Biointerface Research in Applied Chemistry
Platinum Open Access Journal (ISSN: 2069-5837)

Review
Volume 11, Issue 3, 2021, 10099 - 10118
https://doi.org/10.33263/BRIAC113.1009910118

Recent Advancements and Applications of Inhalable Microparticles Based Drug Delivery Systems in Respiratory Disorders

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Received: 17.09.2020; Revised: 7.10.2020; Accepted: 9.10.2020; Published: 12.10.2020

Abstract: Lower respiratory infections are the third leading cause of death, as stated by the world health organization. The pulmonary route requires reduced dose, exhibits immediate drug release, reduced first-pass hepatic metabolism and adverse effects, and systemic drug release. Therefore, an overview of recent advancements in inhalable microparticles reported in publications and patents published in the last few years has been summarized. Recent innovations in inhaler technology and major challenges in pulmonary drug delivery have been discussed briefly. The analysis was collected through comprehensive literature searches from databases such as PubMed, Google Scholar, and ScienceDirect. The recent patents on inhalable microparticles have been compiled through the PATENTSCOPE database via WIPO website. The keywords used in the search strategy were 'inhalable microparticles', 'polymeric microparticles', 'large porous microparticles', 'solid lipid microparticles', 'cyclodextrin complex microparticles', 'respiratory disorders', 'patent, 'inhaler technology', 'drug deposition', 'pharmacokinetic processes' and 'pulmonary drug delivery' in various combinations. A survey of literature revealed that 44 publications and 14 patents, and 9 recent innovations in inhaler technology had been reported regarding inhalable microparticles in respiratory disorders. This review briefly recapitulates the pharmacokinetic processes involved in the pulmonary drug delivery route, mechanisms of drug deposition in the respiratory tract, types, and production methodology of inhalable microparticles.

Keywords: cyclodextrin complex microparticles; drug deposition; inhalable microparticles; large porous microparticles; polymeric microparticles; respiratory disorders; solid lipid microparticles.

1. Introduction

Lower respiratory infections are the third leading cause of death, as stated by the world health organization. Lungs have huge surface area for absorption (140 m2) and thin (0.1-0.2 µm) absorption mucosal membrane, therefore, lungs play a vital role in the gaseous exchange and oxygen supply to all the cells. Therefore, the pulmonary route has the potential for non-invasive administration for local and systemic drug delivery in the respiratory tract owing to the larger alveolar surface area, rich blood supply, thin blood alveolar barrier, and high permeability [1-3]. This route requires reduced dose, exhibits immediate drug release, reduced first-pass hepatic metabolism and adverse effects, and systemic drug release [4]. Hence, the

pulmonary drug delivery route has gained attention as a preferred route of drug administration to cure several respiratory disorders, as displayed in Figure 1. The drug targeting approaches consist of direct drug delivery into the lungs, primarily through inhalation medication exploiting dry powder inhalers. The disadvantages of the pulmonary route include complexity in pulmonary drug devices, diminutive duration of action owing to fast removal of active ingredients from lungs, inadequate drug absorption due to physical barriers, and local side effects attributable to pharyngeal deposition [5]. Inhalable microparticles have appeared as considerable development for the management of respiratory disorders on account of improved drug's therapeutic index, prolonged biological half-life, and reduced toxicity [6-8].

For a compilation of this review, the literature was collected from databases such as PubMed, Google Scholar, and ScienceDirect. The recent patents on inhalable microparticles for respiratory disorders have been compiled through the PATENTSCOPE database via WIPO website. The keywords used in the search strategy were inhalable microparticles', 'polymeric microparticles', 'large porous microparticles', 'solid lipid microparticles', 'cyclodextrin complex microparticles', 'respiratory disorders', 'patent, 'inhaler technology', 'drug deposition', 'pharmacokinetic processes' and 'pulmonary drug delivery' in various combinations. The present review article briefly recapitulates pharmacokinetic processes involved in the pulmonary drug delivery route, mechanisms of drug deposition in the respiratory tract, types of inhalable microparticles, and production methodology. An overview of recent advancements in inhalable microparticles reported in publications and patents published in the last few years has been summarized. Recent innovations in inhaler technology and major challenges in pulmonary drug delivery have been discussed briefly.

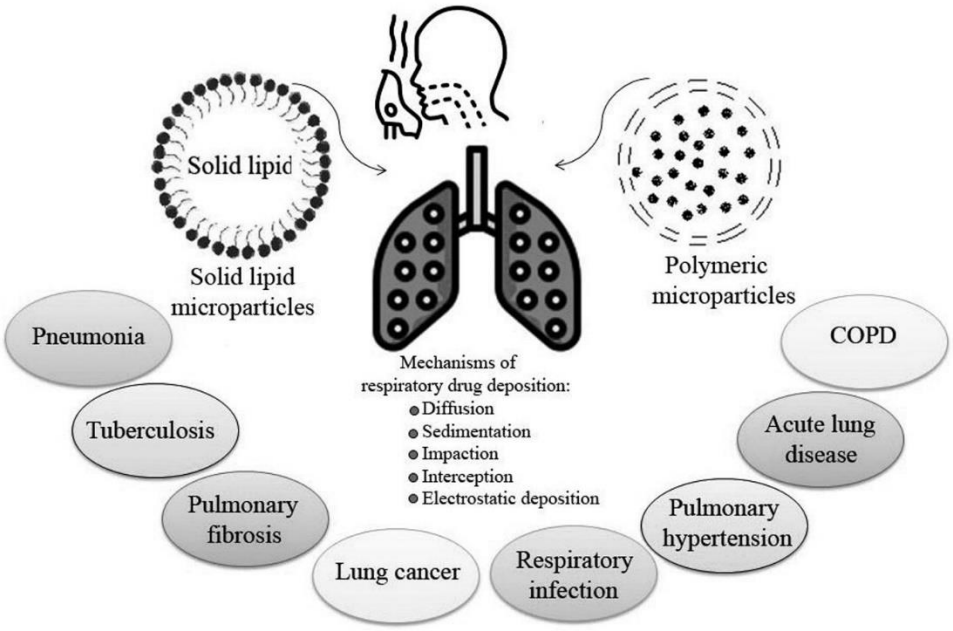

Figure 1. Application of microparticles based on pulmonary drug delivery systems for the management of various types of respiratory disorders.

