Pulmonary drug delivery: Role of antibiotic formulations for treatment of respiratory tract infections

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Abstract
Respiratory infections cause an extensive health problem in the world. The common treatment for respiratory infections is the administration of antibiotics orally or parenterally in a high dose. Unfortunately, these therapies of high-dose antimicrobials have many disadvantages, such as severe side effects. Consequently, the development of an inhaled formulation provides the delivery of the therapeutic dose of the drug to the organ of interest without overt systemic effects. Novel technological advances have led to the development of inhaled antibiotics. Recent particle engineering techniques for dry powder inhalers (DPI) or mesh nebulizers have higher aerosolization efficiencies and promote the delivery of high-dose antibiotics to the lungs. However, advanced formulation strategies are in high demand for the development of new formulations for more types of antibiotics. Despite all the current research, patient compliance with pulmonary dosage forms remains to be very low because of the inappropriate administration techniques. Hence, this review focuses on three key aspects of the pulmonary dosage forms of antibiotics; the marketed products, the formulation approaches under research and innovative formulation strategies for achieving drug delivery through the respiratory tract.

Key words: *antibiotic dosage form, Inhaled formulation, dry powder inhalation, nebulization, particle design, antibiotic combination, ishikawa diagram*

1. Introduction

Inhaled therapy for medicinal purposes was used at least 4,000 years ago, but using antibiotics in a pulmonary dosage form takes back to 1948, when Abbot Laboratories developed the Aerohalor for the inhalation of Penicillin G powder [1]. However, large-scale therapeutic advancement dates back to 1997, when tobramycin for inhalation was approved by the U.S. Food and Drug Administration (FDA) for use in patients with cystic fibrosis [2]. Respiratory tract infections affect people in all ages and are very common [3-5]. Globally, infections of the lower respiratory tract are among the top three major causes of morbidity and every year, these can be responsible for approximately 3.5 million deaths in the world [6]. The most common treatment for respiratory infections involves the oral or parenteral administration of high doses of single or combined antibiotics, which can show undesirable side effects because of high systemic bioavailability [7, 8]. The ability to deliver therapeutic agents to the site of action may allow efficient treatments of infectious diseases of the respiratory tract and has many advantages over other routes [9].

The large surface area of the lungs is supplied by the excessive blood capillary network, which plays a role in the rapid absorption of the drug in the lungs. So the absorbed drug can directly reach the blood circulation, thus evading first pass metabolism through this non-invasive drug delivery system [10, 11].

Therefore, the delivery of even low concentrations of antibiotics to the lungs at the site of infection leads to much higher concentrations of antibiotics in the lungs, while reducing systemic exposure and the risk of toxicity, and yielding therapeutic effects with smaller drug doses than the oral or parenteral route [12, 13].

One example is when an aminoglycoside antibiotic amikacin is given by IV administration, the drug concentration in the serum is three times higher than in the bronchial tissues, however, when amikacin is given by inhalation, drug concentration is 1000 times higher in the bronchial tis-

sues than in the serum [14]. The other advantage of using a pulmonary dosage form of antibiotics in the treatment of chronic infections is that it is not associated with pain and it increases patient comfort and compliance, causing rational treatment outcome. Therefore, it enhances the quality of life, shortens the hospitalization period and significantly decreases morbidity and mortality [15-18].

Currently, there are no drugs available that can stop the progression of Chronic Obstructive Pulmonary Disease (COPD), but inhaled therapies have proved fruitful by preventing progression in many trials. Previously, many oral therapies were available for the treatment of idiopathic pulmonary hypertension, however, new interventions are needed to increase patient compliance, which may affect disease progression. There has also been an increase in the development of aerosolized liposomal formulations for the treatment of pulmonary neoplasia and 9-nitro-20(S)-camptothecin liposomal therapy has already been in clinical trials [19].

In spite of the great advantages of pulmonary dosage forms of antibiotics for the treatment of respiratory infection, there are a few disadvantages for this route, which cause limitations when using antibiotics in a pulmonary dosage form [20]. Metabolic enzymes found in the lungs metabolize the antibiotics, however, the pathways and metabolic activities are different from degradation observed in the gastrointestinal tract [21]. Antibiotics can be cleared by the activity of alveolar macrophages found in the pulmonary alveoli, and the activity of these macrophages is relatively high since they are located at one of the extensive borders between the body and the outside environment [22, 23]. On the other hand, the inhalation of antibiotics may cause severe local irritation, wheezing, bronchospasm and coughing in patients [24].

In consideration of all these advantages and disadvantages, the development of inhaled antibiotics to treat lung infection is a largely active field, with four approved products in the USA and others in the late stages of clinical progress [13].

In this review, we have discussed the pulmonary dosage forms of antibiotics for the treatment of respiratory infections. Then particular inhaled formulations have been reviewed, highlighting fields where further research is required, e.g., particle engineering and particle preparation, and innovative formulations of pulmonary dosage forms. Then different methods of liposome preparation of antibiotics have been reviewed, and finally some of the formulations which contain a combination of antibiotics have been studied.

2. Inhaled antibiotic formulations in the market and in the development phase

2.1. Approved antibiotic formulations and their delivery routes

The comparison of the general treatment guideline of respiratory tract infections and literature data about the pulmonary dosage form of antibiotics shows that these two lines are not parallel. The data show most research and investigations of pulmonary dosage forms of antibiotics focus on the treatment of cystic fibrosis rather than generally on the treatment of respiratory tract infection [25-27]. Cystic Fibrosis (CF) is an inherited disease caused by different mutations of the transmembrane conductance regulatory gene, and consequently respiratory failure follows after the chronic inflammation of the respiratory tract [28-30]. Currently, CF is the particular pulmonary infectious disease in which inhaled antibiotics have received FDA and European Medicines Agency (EMA) approval [24]. Future inhaled antibiotic trials have to focus on pulmonary diseases other than CF with large-scale manufacturing of marketed products for treating the variety of pulmonary infections. Hence, the pulmonary dosage form of antibiotics can be used for the treatment of upper respiratory tract infections such as pharyngitis, tonsillitis, laryngitis, tracheitis, or lower respiratory tract infections like acute bronchitis and pneumonia often following after common cold and influenza [31-33]. Therefore, there will be a possibility for eradicating a broad spectrum of Gram-positive and Gram-negative bacteria from the respiratory system. The antibiotics discussed in this review have been a subject of research and investigation over the years. Nowadays they are under clinical investigation or marketing. Table I illustrates the groups of antibiotics in different dosage forms that are present in the market. So based on the data of table 1, we can assume that many different oral and parenteral dosage forms of antibacterial agents have been formulated; however, as Figure 1 shows, only 0.01% of antibiotic formulations exist in pulmonary dosage form and 0.04% of the total group of antibiotics involves inhaled formulations. Figure 2 shows the ratio of different products in the USA and the UK.

