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REVIEW ARTICLE

LUNG TARGETING OF ANTITUBERCULAR DRUGS BY MICROSPHERE: A REVIEW

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ABSTRACT

Targeted drug delivery system or site-specific drug delivery systems are systems that can deliver the drug selectively to the diseased site, in a specified steady concentration, for a prescribed time. This site specific or targeted delivery combined with delivery at an optimal rate would not only improve the efficacy of a drug but would also reduce the possibility of unwanted toxic side effects of the drug, thus improving the therapeutic index. The lung is an attractive target for drug delivery due to noninvasive administration via inhalation aerosols, avoidance of first-pass metabolism, direct delivery to the site of action for the treatment of respiratory diseases, and the availability of a huge surface area for local drug action and systemic absorption of drug. Microspheres are spherical & free flowing particles ranging in average particle size from 1 to 50 microns which consist of proteins or synthetic polymers. Some of the problems of overcome by producing control drug delivery system which enhances the therapeutic efficacy of a given drug. One such approach is using microspheres as carriers for drugs. This review focuses on the current status and explores the potential of microsphere carrier systems in pulmonary drug delivery with special attention to their pharmaceutical aspects.

Keywords: Lung Targeting, Pulmonary Microspheres, Inhalable Microspheres, Antitubercular drug microsphere

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INTRODUCTION

Several particle engineering technologies have recently emerged, which have enabled inhaled microspheres to seek to manipulate pulmonary biopharmaceuticals, and to improve therapeutic efficacy for both local and systemic treatments. These microspheres may be designed to sustain drug release, to prolong lung retention, to achieve drug targeting and/or to enhance drug absorption and thereby, to seek the potentials of reducing dosing frequency and/or drug dose, while maintaining therapeutic efficacy and/or reducing adverse effects. While product development is still in process, in many cases, considerable therapeutic benefits[1]. Pulmonary tuberculosis remains the commonest form of this disease and the development of methods for delivering antitubercular drugs directly to the lungs via the respiratory route is a rational therapeutic goal. The obvious advantages of inhaled therapy include direct drug delivery to the diseased organ,

targeting to alveolar macrophages harbouring the mycobacteria, reduced risk of systemic toxicity and improved patient compliance. Research efforts have demonstrated the feasibility of various drug delivery systems employing liposomes, polymeric microparticles and nanoparticles to serve as inhalable antitubercular drug carriers. In particular, nanoparticles have emerged as a remarkably useful tool for this purpose[2]. The terminology “microparticle” (size comprised between 1 and 999 μm) includes the microspheres (uniform sphere constituted of a polymeric matrix) and the microcapsules (container constituted of an oily core surrounded by a thin polymeric membrane).Biodegradable microspheres, designed from natural or synthetic polymers, have been largely used as drug targeting systems via different routes. Hydrophilic and lipophilic molecules can be encapsulated or incorporated into microspheres. Compared to liposomes, microspheres have an in vivo and in vitro more stable physicochemical behaviour and should allow a slower release and a longer pharmacological activity of the encapsulated drugs[3,4]. Biodegradable microspheres are prepared by using varied polymers: albumin, chitosan, polysaccharide, poly(lactic-co-glycolic) acid, poly(lactic) acid, poly(butylcyanoacrylate) and poly(lactic-co-lysine graft lysine). Microspheres can be produced following different requirements such as the morphology, the size and the porosity by varying different technological parameters during their preparation. Microspheres are less hygroscopic and are then less liable to swell in the presence of moisture located into the lungs.[5] The rate of drug release from the microspheres dictates their therapeutic action. Release is governed by the

molecular structure of the drug and the polymer, the resistance of the polymer to degradation, and the surface area along with the porosity of the microspheres. The internal structure of the microspheres can vary as a function of the microencapsulation process employed. Controlled drug release from microspheres occurs by diffusion of the drug through a polymeric excipient, diffusion of the entrapped drug through the pores in the polymeric microspheres.[6]

A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug .To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects[99]. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm[100].

