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Nanocarriers for Mycobacterium Tuberculosis

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Abstract: **Tuberculosis (TB) is considered as one of the biggest threats to the global health and one of the major reasons for death worldwide. It is considered to be caused by bacteria which are susceptible to drugs and its treatment is a lengthy process requiring a minimum of six months of medication. Subsequently, this results in incomplete treatment of the patient. One of the newly adopted Sustainable Development Goals by WHO is to end this TB epidemic by 2030. Nanoparticle technology helps to reduce the duration of treatment and helps in effective delivery of the drugs. This review article aims to highlight effective and the multiple advantages of nanoparticles in drug delivery of tuberculosis.**

However, in some cases nanoparticles also bring with them unique challenges to our society and environment, due to their toxic nature. In this review article, we have highlighted the role of nanoparticles for diagnosis, treatment, and in drug delivery.

Index Terms: **TB, Nanoparticle technology, nanoparticles, drug delivery, quantum dots, toxicity.**

I. Introduction

Tuberculosis (TB) is an infectious disease declared by World Health Organisation, (2016) caused by the bacterium Mycobacterium tuberculosis (MTB) which is mostly affecting lungs. It is spread by sneezing, coughing, or spitting bacilli in the air. A person needs to inhale only a small number of bacilli to get infected. The symptoms of TB are fever, weight loss, chills, night sweats and chronic cough with blood-containing sputum. It kills approximately two million people every year making it a global epidemic disease.

Different techniques are used for diagnosis of TB. Imaging being the basic technique of all. Others include breath analysing techniques, immunologic tests of tissues, magnetic resonance imaging, computed tomography. Sadaphal, P., Rao, J., Comstock, G. W. & Beg M. F. (2008) have reported Ziehl-Neelsen stain technique. Volatile organic compounds (VOCs) are often used for diagnosis of TB. Use of quantum dots (nanoscale semiconductor crystals) (QDs) has gained impetus during recent years due to their electronic and tunable optical emission properties. Matea, C. T., Mocan, T., Tabaran, F., Pop, T., Mosteanu, O., Puia, C., Iancu, C. & Mocan L. (2017) have shown that Quantum dots can be used as theranostic platform i.e., for detection and treatment together. Yang, H., Qin, L., Wang, Y., Zhang, B., Liu, Z., Ma, H., Lu, J., Huang, X., Shi, D., & Hu, Z. (2015) used nano detection method i.e., they coupled quantum dots (QDs) and magnetic microspheres for diagnosis of Mycobacterium tuberculosis. Bhattacharyya, D., Sarswat, P. K. & Free, M. L. (2017) have reported synthesis of carbon dots and CdSe QDs fluorescent sensor system which enables quick diagnosis of TB.

Treatment of TB is very lengthy process and requires almost 6 months for curing it completely. If the treatment is left in between, it results in drug resistant TB as reported in a Global Report, Multidrug and extensively drug resistant TB: (2010). The reason being that either the drugs used for treatment reach the infected site slowly, or they don't remain there for long to produce the desired effect. Also, the available drugs have severe side effects. World Health Organization introduced DOTS program (Direct Observed Therapy, short course) but it has not been able to resolve the cases of drug resistant TB. Hence, there is need for alternative, faster methods of medications.

Today the drugs are required which have fewer side effects, are easily available, are stable and have controlled release hence the focus is towards microemulsions as reported by Chan, J., El Maghraby, G. M. M., Craig, J. P. & Alany, R. G. (2007). Microemulsions are highly stable and transparent and when used as drug delivery systems they increase the solubility of the drug, thus increasing its bioavailability. Mostly, microemulsions are used to encapsulate different solubility drugs as shown by Nornoo, A.O., Osborne, D. W. & Chow, D. S. L. (2008) and

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Narang, A. S., Delmarre, D. & Gao, D. (2007). Because of high solubility, easy absorption, less toxicity, microemulsions are used nowadays as drug delivery systems (DDS). Mehta, S. K., Kaur, G. & Bhasin, K. K. (2007) have reported that Microemulsion composed of phosphate buffer, oleic acid, Tween 80, ethanol has proved as effective drug delivery system (DDS) for an antitubercular drug isoniazid.