2. Pharmacokinetic Processes in Pulmonary Drug Delivery Route

Conventional methods of administration, like intravenous and oral routes, have distinctive pharmacokinetic considerations. Before absorption into the systemic circulation, drugs taken orally shall permeate the gastrointestinal (GI) tract, portal vein, and liver. As a result, the dissolution and solubility process in GI fluid plays an important role in the rate and

extent of absorption. Following dissolution, passive permeability, the intestinal metabolism, as well as active uptake process, regulates drug absorption through the intestinal membrane, and eventually, the drug undergoes systemic bioavailability [7,9]. Conversely, intravenous administration includes infusion or injection of drug molecules instantly into the bloodstream, thus circumventing the gastrointestinal absorption step as well as the intestinal and hepatic first metabolism [10]. However, in respiratory diseases, the main target organ is the lung. Therefore, the main drawback of oral or intravenous administration is that the target is often un-located in the plasma or blood, and consequently, pulmonary selectivity could not be achieved via systemic administration [11]. Figure 2 illustrates the six-stage pharmacokinetic processes involved subsequent to pulmonary administration.

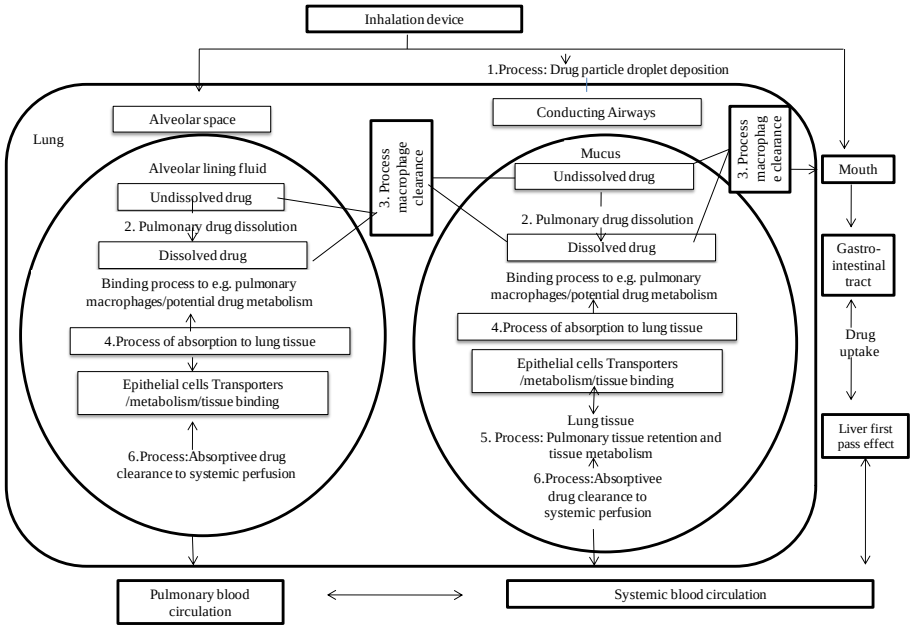

Figure 2. Pharmacokinetic processes following pulmonary drug delivery.

2.1. Stage 1: Drug particle or droplet deposition.

Accumulation of drug particles or droplets has been the first stage after inhalation. A small proportion of the dose gets reposed in the system, whereas the remaining drug particles or droplets get distributed to the pulmonary tract. The deposition takes place in the mouth, throat region, the conducting airways, and/or the space in the alveoli as particles travel across the airway system. The total portion of the drug accumulated in the lung is usually referred to as the lung dose. Aerodynamic diameter, inhalation flow, device properties, and disease-related factors are some of the elements that influence the dose of lung excepting the physicochemical properties of the drug itself [12-15]. Particles or droplets that fail to enter the lung are consequently swallowed, while others that enter the lung are exhaled [16,17]. Novel inhalation systems have been developed to release particles having aerodynamic diameters of 1-5 μm for optimizing the lung dose and amount of particles that are effectively delivered to their target site [18].

2.2. Stage 2: Pulmonary drug dissolution.

Following drug particle or droplet deposition, particles must disperse within the fluids of epithelial cells. Physiologic factors, formulation of a drug as well as its physicochemical properties such as dissolution characteristics, play an essential role in pulmonary drug

dissolution [17]. Slow dissolution as a rate-limiting step is obligatory as it prolongs lung retention, although with a simultaneous increase in the possibility that drug particles may get cleaned by mucociliary clearance.

2.3. Stage 3: Mucociliary clearance and macrophage clearance.

Deposited pulmonary dose, as well as lungs-specific clearance mechanisms, are a few critical factors that play a major role in deposited drug particle pulmonary bioavailability. The removal of drug molecules has been primarily achieved by mucociliary clearance, an essential mechanism of pulmonary defense throughout the respiratory tract against tiny particles or microbes [23]. Through striking the intrinsic cilia via the pharynx, an upwards passage of mucus has been carried out during this period. As a result, fine particles brought to the pharynx through mucociliary clearance have been ingested as well as distributed into the gastrointestinal tract. This phenomenon is most rapid in large air passages since mucociliary clearance improves with quite a larger airway circumference and a higher density mucus membrane [24]. The relevance of mucociliary clearance is quite complicated, which gets influenced through both medications as well as the character traits of an individual.

2.4. Stage 4: Absorption to lung tissue.

Active ingredients which adequately evade mechanisms of respiratory clearance as well as distribute throughout the fluid of epithelial cells might also promptly be absorbed into lung tissue. Accumulation via respiratory barriers is affected by either the features of patient-specific air passages or the characteristics of drugs. Lipophilic drugs have been easily absorbed by passive transcellular diffusion with epithelial cells upon dissolution [25]. Therefore, hydrophilic substances get absorbed through intercellular gap junctions via paracellular diffusion through the aqueous epithelium pores [26-30].