Table I *Summary of different key formulations of antibiotics in the USA and the UK/Europe. (Compiled from EMA's website:* www.ema.europa.eu*, FDA's database:* www.fda.gov/home*, National Institute of Pharmacy and food website:* www.ogyei.gov.hu*)*

Group of Penicillins	**USA**	**UK/Europe**
Amoxicillin	Capsule, Chewable tablet, Drops, Extended-release tablet, Tablet for suspension, Suspension	Oral hard Capsule, Dipersible tablet, Oral suspension, Powder for oral suspension, Powder for solution for injection and infusion
Ampicillin	Injection, Solution, Suspension, Powder for solution for injection, Capsules	Oral suspension, Powder for solution for injection, Powder for oral suspension, Capsules
Dicloxacillin	Capsule, Oral suspension	
Carbenicillin indanyl	Capsule	Capsule
Nafcillin	Injection, Infusion	
Oxacillin	Powder for injection, Infusion solution, Tablet	Capsule, Powder for solution for injection
Penicillin G	Injection, Infusion, Tablet	Injection, Infusion, Powder for injection, Tablet
Penicillin V	Oral solution, Tablet	Oral solution, Tablet
Piperacillin	Injection, Infusion	Injection, Infusion
Ticarcillin	Infusion	Infusion
Group of Cephalosporins	**USA**	**UK/Europe**
Cefaclor	Capsule, Film coated tablet, Paedetric drops	Capsule, Suspension, Powder for suspension
Cefadroxil	Capsule, Suspension, Tablet	Capsule, Granule for oral suspension
Cefazolin	Injection	Powder for injection/ infusion
Cefdinir	Suspension, Capsule	
Cefepime	Injection	
Cefixime	Tablets, Suspension	Granules for oral suspension, Film coated tablets, Powder for oral suspension
Cefotaxime	Injection	Powder for solution, Powder for injection or infusion
Cefotetan	Injection	
Cefoxitin	Infusion	
Cefprozil	Suspension, Tablets	
Ceftazidime	Injection	Powder for solution, Powder for injection or infusion
Ceftibuten	Suspension	
Ceftizoxime	Injection	Injection
Ceftaroline	Intravenous powder for injection	Intravenous powder for injection
Ceftriaxone	Injection	Powder for solution, Powder for injection or infusion
Cefuroxime	Injection, Infusion, Suspension, Tablet	Film-coated tablet, Suspension, Granules for suspension, Tablet, Powder for injection or infusion
Cephalexin	Capsule, Oral suspension, Tablet	Capsule, Oral suspension, Tablet
Group of Carbapenems	**USA**	**UK/Europe**
Doripenem	Injection	
Ertapenem	Injection	Powder for concentrate for solution for infusion
Imipenem	For injection (combination with Cilastatin)	Powder for solution for infusion (combination with Cilastatin)
Meropenem	Powder for injection/infusion	Powder for solution for injection/infusion
Group of Monobactams	**USA**	**UK/Europe**
Aztreonam	Inhalation, Injection, Infusion	Injection
Group of Tetracyclines	**USA**	**UK/Europe**
Demeclocycline	Capsule, Tablet	Capsule, Tablet
Doxycycline	Capsule, Injection, Delayed release tablet, Subgingival controlled release gel	Capsule, Tablet

Minocycline	Extended release capsule, Extended release tablet, Injection, Sublingual, Oral microspheres	Film-coated tablet, Tablet, Capsule
Tetracycline	Tablet, Capsule, Suspension, Topical, Eye ointment	Capsule, Tablet, Eye ointment
Group of Glycylcyclines	**USA**	**UK/Europe**
Tigecycline	Injection	Injection
Group of Aminoglycosides	**USA**	**UK/Europe**
Amikacin	Injection	Injection, Solution for infusion
Gentamicin	Cream, Drops, Injection, Ointment, Solution, Topical	Drops, Infusion, Injection, Solution for injection
Neomycin	Cream, Drops, Injection, Ointment, Solution	Tablet, Drops
Streptomycin	Injection	Injection
Tobramycin	Eye drops, Injection, Inhalation solution, Ointment, Powder, Ophthalmic Solution	Injection, Infusion, Ointment, Eye drops
Group of Macrolides	**USA**	**UK/Europe**
Azithromycin	Injection, Suspension, Tablet, Capsule, Ophthamlic solution, Powder for suspension	Capsule, Film coated tablet, Injection, Suspension, Powder for oral suspension, Powder for solution for injection
Clarithromycin	Extended release tablet, Suspension	Film coated tablet, Granules for Oral suspension, Powder for solution for infusion, Tablet
Erythromycin	Capsule, Delayed release tablet, Delayed release Capsule, Drops, Gel, Infusion, Ointment, Oral suspension, Solution, Infusion, Tablet, Topial pad	Film coated tablet, Gastro-resistant tablet, Granules for oral suspension, Oral suspension, Powder for solution for infusion, Sugar free Oral suspension, Tablet
Telithromycin	Tablet	Film tablet
Group of Fluoroquinolones	**USA**	**UK/Europe**
Nalidixic acid	Suspension, Tablet	Tablet
Ciprofloxacin	Drop, Extended release tablet, injection, Infusion, Ointment, Suspension, Solution, Tablet	Drop, Film coated tablet, Granules for oral suspension, Solution for infusion, Tablet
Norfloxacin	Drop, Suspension, Tablet	Tablet
Ofloxacin	Drop, Solution, Tablet	Tablet
Levofloxacin	Drop, Infusion, Injection concentrate, Oral solution, Solution, Tablet	Film-coated Tablet, Solution for infusion, Tablet
Moxifloxacin	Eye drops, Injection, Tablet	Film- coated tablet, Solution for infusion, Tablet, Eye drops, injection
Group of inhibitors of folate synthesis	**USA**	**UK/Europe**
Mafenide	Cream, Topical Solution	Cream, Topical solution
Silver sulfadiazine	Cream	Cream
Sulfasalazine	Delayed release tablet, Oral suspension, Rectal suspension	Enteric coated tablet, Gastro resistant tablet, Oral suspension, Tablet
Sulfisoxazole	Suspension (combination with erythromycin)	
Groups of Inhibitors of folate reduction	**USA**	**UK/Europe**
Pyrimethamine	Tablet (combination with sulfadoxine)	Tablet (combination with sulfadoxine)
Trimethoprim	Intravenous, Suspension	Suspension, Tablet
Others	**USA**	**UK/Europe**
Chloramphenicol	Capsule, Injection, Infusion	Capsule, Drops, Ointment
Clindamycin	Cream, Foam, Gel, Granules, Injection, Intravenous, Lotion, Solution, Suppository, Suspension, Swab	Capsule, Cream, Hard capsule, Solution for injection, Solution for infusion
Linezolid	Injection, Intravenous, Suspension, Tablet	Film coated tablet, Granules for oral suspension, Solution for infusion
Quinupristin / Dalfopristin	Powder for injection	

