This chapter outlines the hypothesis underlying the proposed study, its overall aim and specific objectives, along with the plan of work. It also provides a rationale for the same, based on the lacunae in the present anti-TB therapy and potential of the proposed approach as outlined in the literature survey.

3.1: Research envisaged:

During the last four decades, therapeutic systems based on polymers (both natural and synthetic) have been shown to be effective in controlling rate or time of drug release, in enhancing drug targeting specificity while lowering the systemic drug toxicity and providing protection for pharmaceutical agents against degradation.

An important consideration in the treatment of tuberculosis is that, the *Mycobacterium tuberculosis* has the ability to persist intracellularly in the host macrophage for long periods of time (Quenelle *et al*., 2001). Therefore, the ability of the antibacterial agent to eradicate the micro-organisms within the macrophage is of key importance.

Most of the anti-mycobacterial agents used presently in such treatments failed to penetrate macrophages. For this purpose, many of the researchers are considering the use of appropriate drug delivery systems, as to make them therapeutically more effective.

It is well known that micro-particulate drug delivery system technology can be used to achieve sustained release of anti-mycobacterial agents, when they are formulated in sizes larger than 50 μm (microspheres are more than this size i.e. may be up to 1000 μm), or to target drug delivery systems to specific cells (i.e., macrophages), when delivery systems are formulated in sizes <150μm.

Rifampicin and isoniazid are both first-line drugs for use in the therapy of tuberculosis and are included in the list of recommended drug regimens for treatment of latent *M. tuberculosis* infection in adults. They have been used in combination for treatment of tuberculosis in clinical trials of human immunodeficiency virus-negative and human immunodeficiency virus-positive persons (Quenelle *et al*., 2001). Both, rifampicin and isoniazid have a short half life ranging from 1 to 4 hrs. Rifampin and isoniazid are required in high-doses and for prolonged treatment (i.e. 4-6 months).

Isoniazid has a pronounced absorption from all the three sections of the small intestine (Mariappan and Singh, 2003) and from intramuscular injection sites.
Isoniazid is inactivated in the liver, mainly by acetylation and dehydrazination; the rate of acetylation is genetically determined and subject to individual variation. Long-term continuous therapy with isoniazid leads to hepatotoxicity and peripheral neuritis. It is thus important to have a drug formulation with controlled release of isoniazid, especially in the small intestine (Rastogi et al., 2007).

Rifampicin develops resistance (Rand et al., 1999), while its numerous side effects have been reported in long term therapy (Mandell and Sande, 1985). For these reasons, several types of novel drug delivery devices have been proposed and characterized for rifampicin administration, in order to maximize the therapeutic and minimize the toxic and side effects of this drug (Jain and Vyas, 1995; Nakhare and Vyas, 1997; Pandey et al., 2003).

Polymeric drug carriers are an important component of sustained drug delivery systems discussed above. Although experience with synthetic polymers is extensive and encouraging, more recently the trend has been to shift towards natural polymers as alginate and chitosan. Main advantages of these polymers are their low cost and compatibility with the encapsulation of a wide range of drugs, with minimal use of organic solvents. Furthermore, bio-adhesion, stability, safety and approval for human use by the US FDA are additional advantages.

Bioenhancers are the agents capable of enhancing the bioavailability and bioefficacy of a particular drug with which it is combined, without typical pharmacological action. The extract of *Carum carvi* alone and in combination with *Zingiber officinale* and or piperine was found to be increase drug release by 20-110% (Qazi et al., 2003; Qazi et. al., 2007). The extensive literature survey points out to the fact that piperine and extract of *Carum carvi* are the most popular and effective bioenhancers used to improve the bioefficacy of a large number of drugs.

### 3.2: Assumptions and hypothesis:

On this background, we propose that the bioenhancers and *in-vitro* drug release are co-related with each other and we use isoniazid and rifampicin as model antitubercular drugs and formulate the microspheres of these drugs using various methods and incorporate the bioenhancers in to the drug-loaded microspheres. Bioenhancers used in the proposed research work are *Piper nigrum* and *Carum carvi*. 
3.3: Aim and Objectives:

**Aim:** The proposed research project aims to advance the present anti-TB therapy of isoniazid and rifampicin by attempting to overcome some of their major constraints (such as compliance and dose-related toxicity) through the design of appropriate drug delivery system.

**Objectives:** The objectives of the research work are:

a. To develop particulate carriers (microsphere formulation) for the delivery of rifampicin and isoniazid (two most widely anti-tubercular agents), and to evaluate their appropriateness for drug delivery

b. To incorporate the herbal bioenhancers i.e. *Piper nigrum* and *Carum carvi* (singly and in combination) into the drug microspheres

c. To evaluate the drug loaded microsphere containing bioenhancers for various characteristics like particle size, percentage yield, percentage entrapment efficiency, percent bioadhesion and intestinal permeability using intestinal sac method and in-vitro drug release.

3.4: Methodology:

This research work attempts to use microparticle drug delivery system for anti-tubercular agents along with use of herbal bioenhancers to study the release profile of drug. Hence, a methodology is designed as:

a. Design and evaluate a novel drug delivery system comprising of microparticles of anti-tubercular agents;

b. Incorporate herbal bioenhancers in the formulation (singly and in combination) and study their effect on bioavailability of anti-TB drugs;

c. Ascertain whether the bioenhancer affects the drug release when drug formulated in the form of microsphere.

d. Ensure that the drug delivery system thus designed is elegant, effective and stable.
3.5: Expected outcomes:

This study is expected to provide an innovative approach to the formulation of the anti-TB agents so as to overcome the present constraints of anti-TB therapy, i.e. loss of efficacy through bacterial resistance, side effects and low patient compliance. It combines a new drug delivery system (microparticles) along with new method to enhance bioavailability (bioenhancers - *Piper nigrum* and *Carum carvi* - singly or in combination) for this purpose.