2.5. Stage 5: Pulmonary tissue retention and tissue metabolism.

The retention, as well as the distribution of absorbed drug throughout the pulmonary tissue, depends on the physicochemical characteristics of an inhaled drug or on patient-specific features of air passages. Amongst the most significant factors are tissue affinity or the pulmonary tissue diffusion coefficient [17,31-35].

2.6. Stage 6: Absorptive drug clearance to the systemic perfusion.

Pulmonary or absorptive clearance is the elimination through perfusion of the drug from the lung tissues into the bloodstream. Nevertheless, the rates of local perfusion vary within the different lung structures as well as in the alveolar area [36]. High perfusion rate facilitates quick equilibrium with alveoli systemic circulation tends to result in quite a short half-life of drug distribution in the pulmonary region. Increased respiratory specificity & low perfusion levels combined with high tissue retention throughout the tracheobronchial location ensures maximum local airway specificity as well as the prolonged-time of equilibrium [37,38].

3. Drug Deposition Mechanisms in Respiratory Tract

Particle deposition mechanisms in the respiratory tract can be divided into two major categories; major mechanisms (diffusion, sedimentation, and impaction) and minor

mechanisms (interception and electrostatic), as depicted in Figure 3 [39,40]. The aerodynamic diameter of a particle with density 1 gcm^{-3} settles in stationary air with constant velocity [41]. Particles having aerodynamic diameters greater than 10, 0.5-5, and 2 to 0.05 μm have an impact on walls of the throat, respiratory bronchioles, and alveoli, respectively [12,42-46].

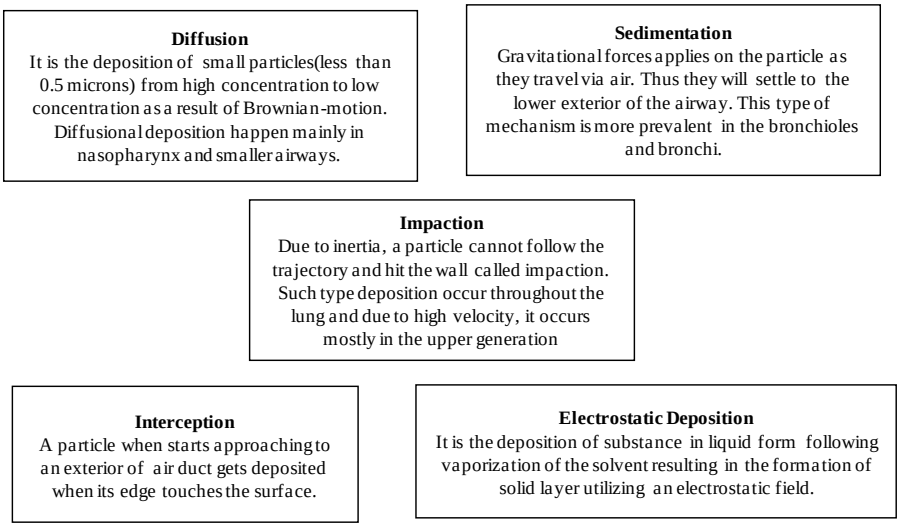

Figure 3. Mechanisms of respiratory drug deposition.

4. Types of Inhalable Microparticles

Microparticles-based drug delivery systems have emerged as the most significant approach for the treatment of respiratory disorders owing to improved drug's therapeutic index, prolonged biological half-life, and reduced toxicity [47]. They are micron-size particles wherein the drug is physically and uniformly dispersed enclosed by walls of synthetic and natural polymer films of varying thickness and degree of permeability acting as a release rate controlling substance. The polymeric microparticles, solid lipid microparticles, large porous microparticles, and drug-cyclodextrin complex microparticles could be utilized as inhalable microparticles [48]. In view of the fact that micro-particles do not conglomerate under shear force and deposit in the deep lung; therefore, they are gaining importance in the area of pulmonary drug delivery [49]. Inhalable microparticles utilize dry powder inhalers for drug delivery, which offers numerous advantages such as propellant-free, convenient to use, and handle. Fine particle fraction (FPF) and aerodynamic diameter are two important parameters that determine dry powder inhalers performance. Particles having an aerodynamic diameter greater than 1 μm are very fine and can be simply exhaled, whereas particles having an aerodynamic diameter less than 5 μm deposit in the region of upper airways. Therefore, to attain safe and effective drug delivery deep into the lungs, these must-have an aerodynamic diameter of 1-5 μm

4.1. Polymeric microparticles.

Polymeric microparticles are particulate dispersions or solid particles with size ranging from 1-1000 um. They are naturally or synthetically derived polymer and are biocompatible and biodegradable such as polylactic acid, polybutylcyanoacrylate, poly (lactic acid-co-lysine) graft, chitosan, and poly lactic-glycolic acid (PLGA) [51-53]. Wang et al. conducted in-vitro and in-vivo studies on docetaxel-loaded chitosan microspheres and found enhanced bioavailability and sustained release with minimum systemic toxicity [54].

4.2. Large porous microparticles (LPMs).

LPMs have an important role to play in the enhancement of deep lung deposition and circumventing uptake of macrophages. LPMs can be defined as light particles possessing low density (< 0.4 gcm^{-3}) and appropriate aerodynamic diameter (1-3 µm). They are extremely porous, which makes them sufficient light to reach profoundly inside the lungs and simply apprehended by lung's macrophages through inhalation. Osmogens or porogen like pluronic, cyclodextrins, hydrogen peroxide, or catalase (gas bubbles) and gas-foaming (ammonium bicarbonate) are utilized for the production of LPMs. Both osmogens and porogens undergo loss out of drugs by surface pores, as a consequence of water channels made inside polymeric matrix [55-58].

