion in the air flow and deposition in the respiratory tract. Thus any factor that affects any of these processes could ultimately influences the bioavailability of the inhaled drug.

Carrier Free system: In this carrier strategy, the drug particle which is to be inhaled must have aerodynamic diameter less than 5 µm and present either in the form of single compound or as an encapsulated particles.

Carrier Based system: Lactose is the most common and frequently used carrier in DPI formulations, Carrier particles offers several advantages like: improve drug particle flow ability, improved dosing accuracy, minimum dose variability, ease of handling during manufacturing operations, inhalation efficiency increases etc. and lactose as a carrier have all these characteristics. Carrier particles should have several characteristics such as physically and chemical stable, biocompatibile and biodegradabile, compatible with the various drugs and must be inert and economical [10-11].

Alpha-lactose monohydrate is typically used as 'the' carrier in dry powder inhalers. There is an urgency to find suitable alternative carriers due to several drawbacks of lactose and modified lactose as a carrier for dry powder inhalers like mannitol, glucose, sorbitol, maltitol and xylitol. From all the sugars, mannitol pretends to be most promising carrier for DPIs as compared to sorbitol, maltitol and xylitol sugars due to their hygroscopic nature. Carriers like crystallized mannitol (Pearlitol 110 C), spray-dried mannitol (Pearlitol 100 SD), crystallized maltitol (Maltisorb P90) etc were used ,it was found that crystallized forms of the carrier is better than spray-dried forms as it offers lower adhesion and better release of the active ingredient. By mixing micronized drug with larger lactose carrier particles DPI formulations are

basically prepared. It is prepared in such a way that results in good blend uniformity and better flow characteristics. It is most important that, when the formulation is delivered to the patient via a inhalation device the drug particles are released to provide a safe and efficacious dose to the patient [12].

Integration of formulation in a DPI device

In the development of a new DPI formulation, DPI device is the primary facto of concern. It is essential to have knowledge about computational fluid dynamics (CFD) while designing DPI devices. Particle flow, shear stress and potential particle impaction within the device is analysed by CFD. Consequently this data may be utilized to estimate the in vitro aerosolisation efficiency of a model drug [13] .

FACTORS AFFECTING DEVELOPMENT OF DPI DEVICES

Humidity: In the dry powder inhalers (DPIs), due to the interactions between the active substance and the excipient adhesion results. The delivery of the drug is believed to be affected by the morphologies of the carrier and the micronized drug particle. Van der Waals and electrostatic forces are the primary adhesion forces for a dry uncharged particle on a dry uncharged substrate. The total adhesion force increases in humid environments due to capillarity condensation which leads to rise to a very large capillarity force. The capillarity force dominates when the RH is above 50% [11].

Interparticulate forces: Flow and dispersion properties of the micronised and microcrystalline powders (particles smaller than 5μm), used for inhalation therapy are predominantly influenced by the Interparticulate force. Chemical and physical of the bulk drug, have been attempted in order to enhance inhalable dose performance.

Particle size: It is assumed that by controlling the particle size, aerosols may be targeted to a particular lung site. However, the complexity of the respiratory tract and the patient's respiratory dynamics cannot be ignored. Regardless, there are several clinical studies which established the importance of particle size on deposition and affective clinical response. The effectiveness of the inhaled drug inside the human respiratory tract is also affected by the size, shape and density of the inhaled particles.

Physical properties of powders: DPI provides powder pharmaceuticals in aerosol forms to the patients. The powdered drug is either loaded by the user into the DPI before use or stored in the DPI. To generate an aerosol the powder in its static state must be fluidized and entrained in to the patient's inspiratory air flow. The powder is subjected to numerous cohesive and adhesive forces that must be overcome to get dispersed. Optimisation and control of flow and dispersion (deaggregation) characteristics of the formulations is of critical importance in the development of DPI. These properties are governed by adhesive forces between particles including vanderwall forces, electrostatic forces and surface tension of absorbed liquid layers. These forces are influenced by various physiochemical properties like particle density, size distribution, particle morphology and surface composition. Several cohesive and adhesive forces are exerted on particle on particles characteristics such as size, shape and crystalline form and powder characteristcs such as packing density and equilibrium moisture content.