POLYMERS ARE USED FOR MICROSPHERE

They are classified into two types

1. Synthetic Polymers

2. Natural polymers

1. Synthetic polymers are divided into two types.

a. Non-biodegradable polymers

e.g. Polymethyl methacrylate (PMMA)

Acrolein

Glycidyl methacrylate

Epoxy polymers

b. Biodegradable polymers

e.g. Lactides, Glycolides & their co polymers

Poly alkyl cyanoacrylates

Poly anhydrides

2. Natural polymers obtained from different sources like Proteins,

Carbohydrates and chemically modified carbohydrates.

Proteins: Albumin, Gelatin, and Collagen

Carbohydrates: Agarose, Carrageenan, Chitosan, Starch[101]

METHOD OF PREPARATION OF MICROSPHERES

1. Protein gelation technique.
2. Single Emulsion polymerization technique.
3.Double Emulsion polymerization technique.
4. Multiple emulsion polymerization technique.
5. Solvent evaporation technique.
6. Sonication technique.
7. Spray and freeze drying technique.
8. Emulsification-heat stabilization technique.
9. Quasi-emulsion solvent diffusion method of the spherical crystallization technique.
10. Spray congealing
11. Phase separation coaservation method
12. Polymerization technique
13. Solvent extraction method [99]

NEED OF DRUG TARGETING

Antitubercular inhaled therapy has come a long way to a stage of experimental reality with potential clinical applications. The importance of the subject stems from the fact that tuberculosis (TB) continues to be a leading killer disease causing 3 million deaths annually[7,8] and has emerged as an occupational disease in the health care system.3 Oral therapy using the currently employed antitubercular drugs (ATDs) is very effective, but is still associated with a number of significant drawbacks. More than 80% of TB cases are of pulmonary TB alone and high drug doses are required to be administered because only a small fraction of the total dose reaches the lungs after oral administration. Even this small fraction is cleared in a matter of a few hours thus explaining the necessity to administer multiple ATDs on a regular basis, a regimen which the majority of TB patients find difficult to adhere to. Clearly, ATD delivery systems which can be administered via the pulmonary route and can avoid the daily dosing, would be a vast improvement because they would help in: (i) direct drug delivery to the diseased organ; (ii) targeting to alveolar macrophages which are used by the mycobacteria as a safe site for their prolonged survival; (iii) reduced systemic toxicity of the drugs; and (iv) improved patient

compliance. The present review highlights the progress made in antitubercular inhaled therapy especially with the ATDs formulated into suitable delivery systems[8].

ANTITUBERCULAR DRUGS USED TREATMENT FOR TUBERCULOSIS

First line drugs: These drugs are high efficacy as well as low toxicity

- Isoniazid
- Rifampicin
- Pyrazianamide
- Ethambutol
- Streptomycin

Second line drug: These drugs are low effficacy and high toxicity

- Thiacetazone
- Para amino salicyclic acid(pas)
- Ethionamide
- Cycloserine
- Kanamycin
- Amikacin
- Capreomycin

Newer drug

- Ciprofloxin
- Ofloxine
- Clarrithromycin
- Azithromycin
- Rifabutin

RESPIRATORY SYSTEM AND LUNG ANATOMY

The respiratory system consists of the conducting airway and respiratory regions (Figure 1.1). The conducting airway essentially consists of nasal cavity,nasopharynx, bronchi and bronchioles. Airways distal to the bronchioles constitute the respiratory region, which include the respiratory bronchioles, the alveolar ducts and the alveolar sacs. The latter structures (the alveoli), which are the important parts in this study, are composed almost exclusively of a nonciliated epithelial membrane. The alveolar walls contain a dense network of capillaries and connective tissue fibers.

The lungs have in fact been demonstrated an efficient port of entry to the bloodstream due to:

i. The tremendous surface area of the alveoli (100 m^2), immediately accessible to drug;

ii. A relatively low metabolic activity locally, as well as a lack of first-pass hepatic metabolism; and

iii. The elevated blood flow(5 l/min) which rapidly distributes molecules throughout the body.