4.3. Solid lipid microparticles (SLMs).

SLMs have spherical shapes and sizes in the range of 1 to 1000 µm. They are lipid matrix composed of glyceride, fatty acid, fatty alcohol, and solid wax, possessing high melting points. In recent years, SLMs could serve as a good alternative and acceptable method for pulmonary drug delivery. Currently, for the development of inhalable SLMs, cisplatin was mixed with a solubilized lipid and PEGylated component using high-pressure homogenization and spray-dried [59,60].

4.4. Cyclodextrin complex microparticles.

Cyclodextrins (CDs) like α-, β- and γ-CDs is composed of cyclic oligosaccharides that are cyclic polymers of α-D-glycopyranose. Because of their high complexation efficiency, high loading capacity along with the low cost of production, β-CDs are frequently used for pharmaceutical applications. Due to their exceptional structure, having an external layer comprising hydroxyl groups along with the lipophilic internal cavity, they result in inclusion complexation formation with the hydrophobic drugs. To reduce the drug irritation following pulmonary delivery CDs have proven to be excellent solubilizing agents in aerosol preparations of poorly water-insoluble drugs. Therefore, CDs are broadly applied as drug carriers for the pulmonary route of drug administration. A safe β-CD derivative, a novel inhalable dry powder formulation of Fisetin (an inclusion complex with sulfobutyl ether-β-cyclodextrin), was developed to augment the aqueous solubility of a drug intended to be used for pulmonary drug delivery [60,61].

5. Production Methodology of Inhalable Microparticles

5.1. Emulsion polymerization technique.

Emulsion polymerization is a simple process in which the monomers are stabilized by using surfactants and are dispersed in an aqueous phase. The obtained microparticles display a low polydispersity index and produce high yields [62].

5.2. Dry coating technique.

In this technique, the prepared microparticles are lyophilized and introduced into Mechanofusion™ apparatus chamber simultaneously with lactose (Pharmatose 325M™). This apparatus consists of a rotating chamber having 200-1600 rpm speed, a stationary blade, and a

scrapper. Microparticles are adsorbed onto the surface of lactose, which can be easily deposited inside the lung [63] (Figure 4).

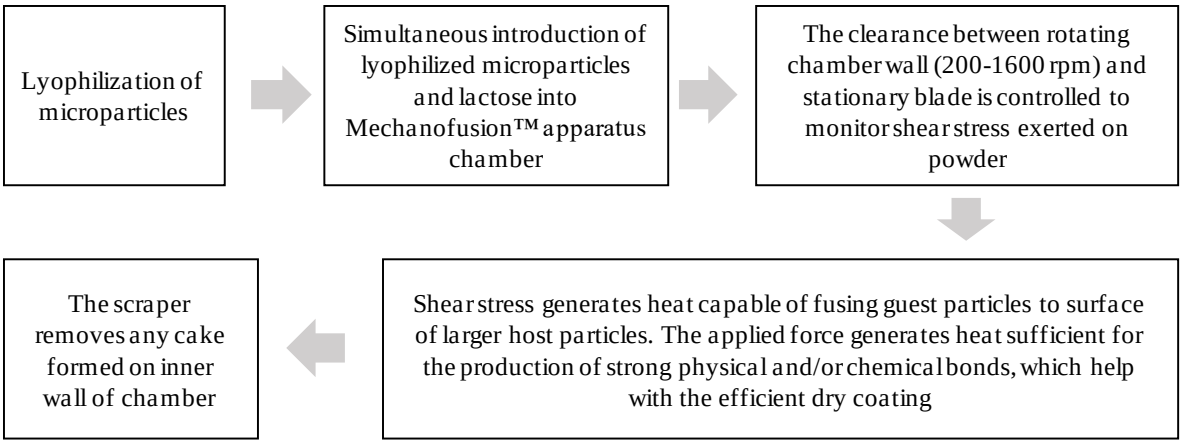

Figure 4. Dry coating technique for microparticles production.

5.3. Air suspension technique.

The process is also known as the Wurster process, was designed by Dale E. Wurster in 1940. Wurster coating is the process of encapsulation of distinct particles by means of differential airflow to create a cyclic movement of material in a fluidized bed (Figure 5) [64].

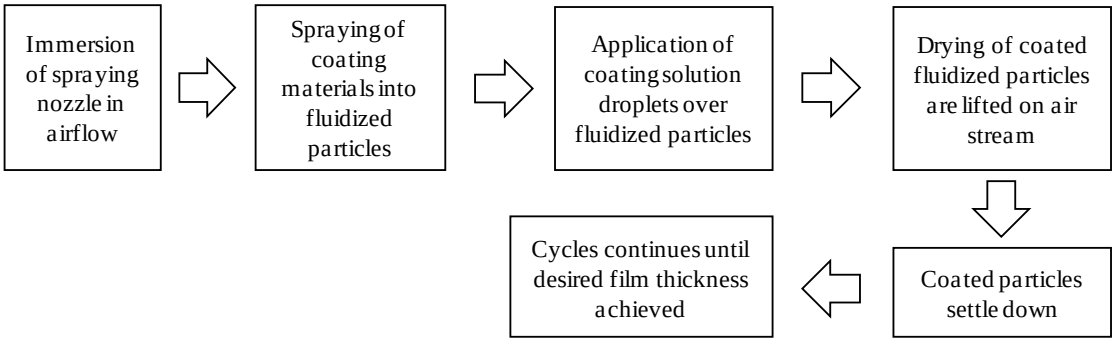

Figure 5. Air suspension technique for microparticles production.

5.4. Spray drying technique.

This technique was a breakthrough in the pharmaceutical industry over previous technologies. It is a dehydration method having high speed, versatility, high encapsulation efficiencies, and easy to scale-up. Parameters that influence the size and morphology of the microparticles are inlet-outlet temperature, nozzle diameter, air or solution volume mixture, pressure, feed rate, and type of atomizer [65] (Figure 6).

