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Review Article

Mucoadhesive targeted pulmonary delivery of nanoparticulated dry powder insufflators-A revolt in TB therapy

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ABSTRACT

The emergence of multidrug-resistant TB (MDR-TB) against first-line drugs and extensively drug resistant TB (XDR-TB) due to misuse of second-line anti tubercular drugs (ATDs) is a further concern. Recommended treatment involves long term and multiple drug therapy with severe side effects. Due to this concern nanoparticle-based systems have significant potential for treatment and prevention of tuberculosis (TB) to overcome the need to administer ATDs at high and frequent doses, would assist in improving patient compliance and circumvent hepatotoxicity and/or nephrotoxicity/ocular toxicity/ototoxicity associated with the prevalent first-line chemotherapy. Nanostructured delivery systems constitute a wide range of systems varying from liposomes, micelles, micro- and nanoemulsions, to polymeric nanoparticles (PNPs) and solid lipid nanoparticles (SLNs). Pulmonary administration of inhaled nanoparticles in the form of dry powder inhalers offer particular advantages for pulmonary administration of anti tubercular drugs (ATDs). Present review comprehensively about different approaches of nanobased drug delivery, devises and techniques for pulmonary delivery of nanoparticle encapsulated ATD.

Keywords: Anti tubercular drugs (ATDs); Nanoparticle-based systems; Dry powder inhalers.

INTRODUCTION

Universally Tuberculosis (TB) exists as a foremost infectious cause of death. The bacteria underlying for this disease is Mycobacterium tuberculosis that can generate either a quiet, latent infection or a growing, vigorous disease. If not or inappropriately cured, it causes continuous tissue degeneration and, ultimately, demise (WHO, 1998, C.D. Mitnick et al., 2008).

An effectual diagnosis and treatment exist as oral anti tubercular drugs (ATDs), but is nevertheless allied with innumerable substantial disadvantages. Among all the types of TB pulmonary tuberculosis is the major one and large dosage is needed to be given as the amount of drug reached at site of target is less to that of total dose administered. Yet this small amount of drug is eliminated within a couple of hours hence amplifying the requisite to prescribe multiple ATDs daily, the treatment that is difficult to stick on by greater part of TB patients. Obviously, systems that deliver ATD to pulmonary route can evade daily dosage and in addition will aid in: (i) straight drug release to the infected tissue/organ; (ii) targeting the safest host cells of mycobacteria for its survival in alveoli i.e., macrophages (iii) alleviating drug toxicity and (iv) enhanced patient compliance. The current article embarks on the development achieved in inhalation therapy of ATDs that are designed in to appropriate delivery systems (Rajesh Pandey and G. K. Khuller, 2005).

A novel device with simplified and innovative technology that comprehends the scientific growth at a nanolevel is nanotechnology. This aids in curing alarming diseases like tuberculosis with nanospheres embedded micro particles targeted to pulmonary mucosa as dry powder insufflators as an extended release drug delivery of ATDs (T.S. Hauck., et al 2010).

Tuberculosis

Transmission

Nevertheless TB is treatable. Universally millions of citizens have been infected and killed in a year (WHO, 1998, Iseman MD 2000, McCray E et al., 1997). The influence of TB on world healthiness is major; in 2006, billions of death cases were reported due to TB (Davidson's Principles and Practice of Medicine, 2010, 886).

Clinical features

The significant route that the tubercle bacilli desires for its infection is respiratory tract. Besides the periodic pulmonary or trache bronchial lymph node calcification, lesions developed in lungs are generally get rid off

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without surplus variations (Heymann, D.L. (Ed.), 2004).Concealed bacilli stay on from the primary infection could develop pulmonary TB either from exogenous reinfection of endogenous reactivation. If without treatment, in just 2 years patients might expire around 65% (Roger Walker and Cate Whittlesea, 2012).

TREATMENT

Antitubercular drugs (ATD)

Among the five first line TB drugs (Isoniazid (INH), rifampin(RIF), pyrazinamide(PYZ), ethambutol(ETH), and streptomycin Isoniazid and rifampicin are most active. Administration of isoniazid-rifampin combination for 9 months duration will prevent 95-98% of TB infection caused by susceptible bacilli.Moreover the total duration of therapy can be reduced to six months by supplementing pyrazinamide to the combination of Isoniazid and Rifampicin. The current testimonial is primarily centered on the usage and progress of first-line ATDs (Bertram G Katzung, 2007).

