

# Development of Dry Powder Inhalers

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**Abstract:** Development of dry powder inhalers involves powder recrystallization, formulation, dispersion, delivery, and deposition of the therapeutic agent in different regions of the airways in prophylaxis/ treatment/ diagnosis of pulmonary and systemic disorders. Conventional powder production by crystallization and milling has many limitations resulting into development of alternative techniques to overcome the problems. In the last decade many patents have been filed claiming improvement in aerosol performance of dry powder inhalers through the use of (i) incorporation of fines of carrier particles to occupy active sites on the surface and use of hydrophobic carriers to facilitate deaggregation through reduced surface energy and particle interaction (ii) reducing aerodynamic diameters through particle engineering and incorporating drug into porous or low particle density, and/or (iii) preparing less cohesive and adhesive particles through corrugated surfaces, low bulk density, reduced surface energy and particle interaction and hydrophobic additives. Moisture within dry powder inhaler (DPI) products has also been shown to influence aerosol performance via capillary force and electrostatic interaction. Better understanding of particle forces and surface energy has been achieved by the use of sophisticated analytical techniques. Understanding the intricacies of particle shape and surface properties influencing specific lung deposition has been further facilitated by the availability of newer and advanced softwares. A critical review of recent patents claiming different approaches to improve lung deposition of dry powder inhalers will help in deciding the focus of the research in the area of technological gaps.

**Keywords:** Lung deposition, dry powder inhalers, particle engineering, monodisperse, respirable fraction.

## INTRODUCTION

Pulmonary drug delivery by Dry Powder Inhalers (DPIs), by virtue of its propellant free nature, high patient compliance, high dose carrying capacity, drug stability and patent protection, has encouraged rapid development in recent past to realize full potential of lungs for local and systemic treatment of diseases. But DPIs are complex in nature and their performance relies on many aspects including the design of inhaler, the powder formulation and the airflow generated by the patient [1-4]. In last decade, performance of DPIs has improved significantly through the use of engineered drug particles and modified excipient systems [5-7]. This review analyzes recent patents filed in the area of DPI formulations and critically evaluates the present and future trends to help the researchers focus their efforts in technological gaps.

## DPI DEVICES

The performance of the DPI system depends not only on the powder formulation but also the inhaler device. However, devices are much less explored than the powder formulations [7]. There is a wide range of passive (breathe driven) and active (power driven) single or multiple dose DPI devices in the market. The market is currently driven by passive devices which rely on the inspiratory airflow of the patient for powder dispersion into individual particles. Each

DPI device has a different air flow resistance that governs the required inspiratory effort by the patient. The higher the resistance of the device, the more difficult it is to generate an inspiratory flow great enough to achieve the maximum dose from the inhaler [4, 8, 9]. However, deposition in the lung tends to increase while using high-resistance inhalers [5].

Even with active research on development of newer DPI devices, the concept of powder interaction with device is not well understood. The relative effect of air turbulence and mechanical impaction (particle-particle and particle-device) for controlling powder dispersion in the device as well as role of capsule and influence of airflow is still unclear [10]. However recent applications of computational fluid dynamics have been helpful in design and development of DPI devices and understand the effect of airflow changes and deagglomeration in the inhaler device. The computational analysis has been helpful to predict significant performance variation of DPIs after small variations in the device design, which may help in future development of DPI devices [11].

## POWDER PRODUCTION METHODS

Conventionally DPIs are produced by crystallizing the powder followed by milling to micronize the drug particles for pulmonary delivery. However, these methods have various limitations such as poor control over powder crystallinity, shape, size, and size distribution. Dry milling produces partially amorphous materials with high surface charge causing particle agglomeration. These problems can be resolved by specialized milling methods. In order to reduce the amorphous content in the material produced by milling, the milling can be carried out at elevated humidity

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(30-70%) to facilitate *in situ* crystallization [12]. Wet milling at lower temperatures is an aqueous-based milling process to reduce particle size to below 400 nm. A conventional ball mill can be used for the process, and the materials selected for the grinding media (e.g., glass, zirconium oxide) were reported to be not crucial. However, the size of the grinding media are preferably 1 mm or less in order to be effective in attribution and imparting less wear to the mill [13]. Since the particles are produced in water, any amorphous regions in the particles would undergo recrystallization. Thus the wet-milled powder is anticipated to be crystalline and more stable to moisture than powders produced by dry milling.

Spray drying was explored in the 1980s as an alternative means of making fine particles with desirable flow and dispersion characteristics without need of using coarse carriers. Spray drying is the most promising alternative method for producing particles above 2  $\mu\text{m}$ . Spray drying has been employed as a method for preparing micron-sized powders for pulmonary administration and has better control on particle formation and hence can be easily translated to large scale production. Previously, DPIs were prepared by spray drying process either by single and/or multiple emulsion technique or co-solvent systems, primarily consisting of an aqueous / organic solvent or combination of aqueous and organic solvents. In spray drying, a drug solution is atomized to fine droplets which are evaporated in a warm air current to form dry particles [14]. Although the drying air temperature can be relatively high (>100°C), the actual temperature of the evaporating droplets is significantly lower due to cooling by the latent heat of vaporization. Thus, thermal degradation of the active ingredient is not so much a concern as it first appears. In addition to drug production, spray drying has been used to produce carrier particles [18]. Spray drying is not limited to aqueous solutions. Spray drying of ethanolic solutions containing antiasthmatic drugs has been reported [15]. Non-aqueous systems have also been used to prepare porous particles suitable for aerosol delivery [16-18]. The properties of the spray dried powders are controlled by both the process (atomizing nozzle type, powder collection technique and droplet drying time and rate) and formulation parameters (effects of the active ingredient) [19, 20].