Drug carrier and carrier size: Optimization and control of particle–particle and particle –inhaler interaction is of critical importance in the development of efficient DPI's. A complicated situation exists in powder formulations- drug particles less than 5 μm aerodynamic diameter to ensure efficient drug deposition but should also exihibit acceptable flow properties required for accurate dose metering. Thus micronized powders are also blended with coarse inert carriers like lactose to improve powder flow. Lactose is often selected as carrier/excipients because of several advantageous properties like low reactivity and toxicity, low water content and its low costs. The number of carrier particles per formulation mass decreases as the carrier size increases, and also the number of drug particles per carrier increases. Furthermore, this carrier size increment results in an increased momentum and reduced number of collisions between carrier–carrier and carrier–device. The increased momentum of larger

carriers is the reason for the slight increase in formulation removal efficiency. However, it is unlikely to be responsible for drug release and aerosolisation efficiency since the increase in carrier size results with a concurrent decrease in drug aerosolisation performance for all formulations.

Particle engineering: One of the most important factor involved in evaluating DPI performance is the engineering of particles required to produce powder formulation that delivers accurate, uniform and efficient doses of drug. In a review Staniforth [14] has outlined the development of improved performance of DPI by preformulation characterization of drug carrier combinations. Staniforth explained the Pascal system which is an example of carrier formulation technology using a novel single step process called as Corrasion. This is a simultaneous milling, mixing and surface modifications of mixtures of 98-100% α lactose monohydrate and 0-2% of amino acid L-leucine [15].

DRY POWDER INHALER FORMULATION

The DPI formulation aims at pulmonary drug delivery having uniform distribution, small dose variation, good flow ability, adequate physical stability in the device before use and good performance in terms of emitted dose and fine particle fraction. The performance of DPI was improved significantly by the utilization of particle engineering thus lowering the aerodynamic diameters of the particles, decreasing particle density (by increasing porosity of particles), altering shape and by creating rough surface (to increase the air drag force).

Liposomal Drug Delivery: Liposomal drug delivery to the respiratory tract is the study of interest, because drugs are deposited locally in the lungs as the target organ, it is biocompatible as more than 85% of lung surfactant is composed of phospholipids. It provides controlled release of drugs for local or systemic action. Taylor and Newton, 1992 [16] has reduced local/systemic side effects and thus improved therapeutic index of the drug and reducing design frequency, total dose and probably cost of therapy. The delivery of drugs encapsulated in liposomes in suspension form to the lung using a nebulizer or pMDI,s are already under clinical investigation. In suspension form, liposomes have problems such as lipid degradation, aggregation and fusion of liposomesresulting in drug leakage during storage and aerosolization to lungs [16-17].

Chitosan-Hyaluronic Acid Nanoparticles:

Production of mucoadhesive nanocarriers made from macromolecular drug heparin, chitosan (CS) and hyaluronic acid (HA), is suitable for pulmonary delivery was reported. For the first time, this drug was tested by conducting ex vivo experiments on mast cells, in order to investigate the potential of the heparin-loaded nanocarriers in antiasthmatic therapy [18]. Ionotropic gelation technique is used for the formation of nanoparticles. CS and blend of HA with unfractionated or low-molecular-weight heparin (UFH and LMWH, respectively) were combined to form nanoparticles. The resulting nanoparticles laden with UFH were between 162 and 217nm in size, and those prepared with LMWH were 152nm. Ex vivo experiments purpose is to evaluate the capacity of heparin to prevent histamine release in rat mast cells indicated that the free or encapsulated drug exhibited the same dose-response behavior. Development of microparticle and nanoparticle based drug delivery systems aims at better management of diverse clinical conditions.

EVALUATION

Appearance and Color: The appearance of the content present in the container and the appearance of the container and closure system (i.e., the valve and its components and the inside of the container) should comply with 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. Cascade impactor and light scattering decay methods have been used to greater extent.

The cascade impactor operates on the principle through a series of nozzles and glass slides stream of particles projected at high velocity, the smaller particles pass on and are collected at higher velocity stages while the larger particles are impacted on the lower velocity stage. The optimum aerodynamic particle diameter for most inhalation products has generally been recognized as being in the range of 1–5 microns. 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 seive shaker or with air-jet sieving. By weighing the material received on each sieve the particle size distribution can be calculated. To known particle size distribution sieves can be calibrated with reference materials. Sieves works well for coarse as well as granulated lactose. Fine powders may often lock the holes present in the seives. Therefore for finer lactose grades air-jet sieving works better but it has a disadvantage that only one sieve screen at a time can be operated.

