ABSTRACT

Tuberculosis (TB) caused by Mycobacterium tuberculosis (Mtb) is a major health problem and has been a cause of human suffering for 70,000 years [1]. According to the latest report by world health organization (WHO) Mtb is the leading cause of mortality arising as a result of infectious diseases [2]. The WHO global health report of 2018 estimated about 1.4 million cases of TB worldwide in 2016 accounting for about 140 TB cases per 0.1 million population. About 10% of these cases were reported in HIV-infected patients whereas 0.49 million people developed multidrug-resistant. The same report states that TB accounted for about 1.67 million deaths in the same year [3]. The clinical approach followed worldwide to treat TB involves use of Directly Observed Treatment Strategy (DOTS) [4]. This practice involves use of first line and second line anti-tubercular drugs containing high doses for about 6-9 months depending upon the bacillary load. However, the use of anti-tubercular drugs containing high doses of the drugs often fails to sterilize the lung tissue of the bacillary load besides inflicting strong adverse effects like vision loss and muscle wasting. In this review, we present a simple but a rationale strategy to treat pulmonary tuberculosis that not only claims to sterilize the airways by delivering the drug directly to the lung tissue but also minimizes other systemic toxic effects. Dry powder inhalations are polymeric or excipient less particle based anti-tubercular formulations that can be inhaled directly via mouth to reach deep lung airways and at the same time phagocytised by the infected macrophage to deliver high payload of the anti-tubercular drugs.

Pulmonary Tuberculosis

Based on the anatomical location, TB is classified as pulmonary TB and extra pulmonary TB. Pulmonary tuberculosis is caused by inhaling droplets of Mtb bacilli into the lung airways and thereby colonizing the lung macrophage to establish primary site of infection [5]. In pulmonary TB, the bacterium inhabits the lungs and induces granulomatous lesions. Extra pulmonary TB occurs in organs beyond lungs such as bone, joints, brain, genitourinary tract, lymph nodes, uterus, intestine etc. TB spreads through droplets containing Mtb[6]. When an infected person sneezes or coughs, the expired aerosol contains bacteria. If these “droplet nuclei” are inhaled by any person nearby, he or she is likely to get infected. In the lungs, Mtb colonizes macrophages, although these cells have evolved to engulf and digest any microbe or particulate matter depositing on the lung epithelium. The ability of the Mtb to survive inside macrophages is due to its ability to modulate the innate and acquired immune response as it resides in lung macrophages[7]. This is the reason that majority of the TB cases are of pulmonary origin (75-80%) as compared to extra pulmonary TB[8].

Dry Powder Inhalations: A pharmaceutical approach to treat pulmonary tuberculosis

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INTRODUCTION

Tuberculosis (TB) caused by Mycobacterium tuberculosis (Mtb) is a major health problem and has been a cause of human suffering for 70,000/years [1]. According to the latest report by world health organization (WHO) Mtb is the leading cause of mortality arising as a result of infectious diseases [2]. The WHO global health report of 2018 estimated about 1.4 million cases of TB worldwide in 2016 accounting for about 140 TB cases per 0.1 million population. About 10% of these cases were reported in HIV infected patients whereas 0.49 million people developed multidrug-resistant. The same report states that TB accounted for about 1.67 million deaths in the same year [3]. The clinical approach followed worldwide to treat TB involves use of Directly Observed Treatment Strategy (DOTS) [4]. This practice involves use of first line and second line anti-tubercular drugs containing high doses for about 6-9 months depending upon the bacillary load. However, the use of anti-tubercular drugs containing high doses of the drugs often fails to sterilize the lung tissue of the bacillary load besides inflicting strong adverse effects like vision loss and muscle wasting. In this review, we present a simple but a rationale strategy to treat pulmonary tuberculosis that not only claims to sterilize the airways by delivering the drug directly to the lung tissue but also minimizes other systemic toxic effects. Dry powder inhalations are polymeric or excipient less particle based anti-tubercular formulations that can be inhaled directly via mouth to reach deep lung airways and at the same time phagocytised by the infected macrophage to deliver high payload of the anti-tubercular drugs.