The other techniques for formulation of stable micron sized DPI products includes milling, simple mixing of carrier with the drug, co-precipitation of drug and carrier by lyophilization and milling, specialized spray-drying, spray freeze drying, ultrasound assisted crystallization, flash crystallization [21], controlled precipitation [22], and supercritical fluid technologies. These methods have the advantages of higher product yield, lower operating temperature, and higher powder crystallinity. However, all the techniques suffer from the disadvantage of high operating cost and impurity.

Spray freeze drying was explored for pharmaceutical application in early 1990s [23]. It involves spraying the drug solution into a freezing medium (usually liquid nitrogen) followed by lyophilization. Compared to spray drying, this process produces light and porous particles with enhanced aerosol performance, and the production yield is almost 100%. The method has been applied to prepare rhDNase and

anti-IgE antibody [24, 25] particles for inhalation and can also be used for anti-asthmatic compounds. However, this is an expensive process and would only be justifiable for expensive drugs as it requires the additional use of liquid nitrogen and the freeze drying step is more time consuming.

The solvent precipitation technique involves sonocrystallization and micro precipitation by opposing liquid jets. Inhalable particles can potentially be obtained by rapid precipitation from aqueous solutions using anti-solvents. However, due to dispersion in the nucleation rate and crystal growth, it is difficult to reproducibly generate particle size in the micron range for aerosol delivery. Recently, ultrasonic radiation has been applied to control the precipitation process. The setup simply comprises an ultrasound probe in a mechanically stirred reaction tank where the anti-solvent is mixed with the drug solution to precipitate the fine drug particles. Various antiasthmatic drugs were prepared using the sono-crystallization technique [26]. In Microprecipitation technique, precipitation occurs in a region of extreme turbulence and intense mixing created by a jet of drug solution opposing a jet of anti-solvent coming through two opposing nozzles mounted in a small chamber [27]. As two liquid jets mix, the anti-solvent causes the drug to precipitate as fine particles. The crucial process parameters include the speed of the liquid jets and concentration of the drug solution. A high jet stream speed or a high drug concentration was found to give finer particles but higher residual solvent level and vice versa. The volume ratio of drug solution to anti-solvent is also expected to affect the precipitation process [27].

Supercritical fluid technology (SCF) has been utilized in various pharmaceutical industrial operations including crystallization, particle size reduction, drug delivery preparation, coating, and product sterilization. It has also been shown to be a viable option in the formulation of particulate drug delivery systems, such as microparticles and nanoparticles, liposomes, and inclusion complexes, which control drug delivery and/or enhance the drug stability and thus can be potentially used for formulation of DPIs. The advantages of SCF technology include use of mild conditions for pharmaceutical processing (which is advantageous for labile proteins and peptides) and production of particles with controllable morphology and narrow size distribution. SCF technology can be used in the preparation of drug delivery systems and/or to improve the formulation properties of certain drug candidates [28-31].

Drug delivery to the lung can be improved not only by using better devices but also through more rationalized formulation. DPI consists of drug and carrier particles either mixed or coprecipitated together into dry powder form. The size of drug / dry powder is important and should be near spherical in shape and monodispersed with aerodynamic diameter range of 0.5 to 3  $\mu\text{m}$  for alveolar region of lung for local effect and systemic absorption and 3 to 5  $\mu\text{m}$  for local action. The commonly used coarse carrier is inhalation grade lactose; commercially available in market in different grades and sizes namely milled lactose, sieved lactose, spray dried lactose and anhydrous lactose etc [32,33]. Other excipients such as mannitol, sucrose, maltose, glucose, trehalose, raffinose, melezitose, lactitol, maltitol and starch etc. were

also tried for development of DPIs [34]. Development of formulations in terms of particle size distribution, particle density, morphology, surface roughness, flowability and surface energy suitable for maximizing drug delivery to lung is of paramount importance to therapeutic DPIs. Hence, a search for novel DPIs for inhalation therapy with excellent aerosolization property and higher respirable fractions, irrespective of the therapeutic agent is continued.

The surface texture of dry powder aerosol system was modified, regarding particularly the need to avoid particle aggregation. The use of large particles apparently reduces the overall surface area of the powder preparation reportedly resulting in improvements in flowability and respirable fraction. Unfortunately, the use of relatively large particles may result in dosing limitations when used in standard DPIs and provide for less than optimal dosing due to the potentially prolonged dissolution times. As such, there still remains a need for standard uniform sized particles that resist aggregation and preserve the flowability and dispersibility of the resulting powder. To advance aerosol powder technology several strategies from novel inhaler to novel particle design [35] have been developed to improve flowability of dry powders and attempted to make them individual particles. Studies on influence of particle surface characteristics [36-38], environmental conditions [39], air flow rate [40] inhaler resistance [41,42] and excipients [43,44] on aerosol generation are explored to improve the delivery efficiency of DPIs. A major initiative has been focused on the particle engineering to lower powder cohesion and improved dispersibility. Coated particles [45], needle crystals [46], large porous particles [47], Trojan particles [48], aerogel powders [49], spray-freeze dried particles [50], pulmosphere, corrugated particles, agglomerated particles [51] and spray dried low density particles [52] are the examples.