Concerns pertaining to treatment

A lengthy medication of 9–12 months was often prescribed to ensure remedial efficiency. At this particular aspect, lower patient conformity as well as compliance to the dosage plans change under significant downsides of the pharmacotherapy. An added important constraint of the ATDs is their variance on bioavailability (L.T. Luyen et al., 2005). In vitro research shows that INH and RIF pairing seems to have quicker and higher disintegration at acidic pH and decline in bioavailability in invivo research distinct to specific drug (L.T. Luyen et al., 2005, C.J. Shishoo et al., 2001). The outcomes identify a desire to formulate an appropriate delivery system that might counter its degradation.

Novel approaches in TB therapy

Relevant to Dose of ATDs, most typical and alarming adverse effects comprises hepatic damage, nephrotoxicity, neurotoxicity, oculotoxicity and ototoxicity and these effects bring the sub stranded modes of drug administration which has become a challenge for drug discovery and development in particular to release rate(L.C. du Toit et al., 2006).

Nanotechnology

The science of nanoparticles is a very good reward for modern pharmacology. Currently nanotechnology was originated as an extremely refined and innovative science, relating to the nanoscale dimensions of elements with unique or improved physicochemical properties especially the free drug (T.S. Hauck et al., 2010). The discovery of nanotechnology made feasible to cure different alarming diseases like tuberculosis and AIDS. Recurrent treatment downfalls plus egression of multidrug level of resistant species, trigger a desire to alleviate the degree of therapy and considerably to minimize drug interactions. These significant aspects encourage the demand for building nanobased carrier systems for drug targets (http://www.usatoday.com/story/news/nation/2012/12/31/fda-tuberculosis-drug/1800367/ (Accessed on December, 2013)).

Nanodrug delivery system enhance ED50 of drugs by stringently restricting their effect to the tissue or organ of action. This technology also might develop acceptability and bioavailability of noxious medicaments (Sakagami M 2006). Various nanobased drug Delivery systems include nanoemulsion, nanosuspension, liposomes, solid lipid nanoparticles, micelles, dendrimers and niosomes.

Nanoemulsion

Nanoemulsions represent a favored nanobased system because of their thermodynamical reliability and ease of sterilization by filtration (S. D'Souza et al., 2002). Since long, large amounts of oil on water dispersions with size range of 10-100nm have been in use for drug delivery and enhanced intake of trapped drug by macrophages (S.H. Kaufmann and A.J. McMichael 2005, H.M. Vordermeier et al., 2006) and for hepatic cell receptors soon after oral administration (S. D'Souza et al., 2002).Envisaged research by Scientists revealed that parenteral rifampicin o/w nanoemulsion has almost 100% efficient in entrapment under good stability and increased particle size more than 3 months with release rate of 40-70% later two hours (Ahmed M, 2008). Further Non-Fickian release of drug from isoniazid microemulsion was disclosed by doing physicochemical analysis (Mehta SK et al., 2008). The changes in the microstructure of first line TB drugs incorporated Tween 80 based mircoemulsion has also been investigated (Mehta SK et al., 2010).

Nanosuspension

Sub -micron colloidal dispersions of pure drugs stabilized with surfactants is known as Nanosuspension (S.P. Klemens et al., 1990). At present, over 8 molecules were under clinical research (Shegokar R et al., 2010). Rifampicin sub micronic particles of size range 400 nm to 3 µm were formulated by investigators employing supercritical-CO_2 aided atomization appropriate to parenteral and aerosolizable release of drug. Due to their low aqueous solubility it appears difficult to perform pre-clinical and clinical investigation of unique drug molecules (Rabinow BE, 2004). Scientific research on different solvents influencing particle size and drug degradation reveals the use of nanoparticles productivity for appropriate TB therapy through pulmonary targeted drug delivery (Reverchon E, 2002, Reverchon E,Della Porta G, 2003).