five or more drugs, at least one of which is given by intramuscular injection[10]. High amount of drug required for the treatment of tuberculosis and other diseases like chronic obstructive pulmonary tuberculosis (COPD) or asthma is serious scenario often accompanying serious adverse events. The local administration of antibiotics at this site of infection (lungs) achieves high concentration of drug as well as reduces systemic side effects as compared to oral and intravenous delivery. It has been established that a single dose of rifampicin (30 mg) given as an inhalation demonstrated superior efficacy over a 500 mg oral dose[11]. The amount of drug concentration (antibiotics) achieved in alveolar macrophages via inhalation delivery achieved 113 fold higher concentration as compared to the oral dose of the same drug [12]. Particulate systems containing antibiotic drugs designed in such a way to release the drug in a sustained manner may decrease the drug dose as well as dosing frequency, however, these formulations are often found to promote drug resistance [13]. The formulation of micro particles including drug with carrier excipient or without excipient and higher drug payload result in an overall increased mass of macro particles. This a serious pharmaceutical problem resulting in high amount of powder adherence to lung tissue prompting challenges of drug clearance from the lung vasculature.

Current Treatment Regimen for tuberculosis

Drugs for TB management are broadly classified as first-line and second-line drugs on the basis of their efficacy and relative toxicity. First-line drugs are those which are more efficacious, comparatively safe and have low toxicity profiles. Second-line drugs generally against drug-sensitive strains of Mtb and display greater toxicity. They are used for drug-resistant TB only because the infectious strains are no longer sensitive to first-line drugs. The decision to use the second line drugs is taken on the basis of treatment guidelines issued by the WHO. Drug-sensitive infections are treated first by H, R, Z, E and/or streptomycin (S) for two months in intensive phase followed by four months continuous phase with two drugs H and R. With the exception of S, which is given intramuscularly all other drugs are administered orally [10]. If drug resistance develops during the treatment or the patient is infected with drug-resistant strain, then first-line drugs are stopped and second-line drugs are included in the regimen. Capreomycin, kanamycin, and amikacin are given as injectable while fluoroquinolones, p-aminosalicylic acid, D-cycloserine, terizidone, and ethionamide are given orally. WHO recommended regimen for MDR-TB consists of combination therapy with three agents from group A (Levofoxacin/moxifloxacin, bedaquiline and linezolid) and one or two agents from group B (cloxafamine and cycloserine/terizidone) in cases where drugs from Group A or B are not efficacious, drugs from group C (ethambutol, delamanid, Z, imipenem-cilastatin, amikacin / streptomycin, ethionamide / prothionamide or p-aminosalicylic acid) are included in the regimen. The classification of group A, B or C is based on the efficacy of anti-TB agents. Group A consists of highly efficacious and strongly recommended agents, group B is the second choice while group C is used on the basis of relative risk and gain analysis. A treatment duration of 18-20 months is recommended which consists of a continuation phase of up to 15-17 months after culture conversion [12].

The Rationale for Inhalation Drugs Delivery

TB infections are mainly caused by aerosol inhalation; it would be wise to choose the same route for drug delivery so as to follow the same pattern of bio-distribution. For pulmonary TB inhalation drug delivery can be a route for delivery of anti-TB drugs. This route is helpful in the reduction of dose (avoids first pass metabolisms), providing a non-sterile formulation for non-invasive drug delivery and targeting drugs to the site of infection. If inhaled drugs are largely retained in the lungs, systemic toxicity can be reduced. The particle containing the anti-TB drugs will either be engulfed by alveolar macrophages or will release the drugs by dissolving in lung surfactant and rapidly releasing the drug content in the vicinity of the bacterial population [11]. Pulmonary drug delivery aims to:

- Deliver higher concentration of drugs in lungs, the site of action in comparison to conventional routes.
- Reduce the dose and duration of administration.
- Good patient compliance.
- Avoids first pass metabolism.

However, despite being meritorious, the inhalation therapy for tuberculosis has not been established yet.