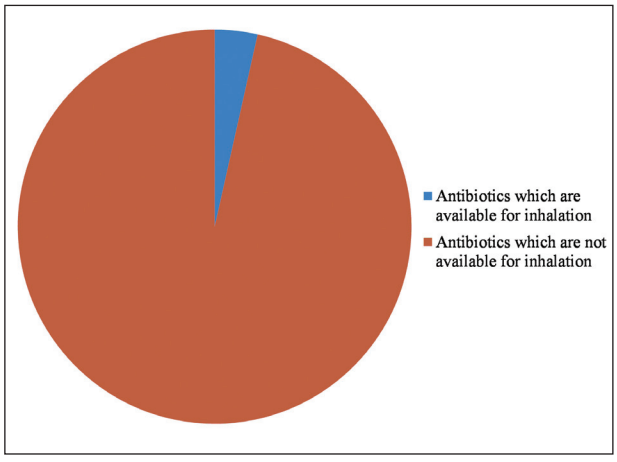

Figure 1 *Ratio of the inhaled antibiotic Vs non-inhaled antibiotic formulation*

2.2. Approved inhaled antibiotic products

2.2.1. Monobactams (Aztreonam)

β-lactam compounds are the first antibiotics to be discovered and widely used in many treatments. In this group, monobactams were developed with enhanced effect against aerobic Gram-negative bacteria. They are inactive against Gram-positive bacteria or anaerobic bacteria. They disrupt the bacterial cell wall [34]. The most common monobactam antibiotic is aztreonam [35]. Since absolute bioavailability is very low (about 1%) after oral administration, it is necessary for aztreonam to be administered intravenously or intramuscularly [36]. This drug is very safe for treating patients who are allergic to penicillins and cephalosporins [37]. Cayston®, aztreonam for inhalation solution, has been approved by FDA and EMA [38].

2.2.2. Fluoroquinolones (Ciprofloxacin, Levofloxacin)

Fluoroquinolones are potent antibacterial agents which target two enzymes, DNA gyrase and DNA topoisomerase IV [39]. Fluoroquinolones are rather well-tolerated and safe antibiotics [40]. Ciprofloxacin is the most potent fluoroquinolone for the treatment of pseudomonal infections associated with CF [41]. A liposomal ciprofloxacin formulation for inhalation is currently in clinical trials for the treatment of respiratory diseases. Dry powder formulations of ciprofloxacin are in the advanced development stage [42]. Levofloxacin is an isomer of ofloxacin, which can be utilized in a wide range of infections due to its broad spectrum of activity [43]. Nebulized levofloxacin solution, Quinsair 240 mg, is now in market [44, 45].

2.2.3. Aminoglycosides (Amikacin, Tobramycin)

Aminoglycosides are essential antibiotics in the treatment of severe and lethal infections [46]. Aminoglycosides exhibit bactericidal activity by inhibiting protein synthesis as they bind to the 30S ribosomal subunit prior to ribosome formation, therefore causing the misreading of mRNA and leaving the bacterium unable to synthesize proteins necessary for bacterium growth [47]. Liposomal amikacin suspension (Arikayce) for inhalation has been approved by FDA for the treatment of respiratory diseases [48]. Tobramycin solution (TOBI Novartis) has been approved in the USA and Europe. Dry powder inhalation tobramycin (TOBI podhaler) has been approved in the USA and Europe [49]. Tobramycin exhibits irreversible ototoxicity or nephrotoxicity as side effects, however, when administered in a pulmo-

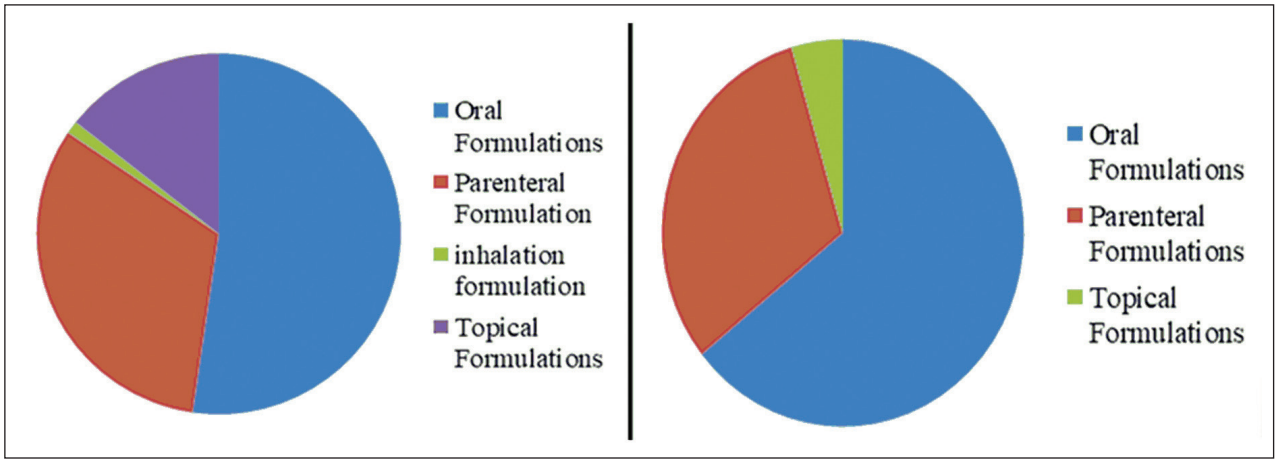

Figure 2 *Ratio of different formulations in USA (left) and UK (right)*

nary dosage form, it does not display these systemic side effects, and it is an affirming study showing that systemic toxicity can be minimized via pulmonary dosage forms [50, 51].