The lungs have two separate circulations. The bronchial circulation, which involves small systemic arteries from the aorta supplies oxygen for the relatively high metabolic needs for lungs. The pulmonary circulation, which serves respiratory function, begins in the pulmonary artery; bring venous blood from the right atrium. The pulmonary arteries subdivide extensively and finally terminate in a dense capillary network around the alveoli. Venous blood returns to the left atrium via veins, which coalesce and eventually form the pulmonary venous system. The venous blood from the bronchial circulation returns to the system circulation via the azygous and pulmonary veins.

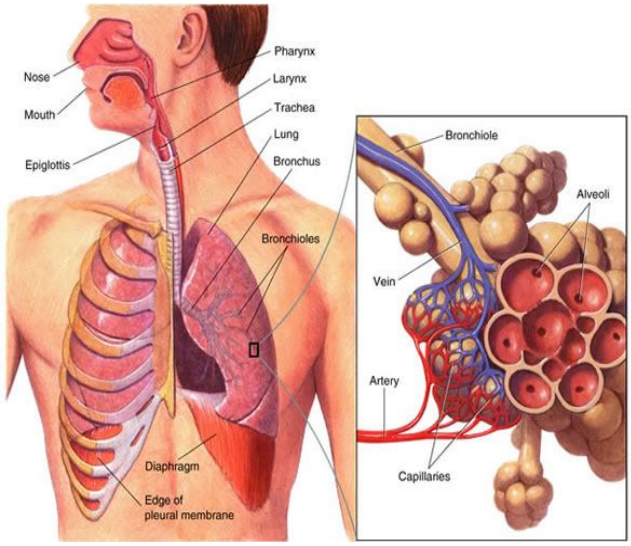

Figure1.1: View of Respiratory system

MICROSPHERE CARRIER SYSTEMS FOR PULMONARY DRUG DELIVERY

Polymeric microparticle particles are widely studied in drug delivery system for parenteral administration[9,10]; however their application to the pulmonary routes are also widely recognized[4]. The main roles of polymeric nano particles in drug delivery system are to carry the drug molecules, to protect drugs from degradation, and to control drug release[78]. Therapeutically used polymeric nanoparticles are composed of biodegradable or biocompatible materials ,such as poly(ε-caprolactone) (PCL), poly(lactic acid)(PLA), poly(lactic-co-glycolic acid) (PLGA), alginicacid, gelatin and chitosan. The chemical structures of polymers for polymeric nanoparticles used in pulmonary delivery systems are shown Figure 2.[11,12,13,14,15-18,19,20,21,22,23,24,25–39].

Due to their biocompatibility, surface modification capability and sustained-release properties, polymeric nanoparticles are intensively studied using various important pulmonary drugs. These pulmonary drug include antiasthmatic drugs,[40,11] antituberculosis drugs[13,14]. Pulmonary hypertension drugs,[12] and anticancer drugs[15]. However, to avoid accumulation of polymer carriers following repeated dosing, the biodegradability and toxicity of polymers over the long term should be closely examined in the formulation of polymeric nanoparticles for pulmonary delivery.Additionally, in vitro lung surfactant models and in vivo studies are required to establish the pulmonary acceptability of polymeric nanocarrier systems, as polymers and their degradation

products can affect the vital surfactant properties in the alveoli which in turn will affect pulmonary immunity control and adversely affect the work of breathing.