Laser diffraction: In the Unites States Pharmacopeia (USP) General Chapter <429> (4) 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. Theories have been developed which quantitatively relate the scattering pattern to the particle size distribution. In ISO 13320:2009 the theories are described [19]. The result of laser diffraction techniques is often expressed as a volume distribution. In Figure 1 a particle size graph of Lactohale® 200 is plotted. 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. The lactose can be dispersed dry or in a suitable liquid e.g. iso-octane or saturated iso-propanol. The preferred method is the dry-dispersion technique. The method between supplier and users should be consistent, validated, understood and shared. This is necessary to understand the outcomes of a measurement. It is helpful to investigate the off-set between machines and laboratories by carrying out a round-robin. The results give a better understanding of the outcomes of a measurement Fig.3.

Moisture Content: 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.

Flow properties of Powder [20]: Carr's Flowability Index: The flow properties of a DPI were measured by the Carr's method which involves following four tests:

1) Angle of repose;
2) Compressibility;
3) angle of spatula; and
4) uniformity coefficient

Hausner's Ratio-Hausner's ratio (HR): was determined from the minimum and maximum bulk density values with the tapping

Packing Properties of Dry Powder Inhalation: The packing properties of the powder used in DPI were determined with the tapping method by utilization of Kawakita's equation for indicating porosity.

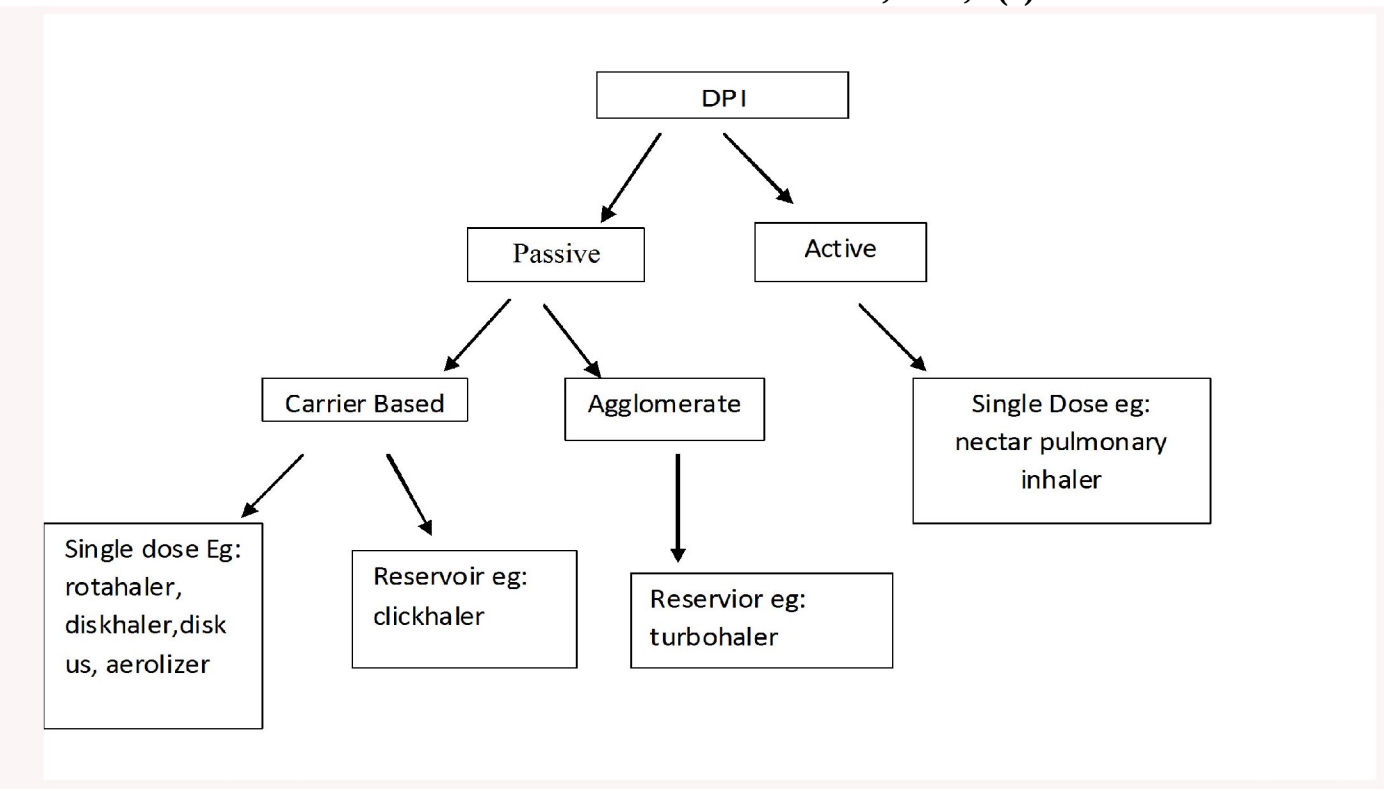

Figure 1 Classification of DPI.