2.2.4. Colistin

Colistin belongs to the polypeptide antibiotics known as polymyxins. Colistin is effective against most Gram-negative bacteria. Colistin can be given intravenously and resistance to colistin is rare [52]. Colistin is polycationic and has both hydrophilic and lipophilic moieties [53]. Colistimethate sodium solution (Colomycin) has been approved in some European countries. Colistin methanesulfonate (Colobreathe) dry powder formulations have been approved in the USA and European countries. Zhou et al. reports a study which reveals that colistin in pulmonary dosage forms rarely results in systemic side effects [54-56].

2.2.5. Vancomycin

Vancomycin is a tricyclic glycopeptide antibiotic, a large hydrophilic molecule that poorly crosses the gastrointestinal mucosa. Vancomycin is effective against Gram-positive bacteria [57] and it has become extremely useful because of its effectiveness against drug-resistant organisms [58]. Dry powder of vancomycin hydrochloride (AeroVanc) for inhalation has not been marketed yet but phase I clinical study reported excellent tolerability of this antibiotic in volunteers. So dry powder formulations of vancomycin are in the upgrading development stage [59].

3. Frequently used antibiotic formulation techniques

There are numerous methods to produce pulmonary drug delivery systems; however, here we tried to focus on methods that are mostly used for pulmonary dosage forms of antibiotics.

3.1. Nebulization

Nebulized antibiotics were used for the treatment of respiratory infection in the 1950s [60]. The nebulization of antibiotics is a method for delivering therapeutic agents in a liquid form (solution or suspension) into the lungs by using nebulizing devices. Droplets with a diameter of approximately 1-5 μm are used for inhalation. This fraction can deposit in the large and small airways and the alveoli. Droplets larger than 5 μm deposit in the upper airways and droplets smaller than 1 μm are gradually exhaled again or may get into the systemic absorption [61, 62]. As a routine rule, nebulizers are suggested if the antibiotic cannot be administered using other devices [63]. Nebulizers are usually used for patients who are critically ill or children not able to use handheld devices due to the smaller geometry of the respiratory tract as well as the lower inhalation flow rates [64]. Nebulizers are also applied for any antibiotic available only in liquid form and not stable in any other form [65]. In the past, intravenous formulations were used to deliver antibiotics with different nebulizers for the treatment of serious respiratory infections. Intravenous formulations of antibiotics may contain additives and preservatives harmful to the lungs or not having appropriate osmolality, pH and particle size, which can cause airway irritation, cough and bronchospasm [66]. During nebulization, antibiotic liquid aerosols are generated by mechanical mechanisms like soft mist inhaler, human powered nebulizer or electrical mechanisms such as vibrating mesh technology, jet nebulizer and ultrasonic wave nebulizer [67]. Recent advances in nebulizer design have been reviewed elsewhere [68]. Conventional jet nebulizers generally have low drug delivery efficiencies and compared to the other types of nebulizers, noisy working and heavy weight are the biggest drawbacks of the jet nebulizer [69]. These issues have been improved by vibrating mesh nebulizers to produce aerosols with greater concentration of droplets and to reduce their administration time. As a consequence, minimal residual volume is exhibited, which in turn yields lower antibiotic waste, rapid output and enhanced drug delivery efficiencies [70-73]. Pulmonary drug delivery by nebulization can also be optimized by digital software regulation and performance feedback systems [74]. Table II enlists some antibiotics designed by nebulization.

3.2. Dry Powder Inhalation

Regarding the possible dosage forms for the pulmonary delivery of antibiotics, one can use a wide variety of formulations, such as dry powder inhalation (DPI). DPI formulations have been used for patient treatment for more than 60 years, but during this period the fundamental formation of DPIs has not changed significantly [75, 76]. DPIs have

Table II *Nebulized antibiotics and their clinical impact*

Therapeutic agent	Method	Characteristic excipient	Clinical/Biopharmaceutical impact
Ciprofloxacin	Liposome formulation by membrane extrusion method	Hydrogenated soy phosphatidylcholine/ cholesterol	Enhanced drug encapsulation/size/ stable release [75].
Ciprofloxacin	Liposome formulation by membrane extrusion	Polysorbate 20/hydrogenated soy phosphatidylcholine/cholesterol	Enhanced release rate [76].
Ciprofloxacin	Liposome formulation by thin film method	(DOTAP)*/ (DOPE)** (PC)***/ cholesterol	Decreased MICs [77].
Colistin	Dry film method	Dioleoyl-phosphatidylcholine	Enhanced release rate [78].

*1,2-Dioleoyloxy-3-trimethylammonium-propane **1,2-dioleoyl-sn-glycero-3-phosphoethanolamine *** phosphatidylcholine

become the first choice of inhaled formulations in European countries. DPIs are formulations containing micronized drug particles with an aerodynamic particle size of less than 5 μm [77]. For adequate deposition to reach the central and alveolar parts of the lungs, the optimal size of particles should be in the region of 1-5 μm. The most important approach in designing DPIs is that the time required for delivering each dose is short and even less than one-third of the time is needed for delivering the same dose for nebulization. This fact is expected to improve patients' adherence [78, 79]. DPIs of antibiotics are more stable, offer ease of administration and have less risk of microbial contamination than parallel liquid formulations [80-82]. DPIs have conventional application as a formulation of micronized drug in a carrier-based system [83]. Because the small particles (1-5μm) tend to stick with each other due to high surface free energy, carriers such as lactose, mannitol and trehalose are used for preventing the agglomeration of particles. These excipients reduce the surface energy, overcome cohesive forces and adhesive forces, and limit the flowability of API particles [83]. That is why the carrier-based system is being explored for surface modification and active targeting. By an appropriate use of the polymer or lipid carrier, the pulmonary drug delivery approach can result in interesting outcomes.