INHALATION OF SYNTHETIC PARTICLES FOR DEEP LUNG DEPOSITION

Inhalation would seem, in principle, a very reasonable route to efficient delivery of therapeutic agents because of the lung's extensive surface area and absorption characteristics. In an adult human, approximately 300 million alveoli define an air–tissue surface area of about 100 m^2 for gas exchange. The semipermeable epithelium is as thin as 0.1–1lm and has an extremely thin alveolar-capillary barrier (600–800 nm) that, even at a passive level, seems well suited for efficient transfer of some drugs and imaging agents [43,44,45,46]. Nonetheless, targeted delivery of drugs into the blood circulating through the lung is not straight forward due to several intrinsic anatomical and physiological challenges within the lung .One key physical parameter that determines the site of deposition within the respiratory tract of inhaled substances, including peptides, proteins, and particulate delivery systems, is the effective size of the substance [47.48]. The mass mean aerodynamic diameter accounts for gravitational settling and is an averaged function of particle size, shape, and density[49]. The aerodynamic diameter da for spherical particles is defined as:

da ¼ ðq=qa

Þ1=2dg

where q is the specific mass density of particle, qa is the density of water (1 g/cm3), and dg is the geometric diameter. For reliable deep lung deposition, da 1–5 lm optimizes deposition in the alveolar region and facilitates systemic bioavailability[49,51]. Particles with da\1 lm tend to diffuse, remain suspended in the airways, and are typically exhaled. Larger particles with da[5 lm deposit in the extrathoracic and bronchial region airways during inspiration with minimal alveolar deposition[52]. There can be exceptions to these rules: particles less than 100nm in diameter can also deposit in the alveolar region by diffusion and adsorption, although generation of such small size droplets or particles has historically been impractical with conventional aerosolization devices [53]. In addition to the lung's complex anatomy and physiology, the alveolar sacs are rich in macrophages that form a key part of the innate immune defense. Particles in the size range of 1–5lm are typical of bacteria and are readily engulfed by phagocytosis; this obviously limits the

bioavailability of any therapeutics for entry into the blood circulation. To overcome this issue, Edwards, Hanes, and coworkers[47] developed large porous particles (LPP) with a geometric diameter of dg 10 lm and also low density (q \ 0.1 g cm23), which promoted deposition deep into the lung and also persisted there by delaying phagocytosis.Systemic absorption was enhanced and insulin delivery highlighted the ability to achieve desirable uptake and systemic effects. Traditional aerosol delivery systems can be effective in achieving immediate and local therapeutic activity of drugs that target several lung diseases[54,55]. However, many small molecule drugs transport rapidly into the blood circulation and are then cleared quickly after inhalation, necessitating repeated inhalation[56,57]. Many macromolecular drugs are susceptible to protease degradation or macrophage uptake, which reduces their overall bioavailability. Therefore, to protect from rapid clearance or degradation and achieve sustained release within the lung, encapsulation in nanoparticles or microparticles has been pursued. Synthetic and natural degradable polymers are common and include poly(lactic-co-glycolic) acid (PLGA) [58.59], poly(ethylene glycol)-block-poly(sebacic acid) (PEG-PSA)[60], and gelatin [61], as well as liposomal delivery systems[62]. Controlled release of insulin from PLGA microparticles in streptozotocin-induced diabetic rat lung resulted in significant reduction of blood glucose at relatively low doses[64].Despite a number of promising results, biodegradable nanoparticle-or microparticle-based drug delivery through the lung has additional major obstacles. In addition to the noted macrophages and proteases, the airways are lined with mucus, an adhesive gel-like substance that traps and transports foreign particles out of the lung, thereby defining yet another major barrier to delivery [65,66]. Muco-inert coatings seem to be able to overcome rapid mucus clearance activity of lung:.demonstrated that optimally PEGylated (2–5 K), large polystyrene nanoparticles (200–500 nm) as well PEG-PSA nanoparticles of similar size effectively minimize the particle–mucus interaction. This allowed the particles to diffuse through human mucus at about 400- to 1,000-fold faster than uncoated polystyrene and pristine PSA nanoparticles [67,68].