Dry Powder Inhalations

The inhalation of the aerosols in clinical use can be accomplished by inhaling smoke, using a nebulizer or more conveniently using a metered dose pressurized inhaler. The dry powder inhalations represent a midway aerosol generation mechanism between nebulization and pressurized devise inhalations. The Dry powder inhalations can be inhaled either in an aqueous or gaseous external medium under positive pressure; the pressure being generated by the inward drawn air turbulence of the patient. Dry powder inhalations formulations administered to asthmatic, pulmonary tuberculosis or cystic fibrosis patients have been found to deliver higher amount of drugs to deep lung airways[10-13]. After administration of dry powder via inhalation the microparticles deliver to the lungs airways and rapidly phagocytised by alveolar macrophages. This process of particles eating is advantageous in diseases like pulmonary TB as it will deliver high load of drug encased particles directly into the niche of Mtb, i.e. the infected macrophages. Therefore particle based therapy to treat TB not only delivers high payload for bacilli sterilization but also ensures drug targeting and therefore minimized systemic side effects associated with antibiotic drugs. Furthermore, microparticles based inhalation therapy has the potential advantage of shortening treatment duration and lowering dose frequency thus improving patient compliance. Mono-drug therapy is not recommended for treatment of TB due to rapidly developing drug resistance [9]. Various authors have reported developing inhalable microparticles including two of the first anti-TB drugs, H and R. The dry powder inhalation contained H and R in the ratio of 1:3. Cmax values of R reach 9.2 µg/ml, and H attained a value of 1.7 to 3 µg/ml. These results suggest that lungs act as a capacitor to store drugs and then dispose to general circulation [8].

Role of inhalation therapy for diseases other than pulmonary disorders

The inhalation therapy is a very important and unique route for administration of antibiotics or drug for treatment of a number of pulmonary diseases. Inhalation routes have also been explored for systemic delivery of drugs that shown low bioavailability after administration via oral route. This route of delivery also prevents first pass metabolism and is also suitable for the drug candidates that require high oral dose to achieve therapeutic concentration in the plasma [12]. In inhalational drug delivery higher drug concentration is maintained at site of action or organ (lungs) through direct delivery. Thus, a very low amount of inhalable particles are used to achieve high bioavailability besides minimising systemic adverse effects. In addition, an inhalation route can provide a very fast onset of action compared with other routes of administration [7]. The pulmonary route is also considered a very effective and efficient route for diseases other than respiratory disorders. One such approach of effectively and safely delivering peptides such as insulin was found to be highly efficacious in improving hyperglycaemia [8]. The
Factors the influencing bioavailability of inhalation drug delivery systems

Various pharmaceutical factors like particle size, aerodynamic diameter of particle and porosity affect the bioavailability of drug. These factors also determine the ability of the drug to reach deep lung airways and hence accumulation of the drug particles in different anatomical regions of the airway. Here we discuss several factors that greatly influence the bioavailability and deposition of inhaled drugs [2].

Dispositions of inhaled formulation:

The lung is a highly perfuse organ and contains about 15 ml of the surfactant solubilised fluid necessary for the solubilisation of the inhaled drug particles. The surface area of the lungs is also very huge (>100 m2) allowing perfusion of the drugs at a very fast rate resulting in higher bioavailability. The inhaled particles reaching lung airways either are dissolved in the lung surfactant to release the drug payload or the particle remain insoluble the lung fluid and are fated to be taken up by the circulating lung macrophages. The solubilised drug in the lung surfactant is then absorbed into the systemic circulation for further distribution in other tissues including redistribution in the lung vasculature. The macrophages also play an important role to determine the fate of the polymeric excipients and intact particles by the process of phagocytosis [7].

Flow properties:

The dry powder inhalations should have good flow property to ensure better performance as well as deposition at the targeted site. Good powder flow is also necessary for efficient filling of the empty capsule shells by the filling machine. The flow properties also play an important role in determining the deposition of the particles in different anatomical regions of the lung. Particles of size less than 5 µm are suitable for deep lung delivery. The enhancement of powder flow properties by particle engineering techniques by spray drying techniques produces low density particles (0.3 g/ml) which are very suitable for deep lung delivery. Suitable use of flow enhancers like L-leucine are used to improve the flow properties of the spray dried particles by introducing the amino glass in the feed solution [8]. Stearic acid has been used in many dry powder formulations to improve the flow properties besides reducing hygroscopic nature of the particles, film forming capability and acting as a bulking agent [11,12].

Alveolar macrophage uptake:

There is significant evidence that alveolar macrophages can engulf particles as large as 90 µm [1], however, size suitable for phagocytosis by alveolar macrophage is between 1-10 µm [2]. The particles for the macrophage uptake should have at last some integrity so that they are not solubilised in the lung surfactant [13].