Another alternative to microemulsions is nanoparticles-based medications and drug delivery systems. Nanotechnology is an emerging branch of interdisciplinary Science which has provided new and innovative ways of drug delivery systems and helped in controlling infections caused by bacteria at the molecular level by transporting drugs to required physiological sites and targeting phagocytic cells infected by intracellular pathogens. Thus, they help in reducing dosage of required drugs. Nanoparticles also play a significant role in the treatment and prevention of tuberculosis (TB).

II. Synthesis of Nanoparticles

Hu, A., Yao, Z., & Yu, X. (2009) have shown the use of micro emulsion method in the preparation of particles of various sizes and shapes. Pileni, M. P. (2003), Chhabra, V., Free, M. L., Kang, P. K., Truesdail, S. E. & Shah, D. O. (1997) have reported synthesis of nanoparticles from microemulsions and their properties. Destree, J. & Nagy, B. (2006), have demonstrated synthesis of nanoparticles from microemulsions and their mechanism. Julian, E., Martin, J., Hollamby & Laura, H. (2006), have reported their formation using reversed micelles.

Nanoparticles are considered to be formed from biodegradable materials which may be synthetic like polyalkylcyanoacrylates or natural like albumin. Due to their small size, they are easily and effectively transported to the target site Thus, nanoparticles prove to be effective transporters and help in delivery of drugs. The drug present in these nanoparticles reaches target site either by degradation or diffusion. Thus, they help in efficient and controlled release of drug. Muller, R. H. Mehnert., W., & Lucks, J.-S. et al., (1995) have shown that these solid lipid nanoparticles are used in effective delivery of drugs in controlled way. Vauthier, C., Dubernet, C., Fattal, E., Pinto-Alphandary, H., Couvreur, P. (2003), Couvreur, P, Barratt, G., Fattal, E., Legrand, P., Vauthier, C. (2002), Soppimath, K. S., Aminabhavi, T. M., Kulkarni, A. R., Rudzinski, W. E. (2001) and many more scientists have given numerous methods for synthesis of bactericidal nanoparticles. Wissing, S. A, Kayser, O. & Mülle, R.H. (2004) in their article have showed the use of different types of lipid nanoparticles and methods of their production. Singh, R., Nawale, L., Arkile, M., Wadhwani, S., Shedbalkar, U., Chopade, S., Sarkar, D. & Chopade, B. A. (2016) have reported the synthesis of silver, gold, and bimetallic nanoparticles from medicinal plants and shown their uses as novel antitubercular agents to selectively kill mycobacteria, resulting in enhanced efficiency.

III. Different Routes of Drug Delivery

A. Oral Administration

Nanoparticle drug delivery system have been useful in number of ways. Due to their small size and stability, oral administration of these drugs is advantageous. They help in release of drugs in sustained manner thereby prolonging the circulation of the drugs and increasing the efficacy, which has been reported by Pandey, R., Zahoor, A., Sharma, S. & Khuller, G. K. (2003) and Sharma, A., Pandey, R., Sharma, S. & Khuller, G. K. (2004). Most commonly a mixture of three drugs encapsulated in poly(lactide-co-glycolide) (PLG) nanoparticles are used. They are Pyrazinamide (PZA), Rifampin (RMP) and Isoniazid (INH). The absorption of the drugs is increased due to bioadhesive property of these nanoparticles, which in turn results in greater bioavailability of the drugs. Sharma, A., Sharma, S., & Khuller, G. K. (2004) have reported that the efficiency of these PLG nanoparticles is further enhanced by attaching wheat germ agglutinin to them.

B. Inhalation

If drug is taken through inhalation, they reach lungs without undergoing metabolism, as a result higher concentration of drug reaches target site thus increasing the efficacy of drugs. Pandey, R. & Khuller, G. K. (2005) have reported that due to small size of nanoparticles, deposition of these particles is very less in the lungs. Advantage in preparation of these nanoparticles is that use of organic solvents is avoided. Also, when drugs (RMP, INH and PZA) are taken via nebulization i.e., respiratory route, therapeutic effect is found to be much more as compared to drug taken through oral administration. Since the drugs reach to the lungs directly, chances of systemic toxicity are reduced.