Lactose is the most typical and frequently used carrier in DPIs but because of clinical issues, lactose cannot be used for drug delivery to diabetic patients and people with lactose intolerance [84-87]. Mannitol, a hexahydric alcohol, has been frequently used as a carrier for aerosol drug delivery [17]. Mannitol is less hygroscopic than lactose and gives a suitable sweet aftertaste, which is a benefit over lactose and enhances the compliance of patients [88]. A therapeutic DPI aerosol for the treatment of CF and chronic bronchitis (BronchitolTM), approved by the FDA and the EMA, contains mannitol as a carrier system [89]. A DPI formulation for the inhalation of ciprofloxacin hydrochloride was prepared with different percentages of mannitol as a combination formulation. Mannitol improved mucous clearance in the respiratory tract while concurrently treating local chronic infection, chronic obstructive pulmonary disease and cystic fibrosis [90]. Trehalose dihydrate is a disaccharide non-reducing sugar and can be used as another carrier. A DPI of trehalose microparticles with low water content was successfully produced by the spray-drying technique [91]. Although trehalose leads to autophagy and can be used for the treatment of Huntington's disease, Parkinson's disease or tauopathies, it does not exhibit any benefit for the treatment of infections [92]. Moreover, DPIs of antibiotics usually have large therapeutic doses (e.g. between 10 mg and 100 mg of antibiotics), thus the carrier causes difficulty in the application of the DPI due to the increased powder volume and the scaled-down use of antibiotics via pulmonary dosage forms [93]. For about the last two decades, there has been significant research on the design of carrier-free systems for DPIs [83]. Applying a carrier-free system makes the delivery of a high dose of antibiotics to the lungs possible by limiting the amount of excipient [94]. Carrier-free formulations can be handled by coating particles with lipids, amino acids and polymers by the mechanofusion dry coating process [95,–98]. The drug deposition of DPI in the lungs is essentially controlled by its aerodynamic behavior. Currently, the aerodynamic properties of DPIs are being improved by changing formulation strategy and particle engineering [99]. These strategies are discussed in detail in Section 3.3.

3.3. Preparation methods for DPIs

3.3.1. Milling (top down)

Milling involves the breakdown of coarse large particles into fine particles by the use of mechanical force. Wet milling and dry milling are the common methods used in the production of pharmaceutical products. As the name indicates, wet milling involves the breakdown of large particles while they remain suspended in liquid medium. Dry milling may be sub-branched into various other forms of milling that do not require moisture content during the breakdown. Wet milling is often used for drugs which have a high residual moisture content [100]. The pharmaceutical industry also uses jet milling, also referred to as fluid energy milling, for most of the pharmaceutical dosage form designs. Jet-milled powders are highly cohesive because of the high surface energies of the particles. This problem can be resolved by adding excipients and carriers. However, this approach seems unfavourable for high-dose antibiotics. The great advantage of this method is that it does not require separation [101-103]. The process of milling can lead to a decrease in the particle size and moderately reduced crystallinity because of the production of amorphous form [104]. So particle engineering is a very important key factor for the production of carrier-free (or with minimum carrier) inhalable powders of antibiotics with good aerosolization behavior [105, 106]. Overall, the process of milling improves drug dissolution and solubility profiles.

3.3.2. Solvent evaporation method (bottom up)

The other process used commonly is the solvent evaporation method. It includes spray-drying, freeze-drying, spray freeze-drying, and supercritical fluid followed by rapid expansion. Spray-drying is a single-step particle formation process and is an appropriate way for particle engineering under a controlled manner for scale-up in industry. It is used for the production of dry powder from a solution, suspension and emulsion by rapid drying in the presence of a hot gas [107]. Amorphous and crystalline materials may be yielded by spray-drying depending on feedstock. This method gives better control over the particle size and shape, yielding powders with a narrow particle distribution and low particle surface energy. Furthermore, it creates possibility for the addition of excipients to promote the dispersibility of the powder, to enhance the stability of the formulation, to improve cellular uptake and to complete a formulation with modified drug release. Carrier-free DPI formulations of ciprofloxacin nanoplex were developed by spray-drying and spray freeze-drying methods. D-Mannitol and L-leucine were used as drying adjuvant and aerosol dispersion enhancer, respectively. Another example is the manufacturing of inhaled tobramycin (TOBI® podhaler®, Novartis) [108-110]. PulmoSphere of tobramycin can also be prepared by treating an emulsion under high-pressure homogenisation followed by spray-drying.

Different excipients have different effects on the mass, particle size, particle morphology and aerodynamic behavior of microparticles [111]. A mannitol–leucine combination resulted in better aerosolization behavior of the therapeutic agent, but mannitol exhibited some degree of recrystallization. A trehalose–leucine combination shows good potential to be used as excipient for the pulmonary delivery of potent antibiotics [109]. Although spray-drying is a conventional method to produce DPIs, the exposure of heat-sensitive antibiotics, e.g. penicillin, to the high temperature of the spray dryer (>100℃) is not appropriate. The nano spray dryer provides very adequate results for the formulation of heat-sensitive materials in submicron particles, with high yields (70% to 90%) related to the conventional spray-drying method [112]. Freeze-drying works by freezing the therapeutic agent and then decreasing the pressure to allow the frozen water in the material to sublimate directly from the solid phase to the gas phase [113]. Freeze-drying has been considered as a good technique to enhance the long-term stability of the microparticles and nanoparticles of antibiotics [114].

The worldwide rise in mortality rates because of antibiotic resistance turned out to be the toughest challenge to modern medicine and therapeutic agents [115]. Monotherapy with a single antibiotic may lead to the development of antibiotic resistance due to newly discovered pathogens, which cause resistance to a broad spectrum of antibiotics [116]. Hence, combination therapies, containing different types of antibiotics, have been introduced to inhibit the development of drug resistance [117]. Antibiotic combinations should be according to the synergistic effect of antibiotics and should avoid interaction [118]. Cospray-drying is the method which can assist in such combination therapy to achieve the desired effect. The cospray-dried combination of ciprofloxacin and doxycy-

Table III *Differences between conventional and QBD approaches*

Characteristic	Conventional	QbD
Pharmaceutical development	Univariate experiments	Multivariate experiments
Manufacturing process	Fixed	Flexible
Process control and control strategy	Slow and by initial intermediate and end product testing	Actual time, risk-based controls shifted upstream
Product designation	It is based on batch data	based on desired product achievement (safety and efficacy)

cline hydrochloride (1:1) is suitable for inhalation and highly effective against *Staphylococcus aureus*, *P. aeruginosa* and *Streptococcus pyogenes* [119]. A formulation consisting of highly porous nanoparticles loaded with tobramycin surrounded by a matrix composed of amorphous clarithromycin, with a median particle size of about 400 nm, was synthesized by high-pressure homogenisation. Interestingly, the results showed that the formulation of the combination of two antibiotics enhanced powder dispersion during inhalation. Local drug deposition profiles were almost similar for the antibiotics and reached the target site concurrently. The dissolution rate revealed that tobramycin and clarithromycin dissolve with ease in the lungs [93]. A formulation comprising ciprofloxacin hydrochloride and gatifloxacin (fourth generation of fluoroquinolone), prepared by the spray-drying method, showed a synergistic antimicrobial effect in the lungs [120].