INHALATION OF NATURAL PARTICLES FOR DEEP LUNG DEPOSITION

The influenza virus strain H5N1 (bird flu) and other strains of influenza have been shown by electron microscopy to exist in filamentous forms that can be more than 1 lm in length[69]. These particles penetrate into the deepest parts of the lung, and so it remains unclear whether the equation above for da is relevant to understanding the hydrodynamics of particles with such high aspect ratios. Inhalation of host-derived, virus laden aerosols (after coughs and sneezes) is

nonetheless a common route to spreading disease, which generally results in respiratory infections and further transmission. Filament-mimicking forms of synthetic nanoparticles are therefore intriguing for more therapeutic purposes. Long and flexible worm-like ‘‘filomicelles’’ (up to 10–20 lm long) have been developed by the authors of this review using various self-assembling and amphiphilic polymers, such as biodegradable poly(ethyleneoxide)–poly (e-caprolactone) (PEO–PCL). Surprisingly, after intravenous injection into rodents, these filomicelles are found to persist in the blood circulation for up to a week, which is much longer than spherical assemblies of the same polymer composition[70]. Hydrophobic drugs and dyes have been loaded into these filomicelles, and for the case of the anticancer drug taxol delivered to tumor xenograftsn mice only the filomicelles were found to sustainably shrink the tumor. The filomicelles also delivered far more drug to the tumor than any other organ, including the lung. In vitro imaging has shown that filomicelles align with flow, including blood flows, evade uptake by phagocytic cells through both shape and flow effects, and will reptake through nanoporous gels that mimic the permeability of tissues. Unpublished studies have now also shown that filomicelles, which are nano in diameter, are sufficiently stable to survive aerosolization with generation of 2- to 5-lm long fragments that seem suitable

TRANSLOCATION OF INHALED MEDICATION TO BLOOD CIRCULATION

As a result of tremendous effort over the last two decades, the first inhaled therapeutics for systemic delivery, Exubera1 (Pfizer/Nectar Pharmaceuticals) based on novel LPP technology was marketed in 2006. Unfortunately, Exubera did not gain adequate patient acceptance due to the lack of precise control on inhaled insulin dose, thus resulting in its withdrawal from the market[71]. Additional candidates for inhaled therapeutics that are currently under investigation include human growth hormone (MW: 22,100 Da) [73], human or salmon calcitonin (MW: 4,500 Da)[74], parathyroid hormones (MW: 9,400 Da)[75.76], cytokines [77], interferon’s[78], and the immunosuppressant polypeptide drug, cyclosporine A (MW: 1,203 Da)[79]. Pharmacokinetic studies of inhaled macromolecular therapeutics show surprisingly high bioavailability, probably due to the enormous alveolar surface area, very low surface fluid volume in lung, ultra-thin diffusion layer, and a high number of the 1–5 nm pores for paracellular transport. The translocation mechanism of inhaled macromolecules from lung to the blood circulation is hypothesized to occur via two different mechanisms .A slow process referred to as ‘‘receptor-mediated transcytosis’’occurs in hours to days for large-size molecules of MW [40kDa and size

‡ 5–6 nm. A fast process of ‘‘paracellular transport’’ occurs in 5–90 min for smaller molecules of MW \ 40 kDa and size 5–6 nm [80]. While the application of synthetic or natural nanomaterials for intravenous delivery of drugs has generated some surprises, such as the persistent circulation of microns-long filomicelles, delivery of drugs via inhalation requires the particulate carrier to translocate from air to blood across the alveolar barrier. Very little is presently known about the translocation of the possible diversity of inhaled particles of the few studies available on the transport of nanoparticles across the lung[81,82], current evidence suggests translocation through the air-blood barrier of gold, silver, polystyrene, and carbon nanoparticles in the size range of 50–200 nm. However, only 2% of inhaled particles were found in the systemic blood circulation in rats after 2 h of inhalation, with a further decrease to 1% after 24 h [83]. Recently, Choi et al. demonstrated that particle size and surface charge are also critical to the biodistribution of inhaled nanoparticles. Near-infrared fluorescent dyes loaded into nanoparticles have demonstrated that particles of size 34 nm with zwitterionic, anionic, and polar surface translocate from lung to blood circulation while cationic particle translocation was far more restricted. Zwitterionic particles of size 6 nm can translocate and enter the blood circulation.