Liposomes

Liposomes are phospholipid bilayered vesicles of nano- to micro range encircling preferred drug encapsulated aqueous core. For sustained release and flow duration they are often formulated with PEG (30).Stealth liposomes are designed by Scientists for pulmonary target-

ing of ATDs. There was a marked raise in buildup of ATDs bio distribution from 5.1% for conventional liposomes to 31% for PEG formulated liposomes after 30 min of IV administration in normal and TB induced mice (Deol P,Khuller GK, 1997).

Solid nanoparticles (SLN)

Solid nanoparticles are lipid based aqueous nanocrystalline suspensions that are solids at normal temperature and are novel carriers next to liposome, lipid emulsion, and polymeric nanoparticle (PNP) (V. Jenning et al., 2002). They have better acceptability, scaling-up possibility, lipophilic or lipophobic drug integration capability, and an enhanced stability of encapsulated drugs. Hence solid nanoparticles are unique in the impression that correlates the qualities of nanoparticles by eliminating their few difficulties (R.H. Muller et al., 2004). Large scale manufacturing with feasibility preventing organic solvents and composition are the impressive benefits of solid nanoparticles (P.M. Bummer 2004).

Micelles

Micelles are liquid colloidal submicroscopic aggregates of surfactants of 20-80nm in size (Jiang W et al., 2007). Its layer is formed by the interaction of lipophobic sections with the aqueous medium stabilizing the aggregate by facilitating the solubilization of amphiphile in water. Alternatively, lipophilic sections create the internal micellar layer that allows the solubilization of inadequately aqueous soluble drugs (J.R.Koup et al., 1986) protecting these by chemical and biological destruction. In order to enhance the enclosed drug incursion in to mycobacterium and its anti tubercular activity, micelles have been significantly lipophilized .The major and important micellar forming materials include poly ethylene-polypropylene oxide (PEO-PPO) block copolymers (linear poloxamers and branched polaxamines), (D.A. Chiappetta et al., 2007).

Dendrimers

Dendrimers are 3D configured nanoparticles with tree designed assortment of process, low molecular weight and multi dispersible and extremely flexible capacity. Previous decades have sprouted this concept by the earliest synthesis of dendrimers namely polyamidoamines (PAMAM), (D.A. Tomalia et al., 2005). With the advantage of dendrimeric core, intrication and conjugation on their texture they were efficient of drug encapsulation (A.D. Emanuele et al., 2005). Encapsulation of drug chiefly relies on lipophilic interactions and hydrogen bonding providing physical binding of the drug to the core. A mannosylated fifth generation (5G) PPI dendrimer is discovered for transport of RIF to macrophages (Kumar PV et al., 2006).

Niosomes

Equimanner to that of liposomes, niosomes were primarily made up of non-ionic surfactant plus with or without inclusion of lipids. Niosomes are liposome like vesicles with charged phospholipids (stearyl amine and diacetylphosphate) and nonionic surfactants (monoalkly or dialkyl polyoxyethylene ether) ensue after cholesterol hydration (M. Smola et al., 2008). Stability, easy scaling up and less cost productivity are the advantages of niosomes over liposomes. They can host lipophobic drugs within their core and have propensity to entrap hydrophobic drugs in lipophilic regions. A range of surfactants (viz. Spans 20, 40, 60, 80, 85) were used with various sized niosomes for effective delivery of loaded rifampicin to the lungs (D.A. Mitchison et al., 2010, G. Scheuch et al., 2006).

Polymeric nanoparticles (PNP)

PNP are specific target drug delivering carriers with good solubility and stability (P.K. Gaur et al., 2010). Potentiality of lipophobic and lipophilic drug loading, easiness of administration through different routes popularize as one of the most valued methods for drug entrapment (L. Brannon-Peppas, 1995).They form two types of systems based on their productive technique such as nanocapsules and nanospheres. In nanocapsules the drug is dissolved in aqueous or non-aqueous solvents and is encased under a polymeric membrane. Perversely, nanospheres are with homogeneous dispersion of active molecules in solid matrices of variable porosity throughout the particle. Biomaterials of broad range been known for PNPs were phased out from the system by opsonization and phagocytosis (D.E. Owens III and N.A. Peppas, 2006). In an effort to mask host immune system recognition and to increase circulatory time, the external surface is modified with hydrophilic chains (PEG). It is one of the most considerably investigated approaches with respect to anti tubercular drug delivery systems.