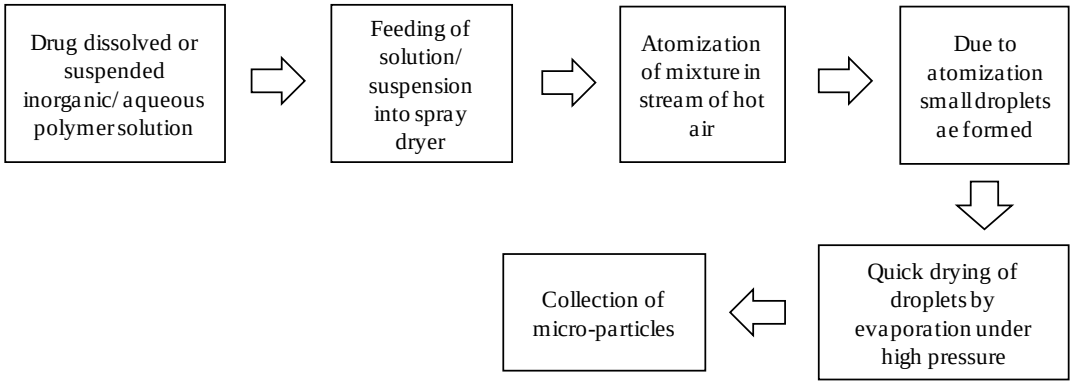

Figure 6. Spray drying technique for microparticles production.

5.5. Spray freeze-drying method.

Spray-freeze-drying is appropriate for extremely thermo-sensitive materials and particularly for lipid microparticles that are unable to withstand the high temperature during the predictable drying process, even for a short time. In this technique, the microparticles are protected from different stresses such as freezing and dehydration through immobilization in the glassy matrix of polysaccharide (Figure 7). However, a crystallization inhibitor is used to maintain the microparticles and polysaccharide in an amorphous state [65].

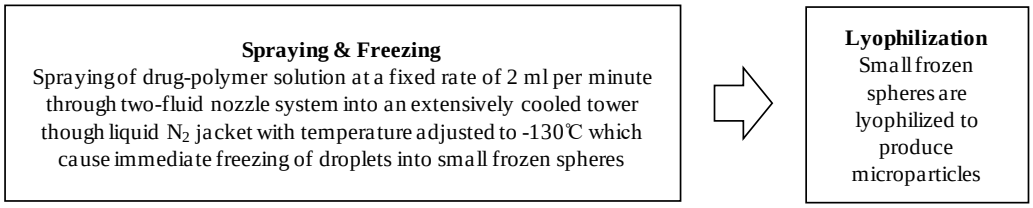

Figure 7. Spray freeze-drying technique for microparticles production.

6. Recent Advancements in Inhalable Microparticles

In view of the fact that lungs are in continuous contact with air, they are susceptible to numerous disorders and diseases like respiratory infections, asthma, chronic obstructive pulmonary disease, pneumonia, tuberculosis, acute respiratory distress syndrome in infants, and chronic lung cancers [3]. Therefore, studies had been conducted to explore the potential of microparticles in pulmonary drug delivery. Kim et al. developed inhalable sustained-release microparticles for co-delivery of doxorubicin along with TRAIL (type II transmembrane protein that stimulates programmed cell death in numerous carcinoma cells) for treatment of metastatic lung carcinoma. Furthermore, the interaction between doxorubicin and Trail suggests that the doxorubicin dosage and its side effects could be significantly reduced [66]. In another study, Zhu and its colleagues evaluated the effect of LPMs for in-situ treatment of primary non-small lung carcinoma. The authors conclude that oridonin plus PLGA-based LPPs possess a geometric diameter of about ~10 µm and an aerodynamic diameter of about 2.72 µm leading to very effective lung deposition [67]. Furthermore, Nafee and its colleagues prepared inhalable microparticles incorporating myricetin SLNs for lung carcinoma. It was established that optimized SLNs have a diameter of 75.98 nm, a zeta-potential of -22.5 mV, and an encapsulation efficiency of 84.5%. In addition, it was concluded that phospholipid complexation provides a five-fold improvement in the loading of drugs [68]. In research performed by Reczyńskaa and its colleagues, paclitaxel loaded microparticles were combined with superparamagnetic iron oxide nanoparticles. *In-vitro* efficacies against malicious epithelial cells of lungs (A549) of microparticles were assessed and found inhibited colony formation and substantially decreased cell viability [69]. In another study, Chaurasiya et al. fabricated paclitaxel loaded bovine serum albumin microparticles as dry powders having dimensions in the range of 0.5 to 3.0 µm. A comparison between formulated microparticles and commercially available taxol compound was made. It was observed that in comparison with taxol, the anticancer activity of developed microparticles showed better drug release profiles [70]. Furthermore, Tewes and colleagues formulated porous microparticles comprising superparamagnetic iron oxide nanoparticles supported by a target-directed magnetic inclined field for cancer nodules [71]. In addition, Cunha and his colleagues prepared an inhalable formulation of chitosan microparticles of rifabutin and isoniazid for lung tuberculosis therapy [72]. It was found that chitosan microparticles are possessing large encapsulation efficiencies