Particle size

In pulmonary drug delivery the particle size produced by different process determines the deposition of these particles at various sites of the airways and hence the availability the drug these sites. In general a particle size of range between 1-5 µm is considered suitable for deep lung delivery [12]. Shape and surface characteristics of the inhalable particles is also considered very important for macrophage uptake [10,11]. Generally particles with hydrophobic surface or composed of hydrophobic polymers like poly (lactic-co-glycolic acid) or poly (l-lactic acid) are considered very suitable for macrophage uptake [13]. In fact macrophage uptake of the particles is considered to be regulated by hydrophobic interactions with polymeric particles. It is also being argued that shape of the particles also influences macrophage uptake, however, contacting surface area between the particle and the macrophage will determine the up regulation of the uptake process. Lucila Gracia et. al. have demonstrated that elliptical geometry of the particles or acicular shape of the inhaled is suitable for macrophage uptake [3]. The inhaled particles are deposited in the respiratory tract by either impaction, sedimentation or interception in different regions of lung airways. However, it’s the size of the particles that determine the travelling journey inside the lung airways.

Mass median aerodynamic diameter and geometric standard deviation

The mass median aerodynamic diameter (MMAD) of a particle is defined as the diameter of an imaginary sphere with a unit density (1 gcm–3) that will settle under gravity with the same velocity as that of the particle under investigation. The theoretical MMAD of a particle is calculated using the following equation:

\[ ae = \chi \]

Where, dae is aerodynamic diameter, \( \rho_t \) is tapped density, and \( \chi \) is the shape factor. The shape factor is calculated with the respect to the shape of a perfect sphere. For non-spherical particles, the value of the shape factor value varies between 1.1 to 1.75 mm. MMAD of the particles less than 5 micron show good deposition into lung airway and is considered as an advantageous factor for deep lung delivery. However, the dispersion of these particles is difficult whilst using a pressurized metered devise. In dry powder inhalations, MMAD has implications in predicting the pattern of the deposited particles based on the size. Microparticles with MMAD value less than 5µm (range 1–5µm) are considered suitable for delivery to apical ends of the bronchial tree. Particles of these MMAD characteristics will be deposited in deep bronchial regions by impaction However, particles with MMAD >5µm can be deposited in bronchial regions via impaction but an additional mass factor of the inhaled particles also to be considered [3]. Aerodynamic characterization of particles besides using theoretical principles can also be calculated experimentally using a multistage cascade impactor that mimics a natural bronchial tree in distribution and deposition of the inhaled particles. The devise comprises of different stages with effective cut-off diameter at each corresponding stage. The powder is inspired in the devise at a specific flow rate. The particles in the powder then circulate in the devise and are deposited at different stages based on the effective cut-off diameter. MMAD, Fine Particle Fraction (FPF), and in-vitro lung deposition are then calculated by plotting a regression curve between percentage cumulative undersize vs. effective cut-off diameter at each stage of the cascade impactor. The effective cut-off diameter corresponding to 50% cumulative undersize on a best-fit log probability graph is taken as MMAD. Geometric Standard Deviation (GSD) is calculated using the formula below:

\[ \text{GSD} = \frac{d_{84}}{d_{16}} \]

Where, \( d_{84} \) = 84% undersize particles, \( d_{16} \) =16% undersize particles.

Techniques for formulating inhalable micro particles

Lyophilisation or freeze-drying method

Lyophilisation or freeze drying is a process in which water is sublimed directly from the vapour phase to the solid ice phase without the formation of the intermediately liquid phase. The process of lyophilisation is utilized to
The process of lyophilisation comprises of three essential steps:

(i) Generation of droplets
(ii) Primary freezing
(iii) Sublimation drying

The process of lyophilisation is often applied to produce porous and dried particles formulated by either solvent evaporation emulsion technique or spray freeze drying. The process however can cause physical damage to the integrity of the particles due to working of the process at very low temperatures (−50°C to −54°C). These problems are often associated with drug leakage from the particles or change in the vesicle shape. However, the use of cryoprotectants like mannitol, amino acids can solve this problem.

Spray-freeze drying:

 Parsian et al., formulated inhalable microparticles containing budesonide, an inhalable corticosteroid by spray freeze-drying method[39]. The formulated microparticles were prepared using hydroxypropyl beta-cyclodextrin (HP-β-CD) and L-leucine glass formers. These particles were porous in nature and had demonstrated considerable aerosolization performance in terms of MMAD, FPF and pulmonary deposition. In another study, Poursina Narges et al. prepared particles of parathyroid hormone using spray freeze drying process[4]. The inhalable particles were evaluated for aerodynamic behaviour as a function of L-leucine and HP-βCD content. Efficacy comparison of the inhalable hormone with the injection suggested outperformance of the respirable particles.