Delivery approaches with nanoparticles

Intra and extra pulmonary diseases are treated by pulmonary route of drug delivery system as the lungs have distinctive features like large surface area, thin epithelial layer, high vascularization and escape of first pass metabolism (Al-Hallak KM et al., 2010).

Pulmonary delivery of nanoparticle encapsulated ATD

Nanoparticles posses the capability to attain a maximum drug filling, reduce the usage of polymers, barrier cross permeability and better therapeutic efficacy. Alveoli targeted net drug delivery is easily approachable by their mucosal adherence by inhalation (Jacobs, C. & Muller, R. H, 2002). PLGA is the most possibly investigated nanoparticulate drug transporter (Bala, I., Hariharan, S. & Kumar, M. N. V. R, 2004). PLGA are extensively used for the preparation of self reinforced preparations and ATD carrier due to their biodegradability and biocompatibility (Anderson J.M. and Shive M.S, 1997- Ain Q et al., 2003). In a murine TB Model the dose frequency was reduced for PLGA nanoparticle (PLGA-NP) encapsulated first line TB drugs (Pandey R.

et al., 2003).A commonly occuirng glycoprotein called wheat germ agglutinin (lectin) was combined with formulation for additional refinement. Similar to drug bounded liposomes, lectin based PLG nanoparticles were also investigated for their chemotherapeutic potential due to widely distribution of lectin receptors in lungs (Abu-Dahab, R, 2001, Vyas, S. P. et al., 2004). Natural polymer based antitubercular drug therapy was explored with chitosan loaded DNA delivery to alveoli encoding TB bacilli T cell epitopes (Bivas-Benita, M et al., 2004).

Devices for drug delivery

Nebulizers or pressurized metered dose inhalers (pMDIs) and dry powder inhalers are the three techniques to inhaled drug delivery each with their exclusive potency and properties (Chow AH et al., 2007). Different types of inhalable nanoparticles can be delivered by nebulizers but the disadvantage of compressed air source necessity restricted their use to hospitals and ambulatory care settings (Dailey LA et al., 2003- Ostrander KD et al., 1999).

Though pMDI is the best preferred inhaled drug-delivery system, certain down sides made an obstacle to formulate nanoparticles and less ideal for delivery of inhalable nanoparticles. These include instability due to sedimentation, crystal growth and polymorphism and chances of accumulation in oropharynx due to high dose velocity (Rance RW, 1974, Timsina MP et al., 1994).

Hence to conquer the down sides of pMDI dry powder inhalers (DPIs) were presented because of their high formulation stability alveolar deposit (Crompton GK, 1991- Vidgren MT, 1988). Designing of significant porous particles with little density and huge geometrical dimension contributed a stage ahead in the pulmonary delivery of DPIs. Their physical characteristics equipped them to avoid natural clearance from lungs and allow alveolar drug release even (Edwards DA, 1997). Diseases like TB, cystic fibrosis and lung cancer were treated well due to combined benefits of nanoscale formulation and localized delivery of nanoparticles from DPIs (Sung JC et al., 2007- Roa WH et al., 2011).

Methodologies for producing particulate matter for lung delivery

A nanojet milling instrument is employed for producing nanoparticles implied for pulmonary drug delivery using nitrogen gas. Few techniques of such were pointed out shortly.

Spray drying technique

Spray drying is an advanced technique for producing solid state respirable colloidal particles (Mosen K et al., 2004, Duddu SP et al., 2002). It was discovered around three decades past for creating fine particles for lower respiratory tract drug delivery. In this strategy the drug solution is provided at ambient temperature and injected to the nozzle in which it is atomized by the nozzle gas. Then this solution is dry up by pre-heated drying gas in a unique compartment to eliminate liquid humidity from the system creating dry particles of 2 µm size. Large scale production of such particles can be easily achieved by this method due to its fine management on particle formation. As this method is avoid of mechanical high energy input it is also appropriate for heat sensitive materials like proteins and peptides (Gilani K et al., 2005, Rogers T et al., 2001).

