NANOTECHNOLOGY BASED DRUG DELIVERY SYSTEMS FOR THE TREATMENT OF TUBERCULOSIS

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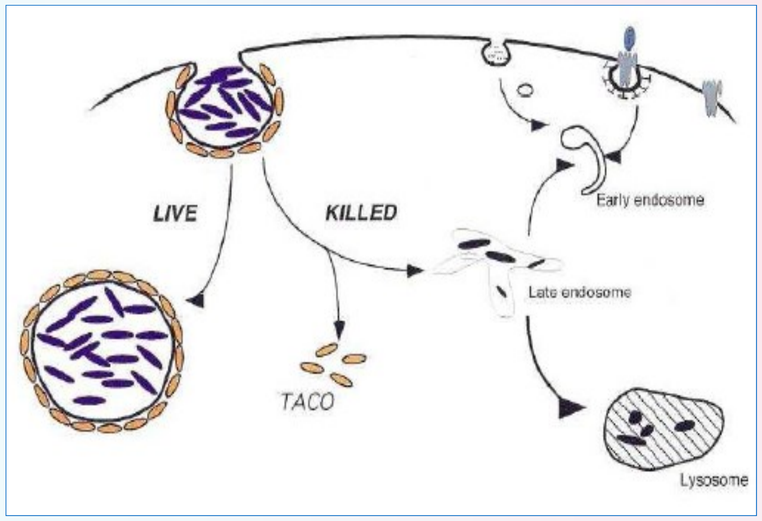
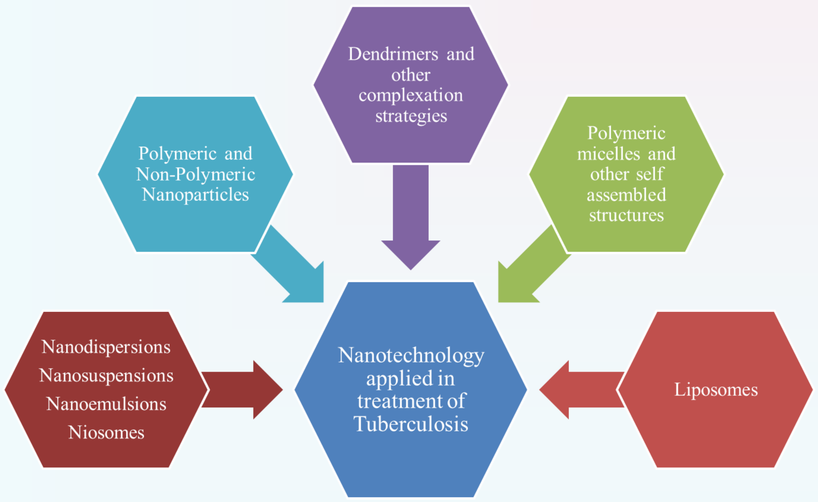
Introduction

- *Tuberculosis* has been a pervasive and fatal infectious disease of the respiratory system [1] and has been one of the most challenging diseases to treat in the sector of public health [2].
- Globally in 2012, about 8.6 million people have been infected with *Mycobacterium tuberculosis* according to WHO report of 2013 and an estimated 1.3 million deaths have been reported out of which India solely accounts for 2.2 million cases in TB [3]. In the recent years the death count up have seen surge especially in developing countries due to this endemic infection [4].
- The entry of *Mycobacterium tuberculosis* initiates TB infection which forms aerosol droplets in respiratory organs. The first contact point to any bacteria has shown engulf mechanism by alveolar macrophages where it is non-specifically phagocytosed followed by Lymphocytes T and bacterial antigens [5]. It multiplies exponentially by killing host defence cells and spreads locally in lymph nodes in Lungs with the help of lymphatic circulation system and this usually takes around 3 to 8 weeks from the date of initiation of infection. At later stages, this infection spreads to distant exasperated organs such as Central Nervous System (CNS), Spleen, liver, kidney, spinal cord and this usually takes around 12 to 14 weeks. [5]
- The first line agents therapy include Streptomycin and Multi-drug combination of Isoniazid (INH), Pyrazinamide (PYZ) and Rifampicin (RIF) and these drugs are usually administered with Ethambutol (ETB). [6].
- The lengthy regime therapy and the increased dosing frequency hampers patient lifestyle to a large extent and thus non-compliance and adherence to administration schedules have been the major cause for curative let-down and it contributes to the development of MDR strains at a resistant stage.
- WHO have proposed DOTS campaign in developing nations and also in underdeveloped countries but have failed probably due to the following points : (i) difficult to follow the regime of the therapy; and (ii) the pricy drugs used in the treatment.
- The development of Nanotechnology based Anti-TB drugs recommends the fixed dose combinations (FDC) of INH and RIF along with administration of PYZ or PYZ with ETB serving as First line treatment.
- The second line drugs have shown relatively higher toxicity as well as expensive than first line agents at the same time less active than former drugs.



Survival mechanisms of the *Mycobacterium,* in the macrophage host.