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). Although this test may not be directly related in terms of performance of inhalation aerosols, it provides assurance of consistency concerning the manufacture of the drug product (e.g., formulation, filling, crimping, and sealing).

Net Content: Several methods can be used to determine whether sufficient product has been placed into each container. The tared cans that have been placed onto the filling line are weighed again and the difference in weight is equal to the net contents. The other method is a destructive method and consists of weighing a full container and then dispersing the contents. The contents are then weighed with provisions being made for the amount retained in the container. Other modifications consists of opening the container and removing as much as the product as possible. These tests are not indicated in determining the actual net content of each container as related to the amount that can actually be dispensed.

Impurities and Degradation Products [21]: 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 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 [21]: 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. Furthermore, proper testing should be done to show that the drug product doesn't support the microorganism's growth and that microbial quality is maintained throughout the expiration period.

Spray Pattern: Comparison of spray pattern obtained from different batches of material or through the use of different valves should be used. The method of comparison is based on the impingement of the spray on a piece of paper that has been treated with a dye-talc mixture. Depending on the nature type of powder, oil soluble or water soluble dye is used.

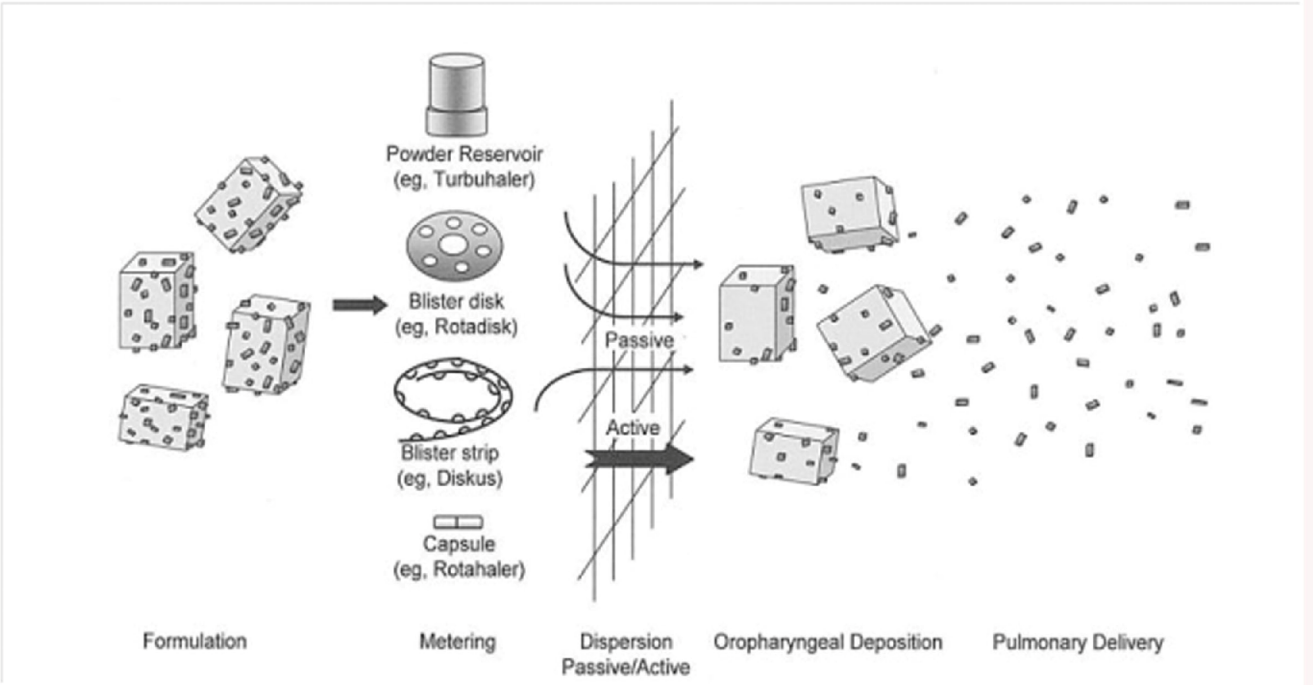

Figure 2 Principle of dry powder inhaler design.