## DRY POWDER INHALER FORMULATIONS

The DPI formulation aims at pulmonary drug delivery having uniform distribution, small dose variation, good flowability, adequate physical stability in the device before use [53] and good performance in terms of emitted dose and fine particle fraction. The performance of dry powder aerosol systems was improved significantly through particle engineering by lowering the aerodynamic diameters of the particles using small geometric diameter of the particles, lowering particle density (by increasing porosity of particles) [54-57], altering shape (elongated particles) [58] and by creating rough surface (to increase the air drag force). The performance was also enhanced by blending and use of ternary mixtures (by using fine carriers and ternary components)[59], by lowering bulk density [56] (loose particle packing to reduce particle contacts), lowering the inter particulate forces in between the particles by creating rough surface (to reduce particle interaction) and by lowering the surface energy by modifying surface composition [2,60]. On the basis of claims of improving aerosol performance, the patents may be classified into the four broad categories such as blends and ternary systems, reducing aerodynamic diameters through porous / low density particle, preparing less cohesive and adhesive particles and novel DPIs.

## 1. Blends and Ternary Systems

Early formulation of DPIs consists of coarse carrier lactose for enhancing the powder flow of the formulations and increasing the powder bulk for capsule filling. The role of carrier in enhancing the aerosol performance of the cohesive drugs was later understood [59] and consequently fine lactose [60-62] and other carrier materials, antistatic agents and lubricants (magnesium stearate) [63], amino acids (leucine) [4], surfactants, phospholipids, derivatized carbohydrates [64] and sugars as glucose, mannitol were tried to improve aerosol performance.

It was found that there are high energy active sites on the surface of the coarse carrier particles thereby leading to a strong adherence of the drug particles to the coarse carriers (Particle size > 20  $\mu\text{m}$ ). Addition of fine carrier particles or particles of ternary additives (Fines < 10  $\mu\text{m}$ ) saturates the active sites of coarse carrier particles partially to which, then, micronized drug is attached. Hence, drug adheres to passive sites i.e. less energy sites and facilitates the deaggregation of the micronized drug during inhalation leading to enhanced respirable fraction [4,65,66]. The presence of a discontinuous covering as opposed to a "coating" is an important and advantageous feature [4]. The sequence and amount of addition of fines and drug to coarse carrier were found to be critical. However, there are few reports of demonstrating mixing sequence not critical in facilitating drug deaggregation [67].

Formation of weak conglomerate between drug, ternary component (a lubricant) and carrier particle was also utilized to distribute drug between coarse carrier and ternary component causing disruption of attractive interactions.

## 2. Reducing Aerodynamic Diameters through Porous/Low Density Particles

Recently, research has been focused towards development of porous/low density particles having particle size in the range of 5  $\mu\text{m}$  to 30  $\mu\text{m}$ , density below 0.4  $\text{g}/\text{cm}^3$ , and mean mass aerodynamic diameter (MMAD) between 1-3  $\mu\text{m}$  to achieve higher respirable fraction and avoid the natural clearance mechanism in lungs (alveolar macrophage uptake) due to higher geometric diameter of the particles. Such aerodynamically light particles also provide a solution to particle aggregation and preserve the flowability of the powder by reducing particle interactions [68]. Various patents claiming development of aerodynamically light particles for efficient delivery of therapeutic agent either for local or systemic action have been claimed, opening a broad area in DPIs for improvement of respirable fraction and overcoming the constraints associated with conventional techniques. The aerodynamically light particles are prepared from variety of materials such as biodegradable polymers as PLA, PGA and their copolymers PLGA, polyester graft copolymer, phospholipids, surfactants as phosphoglycerides for ex. dipalmitoyl phosphatidylcholine (DPPC) and amino acids as leucine [68-73]. The large porous particles are prepared using either double emulsification followed by freeze drying; spray freeze drying and / or spray drying techniques. Various patents have claimed delivery of aerodynamically light particles for delivery of therapeutic, prophylactic and/or diagnostic agents as well as proteins,

peptides and hormones [74] for local delivery to lung as well as systemic delivery to blood stream and different parts of body. A method for delivering a high dose bioactive agent to the pulmonary system, in a single, breath-activated device, composed of a receptacle enclosing a mass of particles having a tap density of less than  $0.4 \text{ g/cm}^3$  and delivering at least about 50% of the mass of particles has been disclosed [75]. Elmore Craig, P.C. in 2003 disclosed method for treating central nervous system disorders by administering therapeutic agents to the respiratory tract, with half the oral dose, by particles having a tap density of less than about  $0.4 \text{ g/cm}^3$  comprising of therapeutic agent and phospholipids, amino acids, and combinations thereof [76,77].

Ventura [86] disclosed spray dried hollow and/or porous microparticles comprising of one or more saturated phospholipids with surfactants having density less than  $0.5 \text{ g/cm}^3$  for treatment and/or prophylaxis against a pulmonary fungal infection which comprised of an antifungal agent and determined the minimum inhibitory concentration of the antifungal agent for inhibiting pulmonary fungal growth. This invention claims pulmonary delivery of antifungal agent with improved or enhanced bioavailability, delivery efficiency, chemical stability, physical stability, and/or reproducibility and covering methods such as supercritical fluid processing, cryogenic milling, spray drying, wet milling, ultrasound, high pressure homogenization, micro-fluidization, crystallization processes under the invention [78].

Patents filed by Advanced Inhalation Research, Inc. [79] disclose spray dried non-polymeric particles of a therapeutic, prophylactic or diagnostic agent having a tap density less than about  $0.4 \text{ g/cm}^3$ , which comprises an asymmetric phospholipid and one or more glycerol fatty acid esters and/or leucine thereby exhibiting sustained release of the agent by inducing slow erosion of the particle matrix [79]. Further, another patent by them was filed disclosing pulmonary delivery of a therapeutic, prophylactic or diagnostic agent that comprise a phospholipid (1 to 46 weight %) and leucine (at least 46 weight %) producing sustained effect of the agent produced using spray drying technique [80]. Advanced Inhalation Research, Inc. in one invention claimed particles containing drug and one or more phospholipids to have a desired phase transition temperature having tap density of preferably less than about  $0.1 \text{ g/cm}^3$ . The particles of the invention were characterized by their matrix transition temperature and the matrix transition temperature was used to design or optimize particle formulations having a desired drug release profile. The particles were prepared by spray-drying methods to boast fast, intermediate or slow drug release rates [81,82]. A hydrophilic or hydrophobic complex of a positively or negatively charged therapeutic agent and a charged molecule of opposite charge are also used for preparing low density particle along with added advantage of control over release of therapeutic agent due to complexation [71].