(93% for isoniazid and 99% for rifabutin) along with aerodynamic diameter (4 µm). In another study, Omar et al. formulated isoniazid-loaded chitosan microparticles and concluded that minimum inhibitory concentration of microparticles showed 63-fold more inhibition on *Mycobacterium tuberculosis* than isoniazid solution, due to the synergism of positively charged microparticles with their cellular penetration activity and promoting their bacterial cell surface binding [73]. In another study, Ni and its colleagues designed microparticles embedded in nanocrystals for sustained pulmonary drug delivery of cinaciguat. It was further established that microparticles have a mean volume diameter of about 3-4 µm, an aerodynamic diameter of about 4-4.5 µm, FPF of 40-45%, and 94-95% emitted dose [74]. In another study, Dufour et al. developed CDs-based spray-dried microparticles incorporating budesonide for the management of bronchial inflammation associated with asthma. It was found FPF was increased from 26.24% (with lactose) to 44.05% (with CDs) [75]. In another study conducted by Mahmoud and a group of researchers, microparticles of alginate were formulated for the pulmonary delivery of roflumilast. It was further reported that microparticles utilizing CDs efficaciously suppress the viability of pro-inflammatory cytokines (TNF-α, IL-6, and IL-10) in comparison with pure drugs [76]. In a recent study, Hu et al. developed inhalable curcumin incorporated PLGA-LPMs and concluded that curcumin LPMs showed potential effects in the treatment of idiopathic pulmonary fibrosis [77]. Jaspart and its colleagues formulated SLMs of salbutamol acetonide. It was found that in comparison with the pure drug, the drug release can be sustained by SLMs [78]. Furthermore, another team of researchers developed microparticles containing clarithromycin for inhalation using chitosan and leucine. It was found that clarithromycin microparticles are capable of interfering with bacteria proliferation, therefore, making it appropriate for pulmonary drug delivery [79]. Another study involved the formulation of inhalable silk-based microparticles to deliver high-payload ciprofloxacin for non-cystic fibrosis bronchiectasis. It was found that the optimal formulation exhibited emitted dose (98.10±1.27%), geometric standard deviation (1.66±0.10), good aerosol efficiency with regard to FPF (45.04±0.84%), and aerodynamic diameter (3.75±0.03 µm) along with the highest drug loading of 80% [80]. Polymeric microparticles of sodium cromoglycate using carboxymethylcellulose, sodium alginate, and sodium hyaluronate were fabricated by the spray-drying method. Drug release, in-vitro aerosolization, and mucoadhesion properties were studied and concluded that polymeric microparticles of sodium cromoglycate promise to be an attractive mucoadhesive inhalable formulation [81].

Table 1. Literature reports on inhalable microparticles for the treatment of respiratory disorders.

Model Drug	Polymers	Type of microparticles	Methodology	Application	Ref.
Paclitaxel	Sodium alginate	Polymeric microparticles	Emulsification technique	Lung cancer	[49]
Doxorubicin	PLGA	Sustained-release polymeric microparticles	w/o/w double emulsification	Lung cancer	[66]
Oridonin	PLGA	Large porous microparticles	Solvent evaporation/ emulsion/freeze-drying method	Non-small cell lung carcinoma	[67]
Myricetin (flavonoid)	Lipoid®-S100, Gelucire-based surfactant, Mannitol, Maltodextrin, L-leucine	SLN loaded respirable microparticles	Complexation/ nano-encapsulation/ Spray drying	Lung cancer	[68]
Iron oxide/ Paclitaxel	Myristic, palmitic, Lauric acid	Nanoparticles-embedded microparticles	Hot oil-in-water emulsification	Lung cancer	[69]

Model Drug	Polymers	Type of microparticles	Methodology	Application	Ref.
Paclitaxel	Bovine serum albumin	SLM	Spray drying technique	Metastatic Lung Cancer	[70]
Super paramagnetic iron oxide microparticles	2-hydroxy-propyl-β-cyclodextrin, Polyethylene glycol	Trojan microparticles	Spray drying	Specific lung delivery under a magnetic gradient field	[71]
Isoniazid/ Rifabutin	Chitosan	SLM	Spray drying	Pulmonary tuberculosis	[72]
Isoniazid	Chitosan	SLM	Spray drying	Tuberculosis	[73]
Cinaciguat	Chitosan	Polymeric microparticles	High-pressure homogenization	Pulmonary hypertension	[74]
Budesonide	Hydroxypropyl-β-cyclodextrin	Polymeric microparticles	Spray drying	Asthma	[75]
Roflumilast	Sodium alginate, Calcium beta-glycero phosphate	SLM	Spray drying	Tumor-associated inflammation	[76]
Curcumin	PLGA	Porous microparticles	Emulsion solvent evaporation	Idiopathic Pulmonary Fibrosis	[77]
Salbutamol acetonide	Glyceryl behenate	SLM	Hot emulsion high-shear homogenization	Asthma and COPD	[78]
Clarithromycin	Leucine and Chitosan	SLM	Controlled magnetic stirring	Tuberculosis	[79]
Ciprofloxacin	Mannitol, Silk fibroin	Silk-based microparticles	Spray drying	Non-cystic fibrosis bronchiectasis	[80]
Sodium Cromoglycate	Sodium hyaluronate, Sodium alginate, Sodium CMC	Polymeric microparticles	Spray drying	Asthma	[81]
Isoniazid and Rifabutin	Poly (l-lactic acid)	Dry powder inhalable polymeric microparticles	Spray drying	Tuberculosis	[82]
Di-sodium cromoglycate	PVA	Controlled release co-spray dried polymeric microparticles	Spray drying	Asthma and respiratory tract inflammation	[83]
Budesonide	Pluronic F-68, Compritol 888	SLM	Phase inversion o/w emulsion technique and spray drying	Asthma	[84]
Budesonide	Chitosan	Polymeric microparticles	Spray drying	Asthma	[85]
Thymopentin	Mannitol, Leucine	SLM	Co-spray drying	Immuno-modulator in autoimmune diseases, infections and cancers	[86]
Cyclosporin	Mannitol	Polymeric microparticles	Spray freeze-drying	COPD	[87]
Rifampicin	Chitosan, ascorbic acid, Leucine	Polymeric microparticles	Spray drying	Tuberculosis	[88]
Doxycycline hyclate	Leucine, Lactose, Sodium alginate, PVA PVP, Starch	Mucoadhesive polymeric microparticles	Spray drying	Tuberculosis	[89]
Heparin	PLGA; Resomer® grades RG502, RG503, RG504	Extended-release polymeric microparticles	Spray drying	Airway hyper-reactivity and inflammation	[90]
Quercetin	Tristearin, Phosphatidylcholine	SLM	Oil in water emulsification by phase inversion with Spray drying	COPD	[91]
Dexamethasone	Poly-caprolactoone, Sodium deoxycholate	Polymeric microparticles	Vibrational Spray drying	Asthma	[92]
Salbutamol sulfate	Dipalmitoyl-phosphatidyl-	SLM	Spray drying	Asthma and COPD	[93]