4. Novel DPI formulation strategies and carriers for inhaled antibiotics

4.1. Preformulation and Quality by Design approach

The majority of research and innovation for pulmonary dosage forms of antibiotics does not achieve scale-up and marketing. The main reasons are the lack of feasible process, the inappropriate way for the efficient and effective control of changes, the inability to achieve reasonable product quality, the high cost with a low yield, the inability to predict effects of scale-up on the final product, the inability to analyze or understand reasons for manufacturing failures, and the large number of batch failure. Hence, Quality by Design (QbD) is necessary before every laboratory research, new formulation, particle engineering and powder formulation [121-124].

The pharmaceutical QbD is a systematic pathway for the development of a new formulation, which begins with a predefined formulation and indicates product and process understanding and process control, based on quality risk management [125]. QbD appears to enhance the assurance of safe and effective drug supply to the patients, and also attempts to significantly improve manufacturing quality administration. QbD principles have been used to regulate product and process quality in industry and have been approved by the FDA for the discovery, formulation and development of drugs [126]. Table III identifies some of the characteristic differences between conventional and experimental design QBD approaches.

So QbD ensures better design of products with fewer problems in manufacturing and allows for the better understanding of how APIs and excipients affect manufacturing. It also leads to a reduction in the overall costs of manufacturing, thus speeding up the process of approvals and accelerating scale-up production [127]. The specific design of the inhaler is very critical in achieving acceptable airflow to deposit the drug into the therapeutically effective region of the lungs [128]. DPI dosage form properties can be controlled by adjusting the particle size, size distribution, particle density, particle morphology and shape [129-131]. The Ishikawa diagram in Figure 3 illustrates the parameters influencing the quality of DPI products in general, assembling all the influencing parameters of the aimed DPI product [97].

An amikacin product for inhalation in CF patients was manufactured by spray-drying the pure drug, and the formulation exhibited great respirability and flowability. An experimental design was applied on the process in relation to six Critical Quality Attributes (CQAs) of the finished product and five Critical Process Parameters (CPPs). The application of the experimental design was set up to achieve amikacin powders with both emitted dose (ED) and fine particle dose (FPD), completely with high regulatory and scientific references [132].

The dry powder formulations of ciprofloxacin hydrochloride were prepared by the spray-drying method following the QbD approach. An advanced quality management method was used to predict the final quality of the product in relation to the QbD-based theoretical preparatory parameters. Dry powder inhalation formulation tests

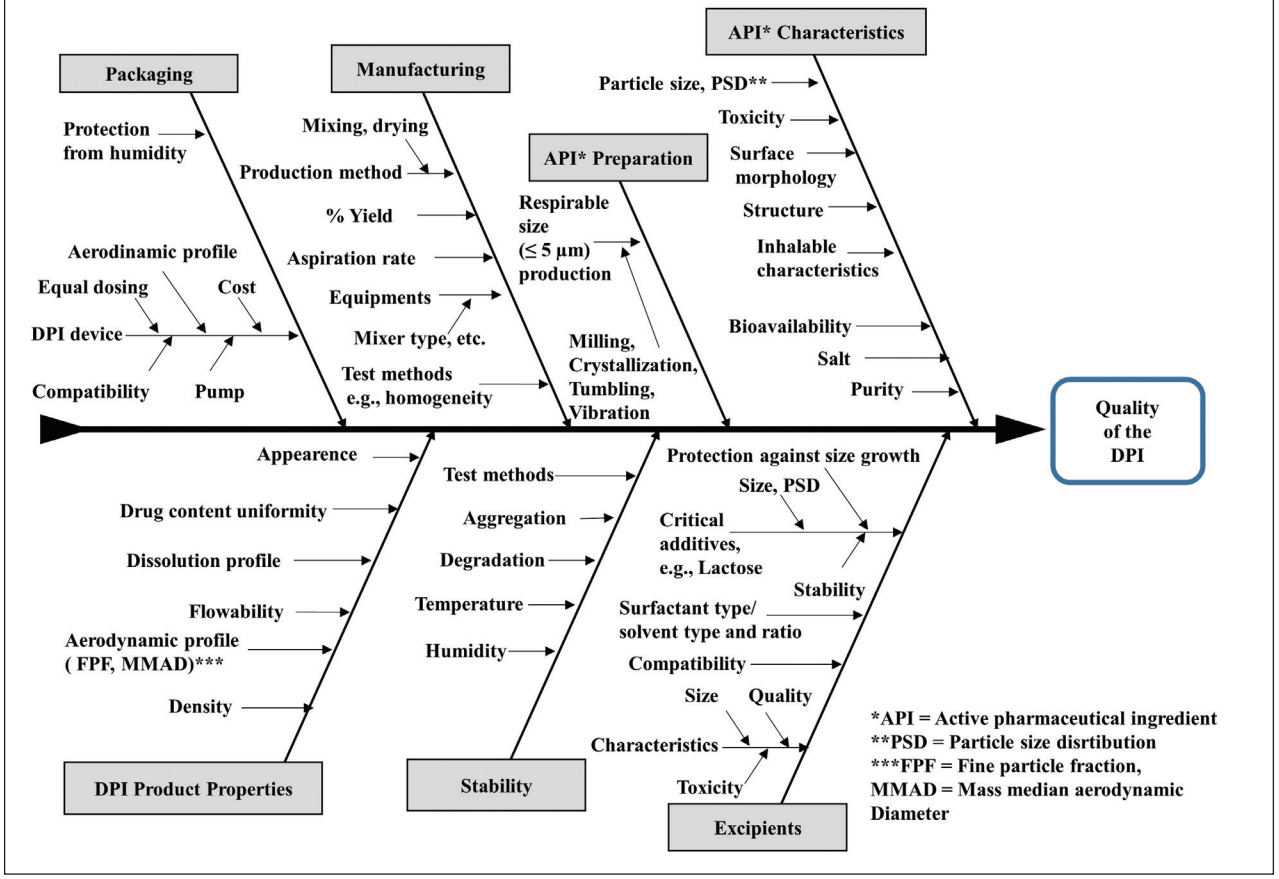

Figure 3 *Ishikawa diagram for DPI formulation in general*

were then successfully performed in practice [133].