### 3. Preparing Less Cohesive and Adhesive Particles

Less cohesive and adhesive particles were developed by particle engineering for enhanced delivery of therapeutics to lungs to overcome the constraints associated with conventional DPIs. Unfortunately, the formation of particulate aggregates and production of powders having poor

flow properties and low dispersivities continue to plague developmental efforts to prepare aerosolizable dry powders for inhalation therapy. Thus, a need exists for improved inhalable aerosols for the pulmonary delivery of therapeutic agents, and in particular, for dry powders having excellent aerosol properties and reduced particle-particle interactions, irrespective of the therapeutic agent to achieve enhanced respirable fraction. Vectura Limited disclosed use of anti-adherent materials at least 60% by weight of active material in development of stable agglomerates of the active material in the powder for effective pulmonary delivery [83]. Stable agglomeration of the active particles with the known powders may lead to decreased deposition of the active material in the lower lung, together with poor dose uniformity because, when the small active particles agglomerates, their particle size may increase up to  $100 \mu\text{m}$  or more. If those agglomerates do not break up when the powder is inhaled, they are unlikely to reach the lower lung due to their size. The addition of the anti-adherent material decreases the cohesion between the particles of the powder containing the active material. It is thought that the additive material interferes with the weak bonding forces, such as Van der Waal's and Coulomb forces, between the small particles which helps to keep the particles separated and may be thought of as weak links or "chain breakers" between the particles and also reducing adhesion of the particles to the walls of the device. When agglomerates of particles are formed, the addition of the additive material decreases the stability of those agglomerates so that they are more likely to break up in the turbulent air stream created on inhalation to form small individual particles which are likely to reach the lower lung. The reduced tendency of the particles to bond strongly either to each other or to the device itself, reduces powder cohesion and adhesion and promotes better flow characteristics which leads to improvement in the dose reproducibility by reducing the variation in the amount of powder metered out for each dose and improving the release of the powder from the device as well as increasing the likelihood that the active material which does leave the device will reach the deep lungs [83]. The various materials which may be useful as antiadherent includes antistatic agents, lubricants as magnesium stearate, amino acids, peptides and polypeptides as leucine, isoleucine, lysine, valine, methionine, cysteine, and phenylalanine and their derivatives [63, 83, 84]. An invention discloses powder particles with smooth surface comprising carrier particles crystalline in nature coated with an additive such as lubricants, anti-adherents and soluble polymers; wherein the particles have a median diameter of greater than  $90 \mu\text{m}$  and a surface rugosity expressed as the fractal dimension of less than or equal to 1.1 for use in inhalation therapy. The coating makes the surface of the particles of the carrier smooth, without any roughness, hollows, clefts and sharp edges, where the drug particles might adhere, without being removed in the aerosol clouds production stage [85].

### 4. Novel DPIs

While the conventional methods of DPIs production for inhalation products may have been sufficient in the past, they are not suitable to produce powders with the required flow and dispersion characteristics to meet the need of enhanced powder performance. Various novel formulations have been

disclosed or are in advanced stage of development to overcome the known constraints of DPIs and to achieve desired properties for efficient delivery of wide variety of therapeutic agents [86]. Various novel approaches disclosed for enhancing the delivery to lungs via DPIs and efficacy of drug by increasing pulmonary residence time, reducing clearance and their method of production have been described in the subsequent paragraphs.

#### 4.1. Liposome and Lipid Based DPI:

Liposomal drug encapsulation has been shown to be promising in sustaining the drug residence time within lung, improving therapeutic index, and delaying systemic dilution and thereby, reducing side effects. Delivery of various therapeutic agents along with lipid compositions can be given to treat pulmonary disorders. Delivery of corticosteroid for asthma [87], ribonucleotides for respiratory influenza [88], amphiphatic drugs and their salts for tumor [89], aminoglycosides (Tobramycin Sulphate, Amikacin Sulphate) and other antibiotics (Ciprofloxacin) for local pulmonary infections and cystic fibrosis [90], has been reported using liposome technology. In liposomal DPI formulations, drug encapsulated liposomes are homogenized, dispersed into carrier and converted into DPI by spray and / or freeze drying. On inhalation, drug encapsulated liposomes get rehydrated in lung and release drug over a period of time.

Liposome-encapsulated opioid analgesic agents delivered by the pulmonary route provide local or systemic analgesia superior to that produced by the solution form of these agents administered by parenteral (intravenous, intramuscular, or subcutaneous injection) or oral routes [91]. New steroidal derivatives obtained by modification of cortico-steroids, with fatty acid esters were incorporated in the lipid portion of liposomes for delivery via inhalation resulting into prolonged steroid retention in the respiratory tract of experimental animals [87]. High dose pharmaceutical liposome aerosol composition comprising about 12-30 mg/ml of a drug and about 130-375 mg of a phospholipid/ml starting reservoir concentration has been disclosed. A high dose drug liposome aerosol composition containing phospholipids may contain cyclosporine-A, budesonide, anti-fungal compounds, antibiotic compounds, anti-viral compounds, and anti-cancer compounds for delivery to lung [92].