Approaches to deliver drugs in TB

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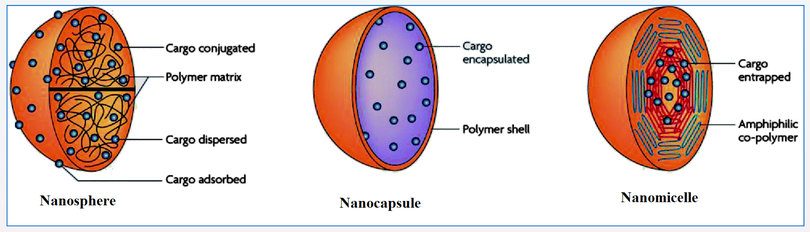

Nanotechnology applied	Drug Candidate used	Description	References
Nanodispersions			
Nanosuspensions	Clofazimine nanocrystalline suspension	Findings showed drug concentrations above the MIC of the pathogen following the administration of the nanoparticles: 81.4, 72.5 and 35.0 mg/kg tissue in spleen, liver and lung, respectively. Moreover, continued treatment led to a significant reduction of bacterial counts in all the organs evaluated. Effectiveness levels were comparable to those of liposomal clofazimine, however, the ease of preparation and the higher physical stability of the nanosuspension were distinguishing.	K. Peters, S. Leitzke, J.E. Diederichs, K. Borner, H. Hahn, R.H. Müller, S. Ehlers, Preparation of a clofazimine nanosuspension for intravenous use and evaluation of its therapeutic efficacy in murine Mycobacterium avium infection, J. Antimicrob. Chemother. 45 (2000) 77–83.
Nanoemulsions	Rifampicin Nanoemulsion (o/w type)	The entrapment efficiency was over 99% and the visual homogeneity was excellent for all the nanoemulsions. In vitro drug release studies indicated an initial burst effect ranging from 40 to 70% after 2 h, followed by a more moderated release afterwards. Finally, stability assays over 3 months indicated slight increases in the droplet size and the viscosity of the systems at 4 and 25 °C.	M. Ahmed, W. Ramadan, D. Rambhu, F. Shakeel, Potential of nanoemulsions for intravenous delivery of rifampicin, Pharmazie 63 (2008) 806–811.
Niosomes	Rifampicin loaded niosomal formulation	In vivo studies showed that by adjusting the size of the carrier, up to 65% of the drug can be localized in the lungs. In a more recent investigation, the same group of scientists extended the investigations and evaluated the biodistribution of niosomes with smaller sizes (1–2 μm) produced with different sorbitan esters (Span® 20, 40, 60, 80 and 85) and cholesterol in a 50:50 percent mol fraction ratio	C.P. Jain, S.P. Vyas, V.K. Dixit, Niosomal system for delivery of rifampicin to lymphatics, Indian J. Pharm. Sci. 68 (2006) 575–578.
Polymeric and Non-Polymeric Nanoparticles	Moxifloxacin loaded PBCA nanoparticles	Drug encapsulation efficiency ranged between 41.0% and 47.6% and the average size was 418 nm. Un-encapsulated drug (≈55%) was not removed from the formulation. Evaluation of the anti-TB activity in mice infected with M. tuberculosis showed a significant decrease in the mycobacteria count in the lungs after IV administration.	E.V. Shipulo, I.I. Lyubimov, O.O. Maksimenko, L.V. Vanchugova, E.A. Oganesyan, P.G. Sveshnikov, S.F. Biketov, E.S. Severin, L.B. Heifets, S.E. Gelperina, Development of a nanosomal formulation of moxifloxacin based on poly (butyl-2-cyanoacrylate), Pharm. Chem. J. 42 (2008) 145–149.
Polymeric micelles and self assembled structures	Rifampicin within polymeric micelles	Other amphiphilic block copolymers synthesized by linking mono and bifunctional PEG precursors of different molecular weight with PCL enabled the fine tuning of the HLB and the enlargement of the micellar core, improving the solubilization extent 5- to 7-fold.	M.A.Moretton,R.J.Glisoni,D. A.Chiappetta, A. Sosnik, Synthesis and characterization of amphiphilic poly/epsilon-caprolactone)-poly (ethyleneglycol) block copolymers. Optimization of the solubility and stability of rifampicin bymeans of encapsulation into polymeric micelles, BIOOMAT 2009, I Workshop on Artificial Organs, Biomaterials and Tissue Engineering, Latin American Society of Biomaterials, Tissue Engineering and Artificial Organs (SLABO), Rosario, Argentina, August 2009.
Liposomes	Gentamicin into liposomes	The encapsulated drug significantly reduced the bacterial count in spleen and liver. In addition, a dose-related reduction of the bacterial load, though no sterilization, was found. Similar results were obtained with different liposome-entrapped second-line antibiotics	S.P. Klemens, M.H. Cynamon, C.E. Swenson, R.S. Ginsberg, Liposome-encapsulated- gentamicin therapy of Mycobacterium avium complex infection in beige mice, Antimicrob. Agents Chemother. 34 (1990) 967–970.
Dendrimers and other complexation strategies	Rifampicin containing dendrimers	That the modified dendrimers sustained the release for about 120 h, as opposed to the fast delivery (<10 h) found with regular dendrimers.	P.V. Kumar, A. Asthana, T. Dutta, N.K. Jain, Intracellular macrophage uptake of rifampicin loaded mannosylated dendrimers, J. Drug Target. 14 (2006) 546–556.

Conclusion

- It can be concluded that nanotechnology based delivery of Anti-TB drugs can be an effective way to deliver the drugs to the target area. With the development of nanotechnology based drug delivery systems, the stability issues can be resolved. It also leads to development of a more efficacious, patient compliant and cost-effective TB pharmacotherapy.
- Moreover, Nanotechnology offers prolonged duration of treatment by increasing the bioavailability of the formulation. This property helps in better patient compliance and enables to administer the regime therapy.

References

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This Poster is presented at NIPiCON-2014 organized by Institute of Pharmacy, Nirma University, Ahmedabad