Delivery methods for treatment of tuberculosis

INTRODUCTION

The Mycobacterium tuberculosis is a rod-shaped bacillus bacterium which is responsible for an infectious disease tuberculosis. Tuberculosis is chronic bacterial, air borne, contagious disease, which commonly affects lungs and spreads from person to person when active TB patient expels bacteria by coughing or sneezing.(Villemagne et al., 2012). After HIV, Tuberculosis claims world's second deadliest disease caused by single infectious agent. (Moualeu et al., 2015). In worlds population, one third of individuals are infected with dormant infection, but only 10% of infected people will be symptomatic.(Villemagne et al., 2012). As mentioned in WHO data, yearly global tuberculosis report 2014, it is estimated that 9 million people were symptomatic and develop active TB and out of them, 1. 5 million people were died in 2013. Probability of occurrence of TB in HIV patients is high because 360000 out of the 1. 5 million deaths were HIV positive. Most of TB cases occur in poorest countries like South-East Asia and West Pacific and African regions. It also affects countries like India and China to some extent. Tuberculosis is a preventable and curable disease with effective diagnosis and treatment because 37 million lives were saved between 2000 and 2013. (WHO, 2014). The effective treatment of tuberculosis follows multi drug regimens, in which first-line therapy includes four drugs (isoniazid, rifampicin, ethambutol, pyrazinamide) administered during initial intensive stage for two months and followed by continuous phase with rifampicin and isoniazid for four months.(Sosnik et al., 2010). When first-line drugs are mismanaged, therapeutic failure occurs, which leads to multi-drug resistant TB (MDR-TB) which is difficult to treat. Then second line agents such as

flouroquinolones and aminoglycosides are given, which are more expensive, more toxicity and less potent. Next stage follows extensively drug resistant TB(XDR-TB) which occurs when second line agents are misused, and disease becomes severe.(Kaur and Singh, 2014). Rifampicin is one of the potent and effective antibiotic and is first drug of choice for long term continuous therapy (six months) and it is having severe side effects as acute renal failure, hepatotoxicity.(Son and McConville, 2011). Chemical name of rifampicin is 3-[[(4-methyl-1-piperazynl)imino]-methyl]-rifamycin.(Argekar et al., 1996). It shows bactericidal activity by binding to β-subunit of the DNA dependent RNA polymerase and inhibits the bacterial RNA synthesis. Rifampicin facing severe toxicity problems can be solved by reducing the frequency of administration and maintaining a controlled release which is possible by lipid based nanoparticles.(Labuschagne et al., 2014). It is classified as BCS class Ó Ó drug (low solubility and high permeability) and due to poor aqueous solubility and poor bioavailability, this drug is best suitable for lipid based nanocarriers which shows good lipid solubility. (Moretton et al., 2010). Cubosomes are lipid based sub-micron, discrete nanoparticles of liquid crystalline phase with cubic crystallographic symmetry.(Achouri et al., 2014). When amphiphilic lipid is made contact with excess water then it forms a self-assembled liquid crystalline structure of bicontinuous cubic phase and inverse hexagonal phases.(Nguyen et al., 2011). Cubosomes are composed of a lipid and surfactant, first lipid (monoolein) due to its amphiphilic nature it has an ability to solubilize both hydrophilic, hydrophobic and amphiphilic molecules. It is non-toxic, biodegradable and biocompatible material, which is approved by FDA inactive ingredients. Second hydrophilic non-ionic surfactant (poloxamer

407), it is triblock copolymer two hydrophilic blocks of polyethylene oxide (PEO) and hydrophobic block of polypropylene oxide (PPO) that is (PEO-PPO-PEO).(Achouri et al., 2014). Cubosomes are best suitable for poorly water soluble drugs, and they increase solubilisation of drug and maintain controlled release.(Boyd, 2003) Rifampicin is the only lipophilic drug in all anti-TB first-line drugs. This drug delivery system enhances drug solubility and bioavailability and reduces toxicity and maintains controlled release at the target site.

In this study, we prepared rifampicin loaded cubosomes by hot melt method. The main objective of the study to reduce the dose and maintain controlled release, and it is also capable of increasing solubility and bioavailability of the drug. The optimized formulation ratio was fixed by the results obtained by varying dependent and independent variables using response surface methodology (RSM) with a 3^2 full factorial design.

Materials & Methods

Rifampicin was obtained as a free sample from Lupin (Lupin pharmaceuticals, Pune), Peceol was purchased from and poloxamer 407 was purchased from and millipore water was used for all experiments.

Preparation of rifampicin loaded cubosomes

Rifampicin loaded cubosomes are prepared by using hot melt method.(Boyd, 2003). In this method, Peceol, poloxamer 407 and drug were taken as organic phase and mixed until the drug is completely entrapped in the dispersed phase. And then organic phase and aqueous phase (water) were

heated at 70ºC and aqueous phase was added slowly to organic phase under stirring. Then bulk cubic gel was fragmented by high speed homogenisation (Ultraturrax, 12000rpm) for 10 minutes and ultrasonication for 5minutes. The final dispersion was stored at room temperature.

Experimental design

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