4.2. Novel formulations and carriers for antibiotics

4.2.1. Microparticles

DPI formulations are usually comprised of micronized drug powder. One of the highest significant upgradations, in powder technologies from the micronization of large drug crystals into a respirable range for use in DPIs, is enhancing their dispersibility by the reduction of interior adhesive forces in the crystals [105]. Pharmaceutical industries have high demand for crystalline pharmacons. Most products for pulmonary dosage forms in the market are being manufactured in the crystalline state.

Crystalline drugs exhibit more stability; and for formulation development, thermodynamically stable polymorphs are selected. Salts are selected for their better solubility, purity and crystallinity relative to the neutral form [134]. For example, a DPI formulation was prepared with the sonicated solution of ciprofloxacin in acetone because of the very low solubility of neutral ciprofloxacin. In this formulation, L-leucine was used as a characteristic excipient [135]. In another DPI formulation, ciprofloxacin hydrochloride was used and the formulation preparation did not require a toxic organic solvent and a complicated method due to the high solubility of the salt form in water. A great advantage of the second formulation is that L-leucine can dissolve in water easily, too. In both cases the DPI showed excellent aerodynamic behavior with a fine particle fraction (FPF) value of more than 80% [133].

The conventional method of drug powder formulation in the microsized range involves crystallization followed by milling to reduce the particle size and to attain the suitable size. This method is not an appropriate method as it implies incomplete control over the particle size, size distribution, particle morphology and crystallinity. Mucoadhesive microparticles are able to swell and hydrate after deposition in the lung epithelial cells [136, 137]. The encapsulation of ciprofloxacin in chitosan is one such example, as the polymer has

swelling properties along with biodegradability and biocompatibility characteristics, and antibacterial and anti-inflammatory properties. Additionally, these swelling microparticles possess bioadhesive properties, promoting adhesion to the pulmonary system and enhancing antibacterial effect [136, 138].

For the microparticles to maintain sustained local antibacterial effect, they should avoid phagocytosis by alveolar macrophages. The particle size range that is optimal for pulmonary inhalation (1–5 μm) is also optimal for phagocytosis [139, 140]. Large porous microparticles, with low density but large geometric diameters, display ideal lung deposition profiles and can overcome phagocytosis challenges [141-143]. Spray-drying is generally used with different excipients like dipalmitoyl-phosphatidylcholine (DPPC) and albumin to produce large porous microparticles [144, 145]. Also, large porous microparticles can be produced by treating solid microparticles with supercritical CO_2 [146, 147]. Another interesting method for the production of large porous microparticles is the application of ammonium bicarbonate as an effervescent porogen, which decomposes into ammonia and carbon dioxide in an acidic aqueous solution or at high temperature [148].

Porous particles of tobramycin and ciprofloxacin produced by the emulsion method followed by spray-drying exhibited enhanced and satisfying flowability and aerosolization performance [149, 150]. A simple double-emulsion method using poly(DL-lactide-co-glycolide) polymer resulted in large porous biodegradable microspheres of capreomycin for pulmonary drug delivery. The morphology of particles displayed a highly porous interior and an outer rough surface [151].

4.2.2 Nanoparticles

Nowadays, nanoparticles are being widely investigated for antibiotic inhalation therapy [152], however, the formulation of nanoparticles for drug delivery application came to the fore in the 1960s [153]. The considerable advantage of nanoparticle formulations is that they improve the solubility and dissolution rate of water-insoluble antibiotics [154]. As an example, the nanoparticles of ciprofloxacin exhibited a speedy dissolution profile compared to the supplied ciprofloxacin powder. Besides, this formulation of nanoparticles of antibiotics enhanced the Minimum Inhibitory Concentration (MIC) and antibacterial activity. It was also observed that amikacin nanoparticles exhibit MIC and a bacteriostatic effect against *P. aeruginosa* compared to less than half of the values for free amikacin [155, 156]. Due to their small size and large surface area, the nanoparticles of the antibiotic showed significant and enhanced aerodynamic behaviour. An example of tobramycin nanoparticles can be noted where the formulation exhibited an FPF of 61% compared to the microparticles of tobramycin with an FPF of 36% [157].

On the other hand, nanoparticles act as foreign materials, with special physiochemical properties, in human bodies and are recorded to have severe adverse effects on the lungs, like inflammation, fibrosis and mutations along with oxidative stress. Further, these damages could cause pulmonary diseases and diseases in the other parts of body [158]. Inhaled nanoparticles can be exhaled because of their extremely low mass. These problems have been rectified by formulating nanoparticles into inhalable microparticles into a matrix or carrier system. These matrices can be synthetic polymers such as PVA, PVP and PLGA; amino acids like L-leucine; or polysaccharides such as chitosan and sodium hyaluronate [159-161].

4.2.3. Solid lipid microparticles and solid lipid nanoparticles

The incorporation of lipid into formulations brought about the development of porous particles with low density [162, 163]. There are various methods which have been reported for the synthesis of solid lipid microparticles (SLM) and solid lipid nanoparticles (SLN) [164]. Some of these methods are double emulsion solvent evaporation with freeze-drying [165], high pressure homogenization followed by spray-drying [166-168], melt emulsification followed by spray-drying [169], melt emulsification followed by freeze-drying [170, 171] and simple spray-drying [144]. SLNs usually have a spherical shape consisting of a solid lipid bulk stabilized by a surfactant. Biological membrane lipids such as phospholipids, and sterols (cholesterol) can be applied as stabilizers [172]. The most important advantages of SLNs from the pulmonary perspective include the possibility of large-scale production and ability of the incorporation of lipophilic and hydrophilic drugs, lack of biotoxicity of the carrier, high loading capacity, drug target delivery and controlling drug release [173].