LUNG VASCULAR TARGETING THROUGH INHALATION DELIVERY

Shortly after inhalation[84]. Indeed, this translocation might be different for self-assembled nano or microstructure versus biodegradable synthetic polymers such as poly (e-aprolactone) due to hydrolytic degradation with time [85]. Although studies invivo have led to important observations that should facilitate the design of smart particles for lung-targeted drug delivery, specific mechanistic pathways remain unclear. Yacobi Studied the mechanisms of nanoparticle interactions with lung alveolar epithelium during translocation utilizing rat alveolar epithelial cell monolayers (RAECM). Polystyrene nanoparticles of size20–100 nm appeared to translocate across RAECM in the apical to basolateral direction transcellularly, primarily via non endocytic pathways with direct involvement of the lipid in the cell’splasma membrane [86]. The results also suggested that 20 nm particles transport two fold to three fold faster than 100–120 nm particles of similar charge while positively charged particles translocated 20- to 40-fold faster than negatively charged particles. Nanoparticles can also be taken up into cells via caveolae-mediated endocytosis with eventual translocation across endothelial cells that line the lung vasculature; transcytosis mechanisms across endothelial cells are also used for nutrients or proteins[87,88] (Fig. 2). If filamentous influenza viruses also transcytose from alveolar space into the lung vascular

space ,then the worm-like filomicelles might be able to align with persistent flows and also transport through paracellular transport[71] (Fig. 2).Locally targeted delivery of drugs to the lung vasculature might be promoted by the use of antibodies that interact with receptors expressed preferentially on pulmonary vascular endothelial cells, particularly in certain lung diseases or inflammatory condition. Have been investigating the targeted delivery of drugs to pulmonary vascular endothelium as an important means for controlling oxidative stress, thrombosis, and inflammation associated with pulmonary diseases. Antibodies to platelet–endothelial cell adhesion molecule 1(PECAM-1) take advantage of the stable expression and high density of PECAM-1 on the luminal surface of the endothelium[89.90]. The inverse problem demonstrated targeting to alveolar epithelium in rat lung after intravenous injection of gold nanoparticle (6 nm) conjugated to a monoclonal antibody (TX3.833) specific for lung caveolae which rapidly transcytose to the alveolar air space via epithelial caveolae. In analogous studies, receptor-mediated translocation of a drug nano conjugate has been observed with brain endothelial cells and translocation of nanoconjugates through the blood–brain barrier: specifically, a drug molecule was conjugated to transferrin (80 kDa) to target transferrin receptor that is overexpressed on the luminal surface of brain endothelial cells and is internalized via clathrin-coated pits to traverse endothelial cells[91,92]. To date, there are no reports of such targeted delivery of nanoparticles or drugs to lung vasculature via inhalation.