Spray drying

Spray dried formulations are the most commonly used inhalable particles for us in various pulmonary diseases including pulmonary TB. The process of spray drying involves atomization of a solution or suspension of a drug via a nozzle under high pressure into a preheated chamber. The atomized solution dries while spraying leaving dried particles to be classified by the cyclone separator. The spray dried particles are sucked into the cyclone separator to separate the small particles from the larger ones and the useful fraction is taken in a collector. Most of the dry powder inhalation reported in literature have been prepared using this technique. The microparticles formulated using this technique have a narrow size of distribution, appropriate MMAD for pulmonary delivery and a smooth morphology resembling more like spheres to hemispheres [12]. Rajeev et al., prepared and optimized particles of ethionamide and d-cycloserine using spray drying process by exploring a central composite design[4]. These particles had a MMAD of 1.73µm, suitable for deep lung delivery. The authors also demonstrated using a mass balance approach to show that major proportion of the particles produce by spray drying process are lost to the outlet filter, prompting challenges to minimize the loss and increase product output. The spray dried particles have not been only used for delivery of drugs used in pulmonary disorders but have been put in utility in other diseases like cancer. In this context, Wu et al., spray dried particles of tacrolimus, a chemotherapeutic used in cancer for deep lung delivery. Laser diffraction studies showed that these particles were of amenable size (1.29–1.62µm) to deliver the drug payload in deep lung tissues[2]. Similarly, bacteriophages have been spray dried to produce dry powder inhalations for treatment of pulmonary tuberculosis by incorporating L-leucine as a glass former and sodium casein as a surfactant [3]. The study is interesting in the context that low temperatures were used to process the bacteriophages in order to prevent loss of viability occurring during high temperature driven drying process. In another study, Dimmer et al., demonstrate the efficacy of resveratrol loaded poly-caprolactone particles prepared by spray drying process in pulmonary hypertension [4]. The study make use of vibrational atomization to produce particles of smooth morphology with a MMAD of 2.32 µm. The feed was sprayed to produce particles using vibrational atomization and different parameters like MMAD, FPF and release pattern were investigated.

Supercritical fluid (SCF) Technology

Supercritical fluids are gases that have been highly compressed into liquids at a temperature and pressure below the critical point. At temperatures and pressure below the critical point the gases behave like liquids when held at lower pressures and assume the gaseous state when the pressure is released. This property of various critical fluids like carbon dioxide has been utilized to dissolve many drugs and polymers below the critical point. The vice versa is also true where the supercritical fluid can act as a non-solvent. In the both the cases fine microparticles can be obtained while changing the pressure or temperature of the fluid to alter the state into gaseous form resulting due to rapid expansion of the supercritical fluid. The technique has been put into utility to produce particles with size as small as 3µm [5]. Kim et. al., have utilized this process to micronize the ipratropium bromide using CO2 as a supercritical fluid [9]. The drug particles produced by this technology were in the size range of 2–3 µm and are suitable for deep lung delivery. Similarly, Patomchaivivat et. al., used a supercritical anti-solvent process to formulate inhalable microparticles of poly(L-lactide) loaded with rifampicin for treatment of pulmonary tuberculosis [7].

Conclusion

The route of administration dry powder inhalation through the pulmonary route is very beneficial for the local and systemic effects. This route delivery of drugs to targeted organs lungs having the large surface area of the lungs and low enzymatic activity. Whenever, the challenges associated with the pulmonary route via inhalation are lung clearance mechanisms, fast metabolic degradation, and systemic absorption [8]. Thus, to overcome these shortcomings, various strategies, such as particulate drug delivery, are being used. Inhalational therapy not only offers advantages to overcome these challenges, but also facilitates local systemic delivery for the treatment of various pulmonary and non-pulmonary disorders[9]. Based on recent advances, it also has the inhalation therapy potential to improve the dose reduction, reduce systemic side effect and improve patient compliance resulting in enhanced therapeutic outcomes as well as reduce duration of treatments for, and improved quality of life of, patients[5].

REFERENCES


