

BIOADHESIVE MICROSPHERES FOR TUBERCULOSIS DRUG DELIVERY

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ABSTRACT

Tuberculosis (TB) is an infectious disease that mainly affects the lungs. For the treatment of tuberculosis, conventional drug delivery system fails to achieve efficient drug delivery system fails to achieve efficient drug delivery at the target site. Today, bioadhesive microspheres became a topic of great interest as a novel carrier for drug delivery. Bioadhesive microspheres offers longer retention time, sustained drug delivery along with patient compliance. Bioadhesive microspheres overcome the various drawbacks associated with conventional drug delivery system for the treatment of tuberculosis. Bioadhesive microspheres considered as a remedial measure which facilitate site-specific drug delivery to a great extent. The present review address the potential application of bioadhesive microspheres as a novel carrier for drug delivery of anti-TB drugs to achieve desired therapeutic results in tuberculosis treatment.

KEYWORDS: Bioadhesive microspheres, tuberculosis, applications, MDR, site-specific, targeted delivery, novel drug delivery system.

INTRODUCTION

Tuberculosis (TB) is a global health problem. TB is an infectious disease caused by a microorganism *Mycobacterium tuberculosis* (Mtb). It spreads mainly through air. Because of *mycobacterium*; single infectious agent, TB is the most common cause of death worldwide in human population. In 2015, there were estimated 10.4 million new TB cases are reported worldwide. According to global tuberculosis report 2016, there were an estimated 480000 new cases of multidrug resistant TB (MDR-TB) in 2015.^[1] TB mainly attacks lungs but it infects other organs also. Symptoms and signs of TB are mainly appears as cough which persist for more than 2-3 weeks. It is important to note that mycobacterial infection is difficult to treat. Being facultative mycobacteria is able to survive within macrophages of host. This would result in occurrence of chronic infection which require long term treatment. Furthermore *mycobacterium* acquire various types of resistance which named as Multi-drug resistance (MDR), Single-drug resistance (SDR), and Extensive drug resistance (XDR). Even drug-susceptible TB is difficult to treat and requires 6-9 months of combination therapy.^[2] This was accompanied by several side effects including poor patient compliance and various systemic side effects like hepatotoxicity. As a consequence of various problems in treating TB and because of increasing incidence of drug-resistant TB, need of new and improved drug delivery system is important.

This present review article is an attempt to highlight the importance of bioadhesive microspheres and their potential to treat life threatening mycobacterial infections and overcome the drawbacks of conventional dosage forms.

Bioadhesive Microspheres – A Novel Approach

Technology gives a novel approach for drug delivery by combining the drug to a carrier particles like bioadhesive microspheres. Bioadhesive microspheres are unique drug delivery system achieved by coupling of bioadhesive characteristics to microspheres. "Bioadhesion" is defined as the adhesion or attachment of a synthetic or biological macromolecule to the surface of biological tissue.^[3]

Liposomes and other type of colloidal carriers mostly failed in targeted drug delivery and show difficulties in reaching targeted tissues, penetrating vascular structure and artifice phagocytic capture by RES.^[4] Targeted delivery could easily achieve using bioadhesive microspheres.

Bioadhesive microspheres overcome the various drawbacks associated with conventional drug delivery systems for TB. Bioadhesive microspheres termed as remedial measure which improve site specific drug delivery to a great extent. It was important to note that compliance is a major issue in the fight against

tuberculosis, which could be effectively resolved by microsphere technology.

Size Range for TB Therapy

Microspheres are carrier mediated drug delivery system in which particle size is ranging from 1-1000 μm range in diameter.^[5] For IV administration, microspheres are formulated in size less than 250 μm in diameter. Especially for treatment of mycobacterial infection, small microspheres are usually used in the size range of 1-10 μm ; as smaller microspheres can be easily phagocytosed by host macrophages which results in higher drug availability to intracellularly replicating organism.^[6] Large microspheres i.e. more than 10 μm can be injected subcutaneously or ingested for extended systemic delivery of larger quantities of drug.^[7] Both size ranges offers wider therapeutic approach that is notable for management of TB.

Benefits of Bioadhesive Microspheres

Bioadhesive microspheres provide sustained and control drug release. Drug release time can be extend from days to months with aid of small microspheres and even for a year or more with large microspheres. As mentioned earlier, with help of small microspheres one can target

drug delivery with specificity to host macrophages. And with large microspheres, systemic controlled release of drug is possible along with patient compliance. Bioadhesive microspheres provide sustained drug delivery of drug accompanied with reduced toxicity associated with elevated levels of blood as a consequence of large oral dosing. Furthermore, Bioadhesive microspheres offers longer retention time along with prolonged release of drug. Effective therapeutic levels with reduced dosing regimens are possible by this novel drug delivery system. Bioadhesive microspheres provide additional advantages like elimination of first pass metabolism, effective absorption with improved bioavailability.^[8] Good drug encapsulation is the extra key feature of Bioadhesive microspheres. In TB management, with the help of Bioadhesive microspheres drug can able to penetrate the intracellular compartments where the *Tubercle bacilli* is present and cause infection. Sustained and controlled drug delivery of anti-TB drugs with site specific action, all become easily possible with Bioadhesive microspheres approach. Table I represents the results of microsphere based drug delivery systems in the management of tuberculosis.