Model Drug	Polymers	Type of microparticles	Methodology	Application	Ref.
	choline, Cholesterol, L-leucine				
Sildenafil	PLGA, Resomer® RG502H	Polymeric microparticles	Spray drying	Respiratory tract infections	[94]
Resveratrol	Tristearin, Chitosan, Phosphatidyl-choline	SLM	Melt emulsification	Nasal Inflammation	[95]
Isoniazid or Rifabutin	Locust bean gum	Polymeric microparticles	Spray drying	Tuberculosis	[96]
Dexamethasone	Vanillyl alcohol-with co-polyoxalate	Porous microparticles	Double emulsification	Airway inflammatory disease	[97]
Insulin	Chitosan, Methyl iodide, Sodium iodide	Polymeric microparticles	Supercritical fluid assisted atomization with hydro-dynamic cavitation mixer	Diabetes mellitus	[98]
Azithromycin	Fumaryl diketopiperazine	Respirable microparticles	Spray drying	Pneumonia	[99]
Rifampicin	L-leucine, L-aspartic acid	Polymeric microparticles	Spray dryer via emulsion	Tuberculosis	[100]
Indomethacin	Epsilon-polylysine, Dextrin, Lactose monohydrate	Dry powder inhalable microparticles	Spray drying	Bronchial inflammatory asthma	[101]
Salmeterol Xinafoate	Pluronic F-68, DDAB, Sodium alginate, Mucin	SLM	Freeze Drying	COPD	[102]
Sildenafil citrate	Sodium alginate, Sodium CMC, Sodium hyaluronate, L-leucine	Hydrogel microparticles	Spray drying	Pulmonary hypertension	[103]
Budenoside	PLGA, PVP	Large porous microparticles	Modified o/w solvent evaporation	Asthma	[104]
Trans-Retinoic acid	PLGA	Spray drying	Spray-drying	Tuberculosis	[105]
Isoniazid/ Rifabutin	Konjac glucomannan	Polymeric microparticles	Spray-drying	Tuberculosis	[106]
Chloramphenicol palmitate/ Thiamphenicol palmitate	PLGA, Lactose monohydrate, Leucine	Sustained-release nano-embedded microparticles	Emulsion solvent evaporation with spray-drying	Multidrug-resistant pulmonary bacterial infections	[107]
Ciprofloxacin	Chitosan	Polymeric microparticles	Ionic gelation	Antibacterial activity in lungs	[108]

Abbreviations: COPD: Chronic obstructive pulmonary disease; DDAB: dimethyldioctadecyl-ammonium bromide; DOTAP: Dioleoyltrimethylammoniumpropane; Fumaryl diketopiperazine: Synthesized via three-step reaction using N_6-trifluoro-acetyl-L-lysine, phosphorus pent-oxide, N-methyl-2-pyrrolidinone; Sodium CMC: Sodium carboxymethyl cellulose; PLGA: Poly (D, L-Lactide-co-glycolide); PVA: Polyvinyl alcohol; PVP: Polyvinyl pyrollidone, Resomer® RG 502H: PLGA 50:50 (MW: 7000-17,000, acid terminated); SLM: Solid lipid microparticles.

Recent publications of inhalable microparticles for pulmonary administration are mentioned in Table 1. Recently published patents of inhalable microparticles have been summarized in Table 2.

Table 2. Recent patents of inhalable microparticles.

Patent No.	Invention	Date of Publication	Ref.
US005451569A	Pulmonary drug delivery system	19 September 1995	[109]
US005855913A	Particles incorporating surfactants for pulmonary drug delivery, unit dose micro-cartridges dry powder, related devices, and methods	5 January 1999	[110]
WO1996036314A3	Method for drug delivery to the pulmonary system	21 November 1996	[111]
WO2004030659A1	Sustained-release porous microparticles for inhalation	15 April 2004	[112]
US20050084455	Inhalable biodegradable microparticles for target-specific drug delivery in tuberculosis and a process thereof	21 April 2005	[113]

Patent No.	Invention	Date of Publication	Ref.
US2007154408	Inhalable Biodegradable microparticles for target-specific drug delivery in tuberculosis and a process thereof.	5 July 2007	[114]
US 20070215149A1	Dry powder inhalers having spiral travel paths	20 September 2007	[115]
US7625865B2	Insulin highly respirable microparticles	1 December 2009	[116]
WO2012017405A1	Microparticles formulation for pulmonary drug delivery of anti-infective molecule for the treatment of infectious diseases	9 February 2012	[117]
US8227409B2	Diketopiperazine with defined isomer contents	24 July 2012	[118]
US00916 1901 B2	Nanoparticles Targeted drug delivery to the lungs using extra-testicular Sertoli cells	20 October 2015	[119]
WO 2016/019253 Al	Dry powder formulations for inhalation	4 February 2016	[120]
JP2016222689	Compositions for treating pain	28 December 2016	[121]
US10342938B2	Dry powder drug delivery system	9 July 2019	[122]

7. Recent Innovations in Inhaler Technology

The pulmonary route has been employed to cure a variety of respiratory diseases from older times. Numerous ancient inhalation therapies that are used to suppress cough are vapors from aromatic herbs or plants, balsams, myrrh, and leaves from plants. Adrenaline had been discovered as a nebulizer solution in the 1920s; in 1925, porcine insulin has been used as a nebulizer for diabetes mellitus in experimental studies, and in 1945 newly discovered penicillin was tested for pulmonary delivery [123,124]. The modern inhalation devices have been listed in Figure 8. Dry powder inhalers (DPIs) are usually employed for the alleviation of respiratory disorders, namely bronchitis, emphysema, and chronic obstructive pulmonary disease (COPD). DPI had also been used for treating diabetes mellitus as inhalable insulin. Recent innovations in inhaler technology of marketed inhalers are described in Table 3.