Another invention claimed a process of preparation and method for the delivery of pharmaceutical agent in the form of nanocochleates. Cochleates are derived from liposomes, which are suspended in an aqueous two-phase polymer solution, enabling the differential partitioning of polar molecule based-structure by phase separation. The liposome-containing two-phase polymer solution, treated with positively charged molecules such as  $\text{Ca}^{2+}$  or  $\text{Zn}^{2+}$ , forms a cochleate precipitate of a particle size less than 1  $\mu\text{m}$ . Novel lipid-based cochleate delivery system were used to achieve efficient systemic and mucosal delivery of pharmaceutical agents [93]. Another set of inventions relate to proliposome powder compositions of a biologically active compound in particulate dispersion in a lipid for inhalation. A process of manufacture of proliposome powder comprising a single phase discrete particles of a biologically active component together with a lipid or mixture of lipids having a phase transition temperature of below 37°C for inhalation has been

described [94]. A DPI formulation comprising a lipid component and an active agent having a liquid phase transition temperature of less than or equal to 37°C on hydration and a liquid phase transition temperature of greater than 57°C in dry form. On inhalation the drug spontaneously encapsulates into lipid inside lungs. The disclosed formulation is useful in treatment of anthrax infection on inhalation [95].

In 2004, a disclosure of phospholipid based powders for rapid absorption of the delivered active agent has been made. Emitted dose and lung deposition of the DPI formulation were claimed to be independent of device resistance and inspiratory flow rates. These inventions also claim reductions in the flow rate dependence in lung deposition and improvements in patient reproducibility [96,97].

A novel lipid particle formulation for the sustained release and delivery of steroids into deep lung was disclosed. The formulation of this invention claims prolonged release of the drug, improved therapeutic ratio, lower toxicity, reduced systemic side effects, and stability for several months. The formulation is in particular suitable for treatment of interstitial lung diseases [87].

#### 4.2. Micro and Nanoparticulate DPI Compositions

Among novel drug delivery systems, next to lipid formulations are micro and nanoparticulate drug delivery systems for pulmonary administration using DPIs. In the last decade, microparticle and nanoparticle based drug delivery systems have been developed with the goal of better management of diverse clinical conditions. Because polymers used in particulate drug delivery system development are biodegradable and biocompatible, they have been the most commonly used drug carriers [98-101].

Use of Ultrafine particles containing cellulose ethers and active drug comprising at least 80% of the powder in the particle size range of 0.5 to 10  $\mu\text{m}$ , has been claimed to deliver the drug to lower airways with sustained release of medicament [102]. A delivery of aerosols containing small particles comprising an aerosol of vaporized drug condensed into particles, having a MMAD between 10 nm and 1 $\mu\text{m}$  for inhalation therapy has been claimed [103].

An aerosol comprising nanoparticle drugs was filed disclosing aqueous dispersions of nanoparticulate aerosol formulations, dry powder nanoparticulate inhaler formulation, propellant-based aerosol formulations, methods of using the formulations in aerosol delivery devices, and methods of making such formulations. The nanoparticles of DPIs comprise insoluble drug particles having a surface modifier on the surface for enhanced dispersibility [104].

Another patent comprising of powder formulation containing nanoparticles for aerosol delivery to the lungs was disclosed. Respirable particles carrying active principles or diagnostics in nanoparticle form were produced by mixing the nanoparticles with liquid carrier, then forming the resultant mixture into respirable particles. The respirable particles were produced by spray-drying or freeze spray drying followed by comminution, for delivery to the lungs via DPIs. Active principles were covalently attached, adsorbed or incorporated to nanoparticles. The drug loading

depends on the functional groups of the biomaterials and on the drug release requirements. Gelatin or other protein based nanoparticles were incorporated into the carrier particles. Abundant functional groups, such as carboxyl and amino groups, on the particle surface enable easy modification and the covalent binding of drugs. Poly butylcyanoacrylate or other synthetic nanoparticles may be incorporated into the carrier particles [105].

Another patent discloses a composition of radiolabelled particles comprising a core of a gamma emitting radionuclide and a shell of a non-radioactive material as carbon that are attached to a second particulate material. The applicability of evaluation of drug distribution following inhalation of the compositions into the respiratory tract was also described [106].

In 2004, DPIs for pulmonary delivery made up of a biologically active substance in crystal form and a biocompatible, electrostatic aggregation-inhibiting substance both having particle diameter of 0.5 to 8  $\mu\text{m}$  having excellent safety, stability, and pulmonary delivery performance has been disclosed. [107]. Preparation of DPIs of peptide solution in liquid form by spray drying to form particles below 5  $\mu\text{m}$  in one step [108] and/or freeze drying with additives followed by jet milling to prepare fine particles has been reported. However, DPIs prepared by spray drying or freeze drying-jet milling method have been reported to cause partial deactivation of the peptides and proteins such as interferons [109]. A US patent claimed protein microspheres produced by contacting an aqueous solution of a macromolecule and a polymer having a high surface area to volume ratio by heating of the solution producing microspheres of defined dimensions (0.1  $\mu\text{m}$  -10.0  $\mu\text{m}$ ) for inhalation therapy. This invention also discloses preparation of microspheres without use of spray drying or milling processes [110].

In 1999, a composition of micronized particles suitable for inhalation comprising an active pharmaceutical substance prepared by solubilizing a poly- L (-) lactide, having a molecular weight in the range from about 1000 to about 10,000, with an active pharmaceutical substance was disclosed. After removing the solvent, the particles were jet milled to an average diameter of about 1  $\mu\text{m}$  to about 10  $\mu\text{m}$  [111]. Another patent describes a modulated release aerosol formulation comprising a polysaccharide polymer having a selected medicament associated therewith, a fluid carrier for carrying and delivering the construct and a stabilizer [112].