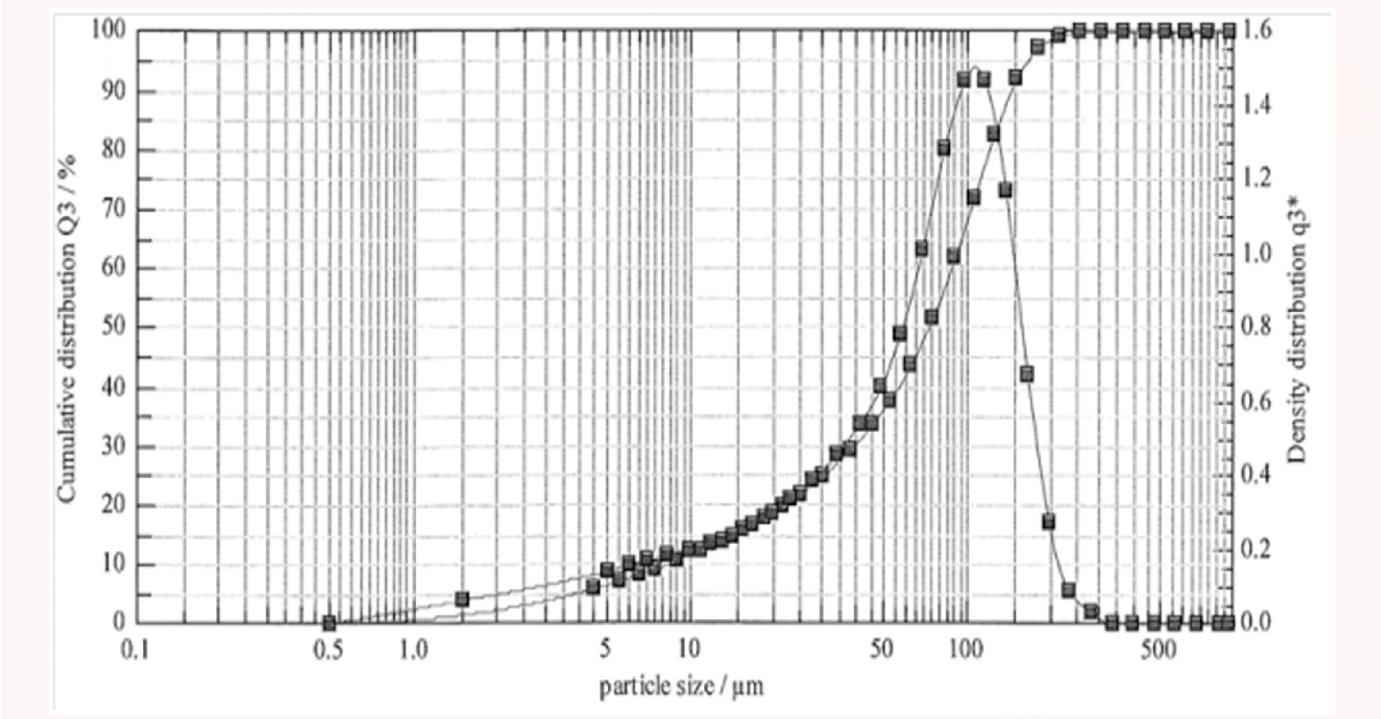

Figure 3 Laser diffraction pattern of Lactohale 200.

Extractables/Leachable [21]: For non-compendial plastic and for rubber container closure components that are in contact with the formulation during storage (e.g., valves), a study should be conducted to determine the extractables profile. It should be determined whether any of the extractables or leachables presents in the formulation at the end of the shelf life of the product. The leachables profile should also be determined for compendial plastics and rubber container closure components. Identification should be attempted for compounds that appear as leachables and also safety assessments should be conducted in accordance with sufficient established safety thresholds. Depending on the levels and types of compounds detected, consideration should be given to including a test and limits for leachables in the drug product specification.