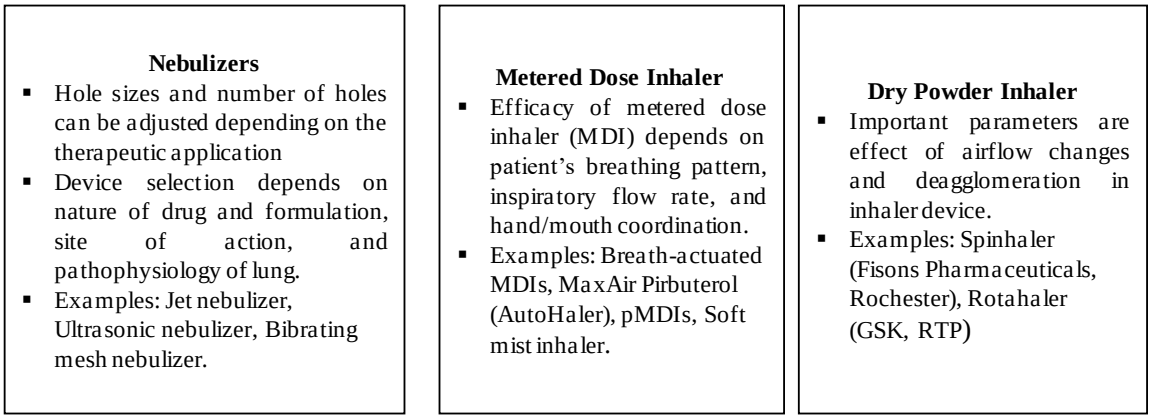

Figure 8. Types and examples of pulmonary drug delivery devices.

Table 3. Recent innovations in inhaler technology of marketed inhalers.

Marketed Brand	Manufacturer	Innovation	Ref.
Technosphere® Insulin	Mankind	It includes a dry-powder composition of insulin in crystal form filled in gelatin capsules. They show very fast absorption as investigated in pharmacokinetics as well as pharmacodynamics studies.	[125]
Exubera®	Nektar/ Pfizer	It uses insulin powder preparation, consisting of excipients like glycine, mannitol, along with 60 percent recombinant human insulin. Pharmacokinetics of insulin using inhalation therapy showed a peak round about 55 min and quick return in comparison with subcutaneous insulin.	[126]
Aerodose®	Aerogen Inc./ Nektar	It is a system using insulin in liquid form aerosolized in the shape of small droplets.	[127]
Spiro system	Dina Pharmacy Inc/Elan Corporation	It offers a dry-powder insulin preparation coated in blister-disks through a breath-actuated inhaler.	[128]

Marketed Brand	Manufacturer	Innovation	Ref.
DCI (Dose counter inhalers)	Dr. Reddy's	It is a new drug delivery device with a single device having 120 metered doses. There is a window in the inhaler that changes color from green to red.	[129]
Turbohaler	Astra Zeneca	This is a 'breath-activated' system, which means that dry powder medicine gets sucked from the system rather than being discharged, as those from other devices.	[130]
Twisthaler	Schering/ Mercks	This displays inspiratory flow at the mouthpiece at 28-60 $Lmin^{-1}$ and delivers approximately 91-112 percent of metered dose	[131]
Easyhaler	Orion	This is an eco-friendly, reliable, and convenient to be used for asthma and COPD therapy.	[131]
AERx	Aradigm	Help in delivering morphine and insulin into the lungs.	[132, 133]

8. Major Challenges in Pulmonary Drug Delivery

8.1. Low-performance inhalation system.

The primary standoff confronting pulmonary drug delivery is often the low efficiency of the inhalation systems available today. The optimum particle size of the aerosol is needed to deliver drugs more deeply into the lung. The optimum particle size for deep lung deposition is 1-5 µm. The pharmaceutical aerosol system must produce particles of desired fine size particles. If the particles are of larger size, they may affect larynx and oropharynx [3].

8.2. Less drug mass per puff and poor formulation stability.

Delivery of many drugs requires milligram doses needed for pulmonary delivery, but mostly in current systems, the total drug per puff carried to the lower respiratory tract is much lower than 1000 µg. The stability of asthmatic drugs is more in liquids in comparison to dry state [3].

8.3. Inappropriate dosing reproducibility.

A problem in delivery device and instability of formulation are some of the reasons responsible for improper dosing reproducibility. Therefore, patient education is required to get maximum dose reproducibility [3].

9. Conclusions

Nowadays, pulmonary drug delivery is becoming very relevant because of large absorptive surface area, elimination of the first-pass metabolism, and very thin diffusion layer that enables rapid absorption of drugs at the target site. Presently, the key drug targeting systems involve drug delivery straightforwardly into the lungs, primarily using inhalation treatment via dry powder inhalers and pressurized metered-dose inhalers. Therefore, inhalable microparticles having aerodynamic diameters of 1-5 µm could be successfully and effectively explored in forthcoming years for the management of respiratory diseases such as cystic fibrosis, COPD, pneumonia, chronic bronchitis, tuberculosis, lung cancer, and asthma.

10. Current & Future Developments

Due to the broad absorptive surface region, elimination of the first-pass metabolism, and quite a thin diffusion layer that allows for quick drug absorption at the targeted lung cells, pulmonary drug delivery is nowadays gaining considerable importance. Polymeric

microparticles, large porous microparticles, solid lipid microparticles, and cyclodextrin complex microparticles having aerodynamic diameters of 1-5 µm could be successfully and effectively explored as inhalable microparticles for producing superior therapeutic effect along with minimized systemic toxicity for respiratory diseases management in forthcoming years.

Funding

This research received no external funding.

Acknowledgments

The authors express gratitude to Chitkara College of Pharmacy, Chitkara University, Punjab, India, for motivational support for the compilation of this review.

Conflicts of Interest

The authors declare no conflict of interest.

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