Table I: Results of microsphere based drug delivery systems in TB therapy.

S. No.	Drug	Inference
1.	Rifampin microsphere	a) Reduce unwanted side effects of anti-TB drugs by potent pharmacological effect. Reduce hepateis accumulation ^[9] . b) Reduced intracellular Mtb increment as compared to free drug given as equivalent dose of rifampin. Target the rifampin drug to macrophages. No patient compliance problem because of routine dosing regimen and levels in blood are pre-planned ^[10] .
2.	Ofloxacin PLGA microspheres	For bone TB ^[11]
3.	Rifampin PLGA microspheres	Good release profile, could be released within 7 days ^[12]

Research Based on Bioadhesive Microspheres for TB Therapy

Several research data reported the use of Bioadhesive microspheres as a promising carrier for delivery of anti-TB drugs. Pandey *et al* (2004) reported that chitosan and sod. alginate microspheres encapsulated three anti-TB drugs RIF, INH and PZ administered orally, the half-life and mean residence time of the drug were increased 13 to 15 times because of microspheres encapsulation.^[13]

Samad *et al* (2008) developed reconstituted powder for suspension of RIF and INF formulated as alginate microspheres. The result showed that RIF slowly diffuses out due to swelling of gelatine in acidic environment and thereby slow sustained drug delivery. The drug delivery system was effective in preventing interaction due to reduced release of INH from ALG microspheres in gastric medium. Hence developed formulation modulated the release of RIF and INH to reduce their interaction. Therefore this type of formulation is therapeutically useful for delivering RIF and INH (anti-TB drugs) successfully.^[14]

To explore these researches several patents on Bioadhesive microspheres for TB therapy are also there, like US specific 20050081455AL (2005) which disclose inhalable biodegradable micro-particles (i.e. microspheres) for target drug delivery to manage TB with two anti-TB drugs (Rifabutin and INH).^[15]

Investigations by Khuller *et al* (2000) also described the use of microspheres for delivery of anti-mycobacterial drugs. In one study, PLGA microspheres give sustained delivery of rifampin for up to 7 weeks *in vitro*.^[16] In another study, Khuller *et al* (2002) formulate an oral formulation of PLGA microsphere for delivery of anti-TB drugs (INH, RIF, Pyrazinamide) in a non-infected mouse model. When evaluated *in vitro*, the PLGA microspheres was appear to be stable in acidic pH for gastric fluid and intestinal fluid. Drug release profile was also found to be up to 20 days.^[17]

Barrow *et al* (1999) evaluated the combined formulation of rifampin loaded small microspheres (i.e. 1-10 μm diameter) and large microspheres (i.e. 10-150 μm

diameter) to treat H37RV infected mice. From first mouse study they demonstrate that programmed sustained release of rifampin was achieved during 26 day experimental period. From second mouse study, they demonstrate that 5.0 and 5.8% (w/w) rifampin loaded small microspheres deliver 3-4 fold increased concentration of rifampin and achieve blood levels in mice i.e. 15 fold above as obtained with 1.8% (w/w) formulation in previous study. Another important factor described by above mentioned study is that rifampin loaded small microspheres can be safely used in combination with an oral regimen of another first line anti-TB drug like isoniazid in this study.^[18]

It was also demonstrated that with Bioadhesive microspheres drug delivery system, good release parameters with very less toxicity can be achieved. Toxicity of rifampin was reduced when given to a human macrophage cell line via a microsphere formulation.^[9]

Hanzhou Feng *et al* (2013) evaluated a formulation for EC, chitosan complex microspheres (EC-CTS-CPM), chitosan provide bio adhesion to CPM (complex microsphere) and EC used as sustained release carrier. Anti-TB drug rifampin was loaded in CPM with cross linking agent genipin (GNP) to control the release rate of CPM. They demonstrate that CTS functioned as the bio-adhesive "shell" and promote pulmonary retention property of the delivery system. *In vivo* studies also showed that CPM were adhere to lungs in bronchoalveolar lavage process, which proved their good pulmonary retention property. They further demonstrate that RBT loaded CPM made of ethyl cellulose and chitosan possessed long time pulmonary retention features.^[19]

Ciaran Lawlor *et al* (2016) also showed that treatment of infected macrophages (from *M. tuberculosis* strains H37Rv and H37Ra) with 2.2 μ m PLGA microspheres reduces the intracellular burden of Mtb and served as a vehicle for targeted drug delivery. They also estimated that 2.2 μ m PLGA microspheres support the anti-mycobacterial activity of Mtb infected macrophages by inducing autophagy. It is mechanism by which cells recycle the cellular components by enclosing them in autophagosomes that further fuse with lysosomes to facilitate the degradation of their contents. Autophagy plays an important role in host defence mechanism by engulfing and degrading microbes.^[20]

CONCLUSION

As outlined in this review article, it is evident that bioadhesive microspheres are unique carrier systems for delivering of anti-TB drugs. They not only provide controlled release drug delivery but can also be used for site-specific delivery of anti-TB drugs. Many studies have already showed that BMs are the better choice of drug delivery system as compared to conventional drug delivery system because of their lots of benefits. Bioadhesive microspheres opens new doors for anti-TB

drug delivery with more patient compliance along with less side effects. In future with continuous research based efforts in this unique carrier system for drug delivery, better treatment options for life threatening TB will be successfully achieved.