CURRENT TRENDS

Inspiromatic is produced by Inspiro Medical, a portfolio company of The Trendlines Group, and is meant to take the place of hard-to-use nebulizers for young children as well as the elderly and people with certain disabilities. Inspiromatic has an internal microcontroller and flow sensor that detects the right time to deliver the medication and automatically disperse the drug particles in the right size without need for forceful inhalation [22].

Twisthaler: This inhalation device is relatively independent of flow rates. It has been demonstrated that with inspiratory flows between 28 l/min and 60 l/min 91% to 112% of the metered dose is delivered at the mouthpiece. The fraction of particles smaller than 6.5 μm amounts up to 40% at an inspiratory flow of 60 l/min. Additionally drug doses released from the Twisthaler® only vary slightly between each dose. The twisthaler is approved by momentosone furoate (Asmanex) [23].

Nexthaler: Cambridge Consultants is working to develop the next generation of dry powder inhaler for Chiesi Farmaceutici SpA, an emerging European pharmaceutical company based in Parma, Italy. The new inhaler aims to be the easiest-to-use dry powder inhaler on the market. The design incorporates features to improve performance and make the device discreet, intuitive to use and futuristic in appearance [24].

HandiHaler: It is used to deliver the contents of Spiriva inhalation capsules containing the bronchodilator tiotropium, used for long-term treatment of chronic obstructive pulmonary disease (COPD) and other obstructive airways disease; to relieve symptoms of bronchospasm [25].

Turbuhalers: It has the dry powder medication inside the tube-shaped inhaler. They have a removable cover and a twisting base. It is a 'breath-activated' device means the dry powder medication is 'sucked' from the device rather than 'fired' like it is from other devices. Turbuhalers may be difficult to use for young children, or adults who are short of breath. It is recommended to have a puffer and spacer available for emergencies [26].

Easyhaler: The Easyhaler®, is developed and patented by Orion, is an environment friendly and efficient, easy to use for the treatment of respiratory illnesses such as asthma and chronic obstructive pulmonary disease (COPD). Orion aims to expand the product family of inhalable Easyhaler® drugs used for treating asthma and chronic obstructive pulmonary disease [27] Fig.4 .

Various marketed products available in the market are shown in Table 1and delivery devices for currently used inhaled drugs for asthma in us is shown in Table.2.

ASPECTS OF REGULATORY GUIDANCE REGARDING PARTICLES IN ORALLY INHALED DRUG PRODUCTS

Orally inhaled and nasal drug products (OINDPs) include DPI, pMDI, nebulizers and nasal sprays. The FDA and EMEA, supported by the pharmacopoeia and International Standards Organization, are responsible for assessing safety, quality and efficacy. In 1998 and 1999, the FDA issued two draft documents providing regulatory guidance on chemistry and manufacturing controls for orally inhaled and nasal drug product [28, 29].

Figure 4 Various inhalers available in market. A: The Inspiromatic device; B: Twisthaler; C: Nexthaler; D: Handihaler ; E: Turbohaler; F: Easyhaler

Product Name	Company name
Acu-Breathe (Respirics) Aerolizer	Novartis
Breezhaler	Novartis
Clickhaler	Vectura
Cyclohaler	Tera
Diskhaler	Glaskosmithkline
Diskus	Glaskosmithkline
Podhaler	Novartis
Pulmojet	Sanifi-Aventis
Skyehaler	Skyepharma
Solis	Sandoz/Novartis
Taifun	Akela
Twisthaler	Schering/Mercks
Turbohaler	Astra Zeneca

Table 1 Marketed products.

Drug	DPI
Formoterol	Fordil Aeroliser (Novartis AG)
Salmeterol (serevent)	Serevent Diskus (Glaskosmithkline)
Tiotropium	Spiriva Handihaler (Boehring Ingelheim)
Budenoside	Pulmicort Flexhaler (Astra Zeneca)
Fluticasone	Flovent Diskus (Glaskosmithkline)
Mometasone	Asmenex Twisthaler (Schering- Plough)

Table 2 Delivery Devices for currently used inhaled drugs for Asthma in US.