Spray freeze drying method

This method is a combination of spray drying and freeze drying development steps spraying drug solution in to a freezing medium (liquid nitrogen) accompanied with lyophilization (Maa YF et al., 2000) making light, fine and porous particles having enhanced aerosol efficiency with 100% productivity (Yu Z et al., 2004). Heat sensitive substances like insulin (Kuo JH et al., 2004) and plasma DNA, could even get developed in dry powder inhalation designs. Nevertheless it is a costly process constrained for exclusively costly drug (Chattopadhyay P et al., 2007).

Supercritical fluid technology

This process is designed as the controlled crystallization of drug from dispersion in carbon dioxide (supercritical fluid) for generation of microparticles, nanoparticles, liposomes and inclusion complexes. This technique is employed concerning drug delivery to lower respiratory tract including proteins and peptides and for the enhancement of formulation characteristics of specific drugs (Rehman M et al., 2004, Rasenack N et al., 2003).

Solvent precipitation method

This particular technique entails sonocrystallization plus micro precipitation by contradicting liquid jets. Crystallized drug molecules at narrow size distribution might be developed by direct controlled crystallization. Accelerated precipitation through aqueous solutions using anti solvents will generate inhalable particles. In recent times, ultrasonic radiation was practiced to regulate the precipitation. By using sonocrystallization technique different drugs were designed for asthma disease (Gratton SE et al., 2007).

Double emulsion/solvent evaporation technique

This technique includes oil in water emulsion preparation with following elimination of the oil phase via vaporization. The organic solvent diffuses out from polymer phase to aqueous phase, made evaporated developing drug-loaded poymeric nanoparticles.An extensive research on biodegradable polymers as carriers for pulmonary solid nanoparticulate drug delivery was carried out by the help of this method.

Particle replication in non-wetting templates (PRINT)

A group of team with Dr. Joseph Desimone developed this top - down particle manufacturing method called PRINT. It generates organic micro and nanoparticles with uniformity in size and shape, surface functionality and aids in packing of small organic therapeutics, protiens, peptides, oligonucleotides, RNA contrast agents, radiotracers and flurophores (Gratton SE et al., 2008, Heidi MM et al., 2009).

CONCLUSION

The key first line and second line antitubercular drugs can be encapsulated using nanotechnology for their controlled release using synthetic and natural polymers. This technology can be considered as an alternative for new molecule discovery which is time taking (20-30 years) and cost effectiveness(100 billion dollars/molecule. Multiple issues like solubility, stability, permeability, drug interactions and adverse effects of antitubercular drugs their remodelling with potentially low MIC were addressed by nanodrug delivery systems. Natural polymers based drug carriers (chitosan) signifies an interesting approach. Furthermore, the generating item is secured and profitable due to innovativeness designated to it.Out of the available choices PLGA NPs present the flexibility of selecting different routes of administration and exhibit a sustained drug release to an extent that it is feasible to replace daily usual free-drug treatment with intermittent doses of NP-based drugs. The improved drug bioavailability and therapeutic efficacy were witnessed even at sub therapeutic doses. In addition to a lower effective dose, the period of chemotherapy can also be shortened by use of these products. These factors are decisive in substantially curtailing the cost of treatment, reducing interactions with anti-HIV drugs, and better management of MDR-TB and latent TB.

The targeted pulmonary drug delivery of nanoparticles to lower respiratory tract offers prospective use in several lung ailments. Inhalation therapy of ATDs is the most effective treatment for pulmonary tuberculosis with good systemic bioavailability also for extra pulmonary TB and endobronchial tuberculosis. Inhalation therapy was now focused on multi drug resistant tuberculosis that was not remedied with conventional drugs.

The complexes and obstacles experiencing the progress of pulmonary drug delivery system provide huge pleasure to the drug formulation researcher, which actually aids him in reducing the medical and technological gaps. Investigators have the opportunity to show understanding between in vitro, in vivo and ex vivo studies that are used to estimate drug absorption from the unimpaired animal. This may possibly provide a sound basis for prospective development in NDDS (Nanocarrier Drug Delivery System) for lung diseases. Ideally, present and prospective investigation attempts would ultimately lead in this approach moving from plain to pinnacle.

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