The DPI formulations consisting of materials as surfactant along with carrier, such as proteins (as albumin), polysaccharides (as dextrans) or polymers (as polyethylene oxide) were disclosed. The formulation has been reported to significantly alter the physical properties such as surface tension and surface elasticity of lung mucus lining fluid. Drugs, especially antivirals or antibiotics, are claimed to be delivered from DPI of this invention [88].

#### **4.3. Delivery of Proteins, Peptides and Macromolecules for Local and Systemic Delivery Using DPIs**

Patent of nanoparticles comprising therapeutic peptides, proteins, nucleic acid molecules, or hydrophilic synthetic molecules with sizes in the micron and submicron range was

filed. The particles have a size preferably between 200 nm to 600 nm. Optionally the biologically active agents contain a polymeric coating [113,114].

A number of companies are in advanced clinical trials with inhaled insulin, and a variety of large and small molecules are under investigation as inhaled formulations for systemic applications. Recent advances in the development of particle technologies and devices now make it possible to formulate, stabilize, and accurately deliver almost any drug to the lungs. More than 25 inhalation drugs in the market for treatment of lung diseases are all absorbed to some extent into the body, most of them quickly, and with very high systemic bioavailabilities.

A patent on pulmonary malarial vaccine relates to particulate compositions comprising nanoparticulates for pulmonary delivery, which provide sustained release of antigens, preferably DNA and/or peptide and/or protein antigens has been developed. Aggregate nanoparticles are in the aerodynamic range of 1-5 microns diameter and fly deep into the lungs. As the aggregate particles degrade in the body, MSP-1 and AMA-1 proteins are released into the blood stimulating a humoral immune response. The individual particles in the range of 0.1 micron are preferentially phagocytosed by APCs which express the proteins encoded by AMA-1 and MSP-1 plasmid DNA thereby initiating the cellular immune response that is necessary for a complete immunity. A particulate vaccine formulation comprised of a mixture of peptides and/or small molecular adjuvants and/or proteins and/or nucleic acid antigenic agents [115].

A method of preventing and treating pulmonary aspergillosis in humans by aerosol spray of a polyene, e.g., amphotericin B or pimarin, or a pharmaceutically acceptable derivative thereof was disclosed [116]. A medicated composition, which contains an active ingredient - meglumine complexes of fungicidal polyene macrolide antibiotics and treatment method utilizing these compositions is described. These compounds possess fungicidal and protistocidal activity and are useful in the treatment of candidosis and aspergillosis. Meglumine complexes of amphotericin B and mycoheptine can be used for treating most systemic mycoses by way of oral and inhalation administration as well as by instillation in treatment of leishmaniasis, schistosomiasis, lambliasis and trichomoniasis covered under the scope of this patent [117].

Spherical and smooth microparticles of a water-soluble material with at least 90% of particles having mass median particle size of 1 to 10  $\mu\text{m}$ , was successfully used in DPIs to deliver the therapeutic or diagnostic agent. A therapeutic composition of substantially dry and discrete microcapsules (1 to 10  $\mu\text{m}$ ) using a non-denatured, water-soluble protein, peptide, or enzyme as wall-forming material and therapeutically effective amount of a therapeutic agent was prepared as DPI [111].

An invention disclosing methods and compositions for pulmonary delivery of insulin, methods and compositions for the aerosolization using dry powder and systemic delivery of insulin provides rapid absorption of insulin into blood circulation while avoiding subcutaneous injection. Surprisingly, it has been found that inhaled dry insulin powders are

deposited in the alveolar regions of the lungs and rapidly absorbed through the epithelial cells of the alveolar region into blood circulation. Thus, pulmonary delivery of insulin powders can be an effective alternative to administration by subcutaneous injection. The insulin powder preferably comprises particles having a diameter less than 10  $\mu\text{m}$ , more preferably less than 7.5  $\mu\text{m}$ , and most preferably below 5  $\mu\text{m}$ , usually being in the range from 0.1  $\mu\text{m}$  to 5  $\mu\text{m}$ . Dry powder insulin compositions of the present invention are absorbed in the lung without the use of penetration enhancers [118]. Nektar therapeutics in 2005 came with the patent disclosing pulmonary administration of chemically modified insulin providing active, hydrophilic polymer-modified derivatives of insulin and exhibiting pharmacokinetic and/or pharmacodynamic properties that are significantly improved over native insulin. The formulations of covalently coupled insulin to one or more molecules of a non-naturally occurring hydrophilic polymer, such as polyalkylene glycol (polyethylene glycol), comprises reacting a polyethylene glycol having a terminal reactive group selected from the group consisting of N-hydroxy-succinimide active esters, active carbonates, aldehydes, and acetals with one or more reactive amino sites on insulin to provide a composition comprising an insulin-hydrophilic polymer conjugate for pulmonary administration [119]. In continuation with systemic delivery of proteins, Nektar disclosed sustained release composition of insulin in the form of insoluble complexes of the pharmaceutically useful protein and a precipitating agent such as covalent metal cations, Hofmeister series salts and pH adjusters at an appropriate ratio to achieve a desired sustained release profile suitable for pulmonary delivery [120]. A patent disclosing a method of preparation of Interleukin-13 antagonist spray-dried powders having MMAD of less than about 10  $\mu\text{m}$  was filed by Nektar. The pharmaceutically acceptable excipients disclosed are carbohydrate, polyols, amino acid, peptide, and buffer alone or in combination [121].