The inhalation solution, suspension and spray guidance was finalized in 2002. In 2002, the FDA launched a new initiative "Pharmaceutical cGMPs for the 21st Century" in which it proposed a new risk-based approach to pharmaceutical manufacturing. This initiative gave birth to PAT, it aimed at better understanding and advancing the processes involved in pharmaceutical development, manufacturing and quality control described in the FDA's Guidance of September 2004 [30]. The goal of PAT is to ensure final product quality by understanding and controlling the processes involved in manufacture. The MDI/DPI guidance is still in draft form. Guidance for industry issued by FDA provides information and recommendations on the tests and general approaches for manufacturers to consider when developing a new drug application for submission to the agency. In principle, such guidance is based on research data and information compiled from industry, academic sources, and the agency's previous experiences. The guidance recommendations should also reflect the capabilities of current drug product technology. The issuance of the orally inhaled and nasal drug products guidance presented a significant advance as they provided for the first time, in documented form, the expectations of the FDA regarding tests that should be performed to assess product quality and regarding specifications for OINDP. When the draft guidances were issued, industry provided a great deal of comment to the agency, noting disagreement with approaches and acceptance criteria for some of the tests and seeking clarification for others [31].

What are the challenges posed by the changing regulatory approach?

While the adoption of new nebulizer guidance is straightforward, implementing QbD (quality by design) in the formulation and of OINDPs presents a unique challenge. QbD is significantly more complex for inhaled products as compared to other dosage form because, for example:

performance of the product is a function of both device and formulation, a patient's operating procedure may influence the received dose. Manufacture of product and usage is influenced by environmental conditions. There is a lack of relevant real-time analytical tools.

Applying QbD in inhaled products is very complex, which may mean that take-up could be slow for OINDP manufacturers; however, regulatory bodies may be merciless of those who fail to adopt the initiative [32-33]. Table 3 and Table 4 given below shows the future DPI and the patent approved or applied.

Device	Company	Drug
Aspirair/active	Vectura	Apomorphine hydrochloride
Omnihaler/active	Innoveta Biomeds Ltd.	-
Taifun	Focus Inhalation	Fentanyl
Cyclovent	Pharmachemie	Opioids (Morphine)
Spiros/breath activated active	Dura	Albuterol sulphate
Acu-Breath	Respirics	Fluticasone propionate
Swinhaler	Otsuka Pharmaceutical Co. Ltd.	Procaterol, budesonide
Procaterol, budesonide	Novartis Pharma/Skye Pharma	Formoterol
Technohaler/passive	Innoveta Biomed Ltd.	-

Table 3 Future DPIs (approved or in development stage). Dash line (–) indicates information is not available.

Device	Patent no.	Delivery type	Company	Ref./Company
DPI	EP2239002 B1	Lock and Blister advancement	Sanovel Illac sanayive Ticaret Anonim sirketi, Istanbul	Zafer Toksoz et al. (2013) 34
DPI	US8381721 B2	Piercing membranr	Oriel Therapeutics, US	Gerald A Thoe et al. (2013) 35
DPI/ Bead like	US20120291780 A1	Bead like actuator	Respira therapeutic Inc.	Martin J Donovan et al. (2012) 36
DPI	EP 1923087 B1	Single dose, capsule	Mannkind Corp., Valancia	Soloman S Steiner et al. (2012) 37
DPI/Metered	EP2314336 A2	Metered Dose	Nortan Healthcare Ltd.,USA	Lawrence Keane et al. (2011) 38
DPI/Breath actuated	EP1294421 B1	Breath actuated	Nortan Healthcare Ltd.,USA	Lawrence Keane et al. (2010) 39
DPI	EP1042025 B1	Blister disk	Vaolis SAS, France	Allan Cmeron et al. (2009) 40
DPI/passive	. US 2008035143 A1	Reservoir	USA	Sievers et al. (2008) 41
DPI	WO 2008001132	Single dose, capsule	Brintech International Limited, UK	Chawla and Paul (2008) 42
Cyclone DPI	Britt. UK Pat. Appl., GB 2439204;WO 2007144614		Cambrdge Consultant Ltd., UK	Smith and Harris (2007) 43
Hinged Cyclone DPI	Britt. UK Pat. Appl., GB 2439205;WO 2007144607	Multi-unit blister pack	Cambrdge Consultant Ltd., UK	Smyth and Truman (2007) 44
Simple Inhaler	WO 2007132217	Multi-unit cartridge	Hovione Inter AG, Switzerland	Villax et al. (2007) 45

Table 4 Future/next generation DPI device (patented/applied for patent).

CONCLUSION

As DPI 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). It is estimated by WHO that worldwide, some 300 million people suffer from Asthma and 240 million people from (COPD). The future research in DPIs will incorporate 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.

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