REFERENCES

1. WHO, WHO Global Tuberculosis Report 2015.
2. Hoagland D.T., Liu J., Lee R.B. New agents for the treatment of drug-resistant Mycobacterium tuberculosis. *Adv. Drug Delivery Rev*, 2016; 102: 55-72.
3. Vasir J.K., Tambwekar K., Garg S. Bioadhesive microspheres as a controlled drug delivery system. *Int. J. Pharm*, 2003; 255: 13-32.
4. Hari B.N.V., Chitra K.P., Bhimavarapu R., karunakaran P., Muthukrishnan N., Rani B.S. Novel technologies: A weapon against tuberculosis. *Ind. J. Pharmacol*, 2010; 42: 338-344.
5. Siri S., Balaji A., Shankar M.S.U., Vijendar A. Microspheres as a promising mucoadhesive drug delivery system. *Int. J. Pharm. Sci Rev*, 2013; 23: 8-14.
6. Barrow W.W. Microsphere technology for chemotherapy of mycobacterial infection. *Current pharmaceutical design*, 2004; 10: 3275-3284.
7. Quenelle D.C., Winchester G.A., Barrow E.L.W., Barrow W.W. Treatment of tuberculosis using a combination of sustained release rifampin loaded microspheres and oral dosing with isoniazid. *Antimicrob Agents Chemother*, 2001; 45: 1637-1644.
8. Jiao Y., Pang X., Liu M., Zhang B., Zhai L. Li. G. Recent progresses in bioadhesive microspheres via transmucosal administration. *Colloids and Surf. B Biointerfaces*, 2016; 140: 361-372.
9. Barrow E.L.W., Winchester G.A., Staas J.K., Quenelle D.C., Barrow W.W. Use of microsphere technology for sustained and targeted delivery of rifampin to Mycobacterium tuberculosis-infected macrophages. *Antimicrob Agents Chemother*, 1998; 42: 2682-2689.
10. Pandey R., Khuller G.K. Antitubercular inhaled therapy: opportunities, progress and challenges. *J. Antimicrob Chemother*, 2005; 55: 430-435.
11. Saurez S, O'Hara P. Respirable PLGA microspheres containing rifampicin for the treatment of tuberculosis; screening in an infectious disease model. *Pharm Res*, 2001; 18: 1315-1319.
12. Liu Zhiqiang., Xiu X. Li, B., Duan C., Zhang J. Li, X., Yang X., Dai W., Johnson H., Zhang H., Feng X. A novel and simple preparative method for uniform sized PLGA microspheres: Preliminary application in antitubercular drug delivery. *Colloids Surf. B Biointerfaces*, 2016; 145: 679-687.
13. Pandey R., Khuller G.K. Chemotherapeutic potential of alginate-chitosan microspheres as anti-tubercular drug carriers. *J. Antimicrob Chemother*, 2004; 53: 635-40.

14. Samad A, Sultana Y, Khar RK. Reconstituted powder for suspension of antitubercular drugs formulated as microspheres for pediatric use. *Drug Discov Ther*, 2008; 2(2): 108-14.
15. Sen H., Javanthu s., Siha R., Sharma R. Inhalable biodegradable microparticles for target specific drug delivery in tuberculosis and process thereof. US20050084455, 2005.
16. Dutt M., Khuller G.K. Poly (DL – lactide-co-glycolide) microparticles as carriers for antimicrobial drug rifampin. *Ind. J Exp Biol*, 2000; 38: 887-894.
17. Sharma A.Q., S. Garg, G.K. Khuller. Role of poly (DL- lactic-co-glycolide) in development of a sustained oral delivery system for antitubercular drug(s). *Int J Pharm*, 2002; 239: 37-46.
18. Quenelle D.C., Staas J.K., Barrow E.L.W., Barrow W.W. Efficacy of microencapsulated rifampin in *Mycobacterium tuberculosis*-infected mice. *Antimicro Agents Chemother*, 1999; 43: 1144-1151.
19. Feng H., Zhang L., Zhu C. Genipin crosslinked ethyl cellulose – chitosan complex microspheres for anti – tuberculosis delivery. *Colloids and Surf B Biointerfaces*, 2013; 103: 530-537.
20. Lawlor C., Connor G.O., Leary S.O., Gallagher P.J., Cryan S.A., Keane J., M.P.O. Sullivan. Treatment of *Mycobacterium tuberculosis*- infected macrophages with poly (lactic-co-glycolic acid) micro particles drives NFkB and autophagy dependent bacillary killing. *PLoS ONE*, 2016; 11(2): e0149167. doi: 10.1371journal.pone.0149167.