In an invention, dispersible macromolecules as inhalable dry powders preferably with MMAD of 0.5-4.0  $\mu\text{m}$  having lung deposition up to 60% was produced by spray drying [122].

Method for administration of growth hormone via pulmonary delivery was disclosed claiming delivery of growth hormone deficiency or a non-growth hormone deficiency disorder treatable with human growth hormone (hGH), which comprises hGH administering to the deep lungs. The pharmaceutical composition of hGH may contain buffers, amino acids, bulking agent, carrier, excipient, antioxidants mono-, di-, and polysaccharides; sugar alcohols, other polyols, surfactants, amino acids alone or combination at about 50% to about 90% by weight of the pharmaceutical composition [123].

An invention discloses a non-invasive system and method for delivering apolipoprotein and amphiphatic compounds into the blood stream following pulmonary administration. The additives used, were from the group of saline, surfactant/phospholipids, benzalkonium chloride, calcium chloride, and sodium citrate. The invention also claims the treatment of cardiovascular disease as well Alzheimer's disease [124].

Table 1 indicates the drugs tried for systemic delivery using DPIs as pulmonary drug delivery system.

**Table 1. Pulmonary Administered Drugs for Systemic Action**

Selected drugs and Macromolecules	Systemic Applications
Calcitonin	Osteoporosis Prophylaxis, Paget's Disease, Hypercalcemia
Erythropoietin (EPO)	Anemia
Factor IX	Hemophilia B
Heparin and Low Molecular Weight Heparin	Blood Clotting
Insulin	Type I and Type II Diabetes
Interferon Alpha	Hepatitis B and C, Hairy Cell Leukemia, Kaposi's Sarcoma
Granulocyte Colony Stimulating Factor (G-CSF)	Neutropenia
Granulocyte Macrophage Colony Factor	Bone Marrow Engraftment/Transplant
Growth Hormone Releasing Factor (GRF)	Short Stature
Interferon Beta	Multiple Sclerosis
Interferon Gamma	Chronic Granulomatous Disease
Interleukin-2	Renal Cancer
Leutinizing Hormone Releasing Hormone (LHRH)	Prostate Cancer, Endometriosis
Somatostatin Analog	Gastrointestinal Cancers
Vasopressin Analog	Diabetes Insipidus, Bed Wetting
Amylin	Type I Diabetes
Ciliary Neurotrophic Factor	Lou Gehrig's Disease
Insulin-Like Growth Factor	Osteoporosis, Nutritional Support
Insulinotropin	Type II Diabetes
Interferon Beta	Hepatitis B and C
Interferon Gamma	Rheumatoid Arthritis
Interleukin-1 Receptor Antagonist	Rheumatoid Arthritis
Interleukin-3	Adjuvant to Chemotherapy
Interleukin-4	Immunodeficiency Disease
Interleukin-6	Thrombocytopenia
Macrophage Colony Stimulating Fungal Disease Factor (M-CSF)	Cancer, Hypercholesterolemia
Nerve Growth Factor	Peripheral Neuropathies

(Table 1) Contd....

Selected drugs and Macromolecules	Systemic Applications
Parathyroid Hormone	Osteoporosis
Somatostatin Analog	Refractory Diarrheas
Thymosin Alpha 1	Hepatitis B and C
IIB/IIIA Inhibitor	Unstable Angina
Alpha-1 Antitrypsin	Cystic Fibrosis
Anti-RSV Antibody	Respiratory Syncytial Virus
Cystic Fibrosis Transmembrane Regulator (CFTR) Gene	Cystic Fibrosis
Deoxyribonuclease (DNase)	Chronic Bronchitis
Bactericidal/Permeability Increasing Protein (BPI)	Adult Respiratory Distress Syndrome (ARDS)
Interleukin-1 Receptor	Asthma

## RECENT TRENDS

A recent patent discloses pretreatment of the patient with the nebulized lidocaine or a lidocaine-like compound to improve airway tolerance and deposition of the agent in the lungs and to make such deposition more safe, efficacious, controllable and predictable. The method of the invention is especially useful for enhancement of deposition of immunosuppressive agents in the lung(s) of transplant patients, improved tolerance of the drugs by reducing cough, and improving pulmonary drug deposition [125]. Inhalable lidocaine formulation having MMAD between 3.5 and 10  $\mu\text{m}$  was disclosed in treatment of asthma for reducing the need for corticosteroids in asthmatic patients. Lidocaine dry powder is delivered by DPI or dose meter, one to several times a day [126].

A metered medication dose of a micronized peptide medicament, such as recombinant human insulin, in dry powder form, to be made available in an adapted DPI with at least one biologically acceptable excipient in dry powder form acting only as a carrier or diluent for a prolonged dose delivery directly from a high barrier seal container to the lung was disclosed [127]. A patent by Microdrug AG disclosed medical DPIs containing an accurately metered dose of a glucagon-like peptide-1 medicament in a moisture-tight and high barrier seal container for pulmonary administration and alternatively, the product may contain a dose of insulin with one or more biologically acceptable stabilizing excipients. The dose loaded in the container is intended for a prolonged delivery by inhalation to the deep lung where the active ingredients are absorbed into the system [128]. Stabilized pharmaceutical formulation, as disclosed by Sanofi-Aventis Pharma Limited, uses a porous adsorbent and a sealed package having over wrap, to protect DPI product in a solid state, in the presence of a reducing sugar [129].

A method of preparing a powder for use in a dry powder inhaler comprising: (a) mixing carrier particles of a size suitable for use in dry powder inhalers with particles of additive material, so that the particles of additive material become attached to the surfaces of the carrier particles; and then (b) mixing active particles with the carrier particles and additive material from step (a) was disclosed. It allows active particles to adhere to the surfaces of the carrier particles and/or additive material, a surface active material used to promote the release of the active particles from the carrier particles on actuation of the inhaler [130].