Table IV *Different DPI formulations with their therapeutic outcome*

Therapeutic agent	Method	Characteristic Excipient	Particle size	Resulting therapeutic outcome
Ciprofloxacin and doxycycline	Spray-drying method	PVA*	Microparticle	Controlled release antibiotics [94].
Levofloxacin	Nanoprecipitation/emulsification–solvent evaporation methods	PLGA**/PCL***	Nanoparticle	Improved antibacterial efficacy [188].
Levofloxacin	Emulsification–solvent evaporation method	PLGA**/phosphatidylcholine	Nanoparticle	Improved antibacterial efficacy [189].
Tobramycin	Emulsion/solvent diffusion method	PLGA**/PVA*/ chitosan/alginate/ lactose	Nanoparticle	Increased encapsulation efficiency/release rate/lung deposition pattern [190].
Amikacin	Solid-lipid coated by solvent diffusion method/ freeze-drying	Sucrose/ Dextrose/Mannitol	Nanoparticle	Long-release term/antibacterial efficacy [159] [160].
Ciprofloxacin	Sonicating/freeze-drying	L-Leucine	Nanoparticle	Increased the dissolution rate/ improved aerodynamic properties [139].
Ciprofloxacin hydrochloride	Spray-drying	L-Leucine/PVA*/ Cyclodextrin	Microparticle	Enhanced the aerodynamic behaviour [137].
Tobramycin	High-pressure homogenisation/spray-drying	Sodium glycocholate	Mixture of micro- and nanoparticles	Enhanced lung deposition [161].
Ciprofloxacin	Self-assembly method	Chitosan/PEG	Loaded nanoparticle in micro hydrogel particles	Suitable aerodynamic characteristics/sustains drug release [140].
Ciprofloxacin	Emulsion/spray-drying	_____	Microparticle	Enhanced tolerability assessments [153].
Ciprofloxacin	Anti-solvent precipitation method/spray-drying	_____	Microparticle	Enhanced aerosol performance [191].

*Poly-vinyl alcohol **poly(lactic-co-glycolic acid) ***Polycaprolactone

4.2.4. Liposomes

Discovered by Dr. Alec Bangham in 1961 [174], liposomes seem to be a relevant and useful choice for pulmonary drug delivery considering their preparation from components compatible with the lungs, with a good safety profile. Arikayce is the first liposomal preparation clinically approved for pulmonary administration. No marketed inhaled liposomal antibiotic preparation was available previously [175]. Liposomal formulations of inhaled antibiotics are considered to be sustained drug delivery systems due to their low and slow solubility. These formulations prolong the action of drug in the infectious part and increase the antibacterial effect. On the other hand, the sustained release of antibiotics minimizes dosing frequency and thereby enhances patient compliance. Liposomal antibiotics can also act as targeted drug delivery systems [176]. The encapsulation of drugs in liposomes also reduces the occurrence of local irritation as that caused by traditional pulmonary dosage forms. Overall, these benefits of liposomal formulations make them an appropriate drug delivery system for antibiotics. The surface-mannose modification of liposomes with mannose promotes the active targeting of macrophages with mannose receptors and provides efficient aerosolized liposomal delivery [177]. Liposome formulations can be administered in a liquid dosage form, e.g. nebulizer. However, some solid preparations prepared by spray-drying or spray freeze-drying can be designed as DPIs [178].

Liposomes are formed immediately when lipids are hydrated in contact with water and then dried afterwards to form spheres. Generally, in a large scale-up process, lipids are first dissolved in an appropriate solvent (mixture of water, ethanol and the other organic solvent in a different ratio) and then rotatory evaporation removes the solvent. A thin layer of lipid film is formed on the wall usually in multilamellar vehicles (MLVs) [179-181]. Another method is the ethanol injection method, in which liposomes are formed after the

injection of the organic phase into the aqueous phase and then by applying diafiltration or ultrafiltration to remove the excess solvent [182, 183]. The possibility of encapsulating hydrophilic and lipophilic drugs and easy scale-up are major merits of this method.

A few DPI formulations with their therapeutic outcomes are mentioned in Table IV.

5. Patient History

The efficacy and tolerability of nebulized antibiotics in trials remain low and only involve a single center or are confounded by inadequate patient enrollment, poor methodology, failures in standardizing or reporting delivery methods, and particle sizes. Different studies have used different doses or formulations as well as differing patient cohorts. Hence, there is no standardized technique for the administration of a given aerosolized drug. These factors make the comparison of efficiency and tolerability difficult and pose challenges when trying to standardize this method of treatment and in establishing best practice [184]. Studies of inhaled antibiotics targeting non-CF pathogens for suppression, eradication or prophylaxis are scarce [75], and no inhaled antibiotics are approved for lungs in non-CF infections, including COPD, melioidosis, pneumonic plague, anthrax, Q fever, tularemia, and for patients with other infections, including non-tuberculous mycobacteria. Despite the need, limited ongoing studies are observed for the dry powder form of vancomycin assessing the efficacy and safety of suppressive therapy for methicillin-resistant Staphylococcus aureus (MRSA) infection. The only recommended prophylactic strategy available is the chronic prophylaxis to prevent the acquisition of S. aureus, which is used primarily in the UK [185].

6. Future perspective and conclusion

Inhalable powders in the form of nanoparticles have potential as a treatment option of respiratory tract infections. Targeted delivery is possible by the optimization of formulation parameters, and new nanoparticle formulation strategies that may enhance safety, stability, dispersion and deposition.

Liposomal formulations of inhaled antibiotics are advanced drug delivery systems designed for sustained drug release and targeted drug delivery to the lungs; nevertheless, low stability and difficulty in liposomal DPI production are notable issues. In this field new techniques and strategies are necessarily required to overcome the challenge of instability of most liposome formulations.

In the development of combination therapy, it is possible to create novel technological methods to design a combination of antibiotics in which each particle can have several layers made of different antibiotics with different bactericidal activities. In this way, resistance by bacteria can be reduced, and therefore a new dimension to antibiotic treatment can be explored.

Inhaled antibiotics for the treatment of respiratory tract infections have a great and long history; however, these therapies focus on CF patients. Right now, there is no academic indication for using inhaled antibiotics for the treatment of non-CF patients. Hence, prescriptions for patients with non-CF respiratory infection will continue to be based on oral or parenteral dosage forms until scientific evidence from progressing clinical trials become available. Literature data concerning non-cystic fibrosis patients in the next years will explain much. Pulmonary dosage forms of antibiotics show interesting results due to high drug concentrations in the respiratory tract with minimum systemic drug exposure. However, the formulation of antibiotics for pulmonary dosage forms is relatively complicated. Antibiotics are administered in higher doses than the other therapeutic agents for asthma or other inflammatory diseases. DPIs have also been favored in recent years for the delivery of inhaled antibiotics. The particle engineering technique is a key factor to improve inhalable formulations that are able to deliver the drug with advanced therapeutic effect. Advanced particle engineering techniques are also being employed to revise the manufacturing of DPI formulation for delivering antibiotics. Pulmonary delivery systems for the treatment of viral lung infections are completely absent, and this area should be explored to develop potent antiviral therapies.

Disclosure

The authors report no conflict of interests in this work.

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