C. Intravenous Administration

This route is useful when drugs are having particle size more than micrometers and they cannot be transported through intravascular way. Nanoparticles have advantage of small size of nanometers and can pass through capillaries. After administration, nanoparticles are endocytosed by macrophages and monocytes. Pinto-Alphandary, H., Andremont, A. & Couvreur, P. (2000) and Kayser, O., Olbrich, C., Croft, S. L. & Kiderlen, A. F. (2003) have shown that targeted delivery of antibiotics and anti TB drugs using nanoparticles increases the amount of drug reaching target site, so lesser dose of drug is required. This increases efficiency of drug and lowers the risk of side effects.

Anisimova, Y. V., Gelperina, S. E., Peloquin, C. A. & Heifets, L. B. (2000) have shown that when streptomycin and INH are encapsulated by poly(butyl cyanoacrylate) nanoparticles, activity against intracellular M. tuberculosis in human monocyte-derived macrophages is enhanced. Patients suffering from M. avium infection are given Clofazimine (a riminophenazine compound) but it has limitation of poor solubility. Peters, K., Leitzke, S.,

Diederichs, J. E., Borner, K., Hahn, H., Muller, R. H. & Ehlers, S. (2000) have reported that to overcome this, drug has been formulated as nanosuspension and administered as intravenous injection which results in increased efficacy.

Mohanty, S., Jena, P., Mehta, R., Pati, R., Banerjee, B., Patil, S. & Sonawane, A. (2013) and Jena, P., Mohanty, S., Mallick, R., Jacob, B. & Sonawane, A. (2012) have reported in their papers that silver nanoparticles (Ag NPs) are used in cases of multidrug resistant mycobacteria to kill bacteria without causing any damage to DNA when mycobactericidal doses were used. However, when higher doses of Ag NPs were used, it resulted in toxicity.

Yang, H. Y., Fu, Y., Jang, M. S., et al. (2016) prepared quantum dots from alloy CdZnSeS/ZnS which were covered with polymer ligands having dihydrolipoic acid, which acted as sensors to examine reaction of clofazimine and proteins. Park, Y., Jeonga, S. & Kim, S. (2017) have reported that due to presence of heavy metal Cd, these QDs are toxic. For therapeutic purpose, they should have minimum toxicity. Vasudevan, D., Gaddam, R. R., Trinchi, A. & Cole, I. (2015) have published that to reduce toxicity, they are coated with micelles made of phospholipids. As a result, their optical properties remain unaltered, due to covering of phospholipid layer and unwanted adsorption is prevented. Other strategy reported by Chan, W. C., Maxwell, D. J., Gao, X., Bailley, R. E., Han, M. & Nie, S. (2002) was conjugation of QDs to antibodies. Thus, by using these techniques, toxicity of these QDs can be reduced.

This field remains of interest for scientific community to develop better drugs, with low toxicity and high efficacy.

Conclusion

Till today, Tuberculosis is considered as global health issue. Nanoparticles serve as effective drugs and also play an important role in drug delivery system. They serve as an alternative approach to antimicrobial treatment and have proved to be potential drugs in treatment of tuberculosis. They are cost effective, have enhanced bioavailability due to which less doses are required, lowering the side effects. They can be administered easily via oral route, inhalation or intravenously. Studies have proved that when nanoparticles are used in lesser quantity against human pathogens, they kill bacteria without causing any damage to host cells. So controlled doses of these drugs, help in the treatment of drug resistant bacteria. Tailored-based nanoparticles can be released in sustained manner. Research is still going on to develop technologies, to reduce the use of organic solvents and proper elimination of nanocarriers and its polymers, after use. Also, emphasis is being given to use of natural polymers like chitosan. Lot of interest has been developed in Quantum dots which serve as theranostic platform i.e., for diagnosis and treatment together. Research is going on to develop nanoparticles-based vaccine for immunization. Thus, nanotechnology proves to be a potential field of study for further development of anti TB drugs with greater efficacy and low toxic effects.

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