An invention related to a refinement of the processing of particles that are to form a dry powder formulation to be administered to the lung using an inhaler device and providing the processing of particles of active material and particles of carrier material in the presence of additive material to provide a powder composition which exhibits excellent powder properties and is economical for production has been disclosed [131].

Hydrophobic and hydrophilic amino acids (dipeptides, tripeptides, derivatives and salts) as stabilizers in freeze-dried interferon- $\gamma$  DPIs for transpulmonary administration were disclosed in the invention. Powder cake so formed disintegrates into fine particles having a mean particle diameter of 10  $\mu\text{m}$  or less, having respirable fraction of 10% or more upon receipt of an air impact [132]. Dry powder inhaler for transpulmonary administration was disclosed wherein freeze-dried composition was housed in non-powder form in a vessel into fine particles by an air impact and administering the resulting fine particles to a user by inhalation [133,134].

Ventura disclosed enhanced dosing efficiency of DPI compositions prepared by simple jet milling and spray drying techniques, of much higher delivered dose of pharmaceutically active agents, small molecules, proteins, carbohydrates or mixtures thereof, having controlled size distribution, with tap density of at least 0.5 g/cc, were used [135].

Pharmaceutical compositions comprising apomorphine or its pharmaceutically acceptable salts or esters having MMAD of 10  $\mu\text{m}$  or less for use in treating sexual dysfunction following pulmonary inhalation were disclosed. The composition also comprises an additive material, in an amount from about 0.15 % to 5 % of the composition by weight, such as leucine, magnesium stearate, lecithin, and sodium steryl fumarate etc. for enhancing the powder flow and reducing particle cohesiveness.

In nut-shell, the patents based on DPIs with improved drug delivery efficiency were increasing day by day claiming delivery of therapeutic agents both for local and systemic delivery indicative of DPIs will be most promising dosage forms.

## CURRENT & FUTURE DEVELOPMENTS

The search for more efficient and novel DPIs capable of delivering therapeutic agent for pulmonary and/or systemic action continues to attract substantial research interest among pharmaceutical industries and academic research institutes. The recent progress in the field of DPIs and introduction of

HMR 4006, Exubera a pulmonary drug delivery system for insulin by Nektar Therapeutics (formerly Inhale Therapeutic Systems) has developed a [HMR 4006, Exubera] should spark considerable efforts towards the development of more efficient and novel DPIs capable of delivering therapeutic agents via pulmonary route for local and/or systemic action overcoming various associated constraints. The superiority of developed DPIs, when coupled with more efficient delivery, monodisperse, *in vitro* characterization, *in vivo* animal studies and clinical trials should provide a powerful tool towards the understanding of crucial parameters and to reach the inventions to market. The next few years should see the emergence of inventions and technologies in the field of Dry Powder Inhalers delivering the therapeutic agents for pulmonary and /or systemic action. To date there are fewer proportions of inventions and technologies see the market with a therapeutic benefit or adverse effect liability. For DPIs, the consequences of their performance in terms if *in vitro*, *in vivo* and clinical studies, formulation and delivery aspects and scale up feasibility should become apparent in the future and will determine whether this is a viable strategy to address the more efficient drug delivery with enhanced therapeutic benefits and reducing the adverse effects.

The future will see stable DPIs with enhanced pulmonary drug delivery having easy process of manufacturing and improved devices by applying computational fluid dynamics to understand more about airflow and deagglomeration in inhaler devices. Impeccable blend of systematic and rational approaches would be necessary to build a useful database on the dependence of lung deposition on the breathing parameters, inhaler design, and powder formulation properties for successful commercialization of technologies.

## CONCLUSIONS

There are several advantages in delivering drugs to the lungs, including targeted delivery, which can improve efficacy and reduce unwanted systemic side effects, a large surface area for absorption, thin alveolar epithelium permitting rapid absorption, absence of first-pass metabolism, rapid onset of action and high bioavailability. Due to recent advances in the post-genomic era and molecular biology, our understanding of the molecular and biochemical composition of the lung, molecular basis of diseases and the barriers to drug delivery has improved. DPIs generally consist of drug (1-5 $\mu\text{m}$ ) and carrier particles (~50-150 $\mu\text{m}$ ) in the size range that is subject to a multitude of interparticulate forces. The influence of the interactive carrier system's physicochemical properties on the performance of carrier-based systems is being used in enhancing aerosolization and pulmonary deposition of DPIs. Hence, better understanding of the interparticulate forces will be used to maximize pulmonary deposition through reduction of cohesive and adhesive forces by simple inexpensive techniques. The carrier particles are a discrete interactive excipient function or a matrix particle that includes the active drug dispersed molecularly or homogeneously within the structure, making it possible to enhance drug targeting. Matrix particles consists of drug and excipients in a matrix and are involved in improving the therapeutic index of a drug by, improving transport and the proportion of drug that reaches its site of action (intracellular and extracellular);

improving stability of the drug *in vivo*; increasing the specific delivery of drug to target tissues; decreasing irritation caused by the drug; decreasing toxicity due to high doses of drug; altering immunogenicity of proteins; and avoidance of alveolar macrophage uptake, mucociliary clearance and rapid absorption. The future research in DPIs will make a use of this knowledge to 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 choice of carrier depends on several factors, including nature and safety of carrier, the type of drug (i.e. protein, hydrophobic or hydrophilic), the device for delivery, the site of action and the disease state. Lung being a vital organ, major contribution in research of DPIs will also include newer excipients to achieve safer pulmonary drug delivery in chronic diseases.

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