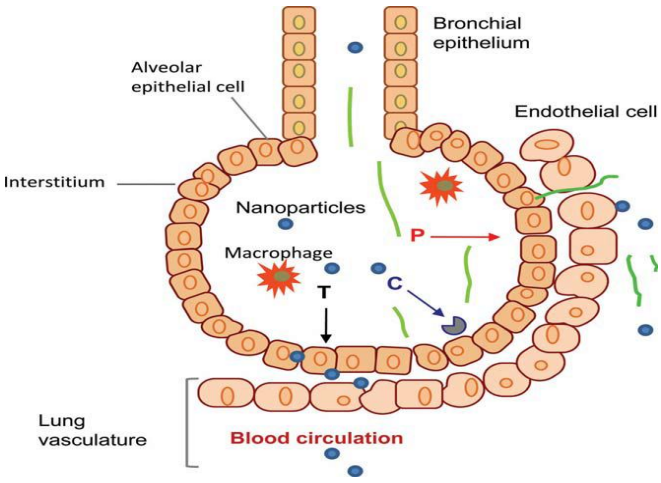

Fig 2: Translocation of inhaled medication to blood circulation

INHALED THERAPY WITH CONVEN- TIONAL OR UNFORMULATED ATDS

Many patients continue to remain sputum smear-positive for Mycobacterium tuberculosis despite ongoing chemotherapy, which is mainly attributable to (other than drug resistance) extensive cavitary lesions where the antimycobacterial drugs fail to reach when administered orally[93,50.]Sacks et al. are selected such patients of pulmonary TB who were sputum smear-positive after at least 2 months of conventional treatment. The patients were treated with gentamicin or kanamycin via nebulization as adjunctive therapy while the conventional drugs were maintained in parallel. The frequency of nebulization was thrice daily whereas the duration was dictated by practical considerations and smear conversion times which ranged from 9 to 122 days. It was observed that 86% (6 out of 7) of the patients with drug susceptible TB and 58% (7 out of 12) of the patients with drug resistant TB underwent smear conversion during the study period, suggesting that residual aminoglycosides in sputum expectorated from pulmonary cavities could inhibit intracavitary bacillary growth and prevent transmission, though not necessarily affecting the bacteria inside the macrophages. Nevertheless, the study did document the supportive role of inhaled aminoglycosides in patients with refractory TB[95,50].Aerosol administration of interferon gamma (IFN-g), a key cytokine in the immunological response against mycobacteria, has also been attempted. The initial studies were inconclusive as the patients receiving adjunctive aerosol IFN-g became smear-negative after 1 month but continued to be culture-positive and the smear response was not sustained[94]. However, when the aerosolized IFN-g therapy was continued for 6 months (thrice weekly), most of the patients showed a definite radiological improvement and a reduction in the size of the cavitary lesions[95.] It appears that merely aerosolizing an antimycobacterial compound may be inadequate; for efficient bacterial killing, drugs need to be formulated into suitable delivery systems thereby ensuring their rapid uptake into macrophages which harbour the tubercle bacilli. The dictum holds true for the majority of intracellular infections, and liposomes as well as micro/nanoparticles have emerged as useful drug carriers in this context.[96,97]Hence, it is not surprising that these carriers have established their potential for antitubercular inhaled therapy.

ADVANTAGE OF LUNG TARGETING DELIVERY

- The surface area of a lung is extremely large (approximately 100 m^2) and the mucosal permeation of drug substances is comparatively easy, because the vascular system is well developed and the wall of the alveolus is extremely thin.
- The activity of drug-metabolizing enzymes with intracellular or extracellular is relatively low, it avoids hepatic first-pass metabolism.
- A very rapid onset of action with very small dose. An oral dose of bronchodilator may take 2–3 h to be fully effective while an inhaled dose usually takes a minimum of 15–30 min.
- Reduces exposure of drug to the systemic circulation and potentially minimizes adverse effects and lower dosage regimens may provide considerable cost saving especially with expensive therapeutic agents

CONCLUSION

Drug delivery via inhalation offers the opportunity for systemic administration of therapeutic drug molecules, which otherwise are administered by less convenient parenteral routes. Inhalable colloidal carriers (microspheres systems) offer numerous advantages. The decrease in particle size leads to an increase in surface area leading to enhanced dissolution rate, as well as relatively uniform distribution of drug dose among the alveoli. In addition, by suspending the drugs in nanoparticles, one can achieve a dose that is higher than that offered by a pure aqueous solution, which is thermodynamically limited by the aqueous solubility of the drug. Microsphere systems can provide the advantage of sustained-release in the lung tissue, resulting in reduced dosing frequency and improved patient compliance. Local delivery of inhalable micro carrier may be a promising alternative to oral or intravenous administration, thus decreasing the incidence of side effects associated with a high drug serum concentration. Although considerable advances have already been made in the design of suitable aerosolized particle for deep lung deposition, the systemic delivery of drug molecules at controlled rates is Utilization of other carriers might provide sustained drug delivery, while ensuring sufficient protection against alveolar macrophage uptake, mucociliary clearance, and enzymatic degradation to the encapsulated drug. Further investigation is necessary into the translocation of inhaled nano or microparticles to achieve high bioavailability of the inhaled drug without compromising the excretion of foreign Materials from the body.

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