Chapter Three

Rationale, Objectives and Plan of Work
3.1. RATIONALE OF WORK

Tuberculosis is a hazardous disease, which gradually swallow the life span of human beings. World wide it is estimated that one third of population is infected with *Mycobacterium tuberculosis* which results in 7.96 million new cases of tuberculosis annually with 80% of all incident cases being found in 22 countries and more than 40% in five South East Asian countries. The World Health Organisation (WHO) recommends the use of fixed dose combination product for therapy to improve patient compliance and reduce the chance of relapse. Unfortunately the combination of drugs in a formulation has been associated with problems of poor bioavailability of rifampicin from fixed dose combination (FDC) product containing isoniazid and/or pyrazinamide. It is a matter of serious concern because of the small therapeutic margin (around 10%) between prescribed dose (10 mg/kg body weight) and the minimum dose (9 mg/kg body weight), less than 9 mg/kg body weight can results in therapeutic failure and hence can be cause of drug resistance.

Several studies indicated that rifampicin bioavailability rapidly lost in presence of isoniazid under acidic stomach condition. Several reasons have been cited for this interaction, but the most appropriate being a chemical reaction between the metabolite of rifampicin, 3-Formyl rifamycin and isoniazid, leading to the formation of isonicotinyl hydrazone of 3-formyl rifamycin (HYD) under acidic condition leading to reduced drug absorption and decreased bioavailability. A work regarding the study of specific absorption site of rifampicin and isoniazid indicate that rifampicin is better absorbed in the stomach and duodenum which is the distal part of the intestine. But the case of isoniazid is different, which is apparently much less permeated through the stomach and is mainly absorbed through the intestine. This means that if a formulation can result in site specific release of two drugs the problem of interaction can be solved i.e. release of rifampicin in the stomach and release of isoniazid in the intestine. Microencapsulation method is most suitable and appropriate method which can be used to segregate the two drugs in the biological fluids. There are several other routes of drug delivery e.g. inhalational and parenteral, which have been explored and it is known that oral route show better patient compliance. Thus this project was designed to develop an oral particulate delivery system with improved oral bioavailability of rifampicin in presence of isoniazid by minimizing the chemical interaction between the metabolites of rifampicin with isoniazid under acidic condition and further to evaluate the antimycobacterial activity of the optimized formulation for intestinal tuberculosis. The selected dosage regimen for the treatment of intestinal tuberculosis was same as they are used for the treatment of pulmonary tuberculosis.
3.2. OBJECTIVES OF WORK

The aim of the present work was the development of oral particulate system of rifampicin and isoniazid for intestinal tuberculosis. The major objectives were:

➢ To develop a site specific particulate delivery system of antimycobacterial drugs, this would overcome the bioavailability problems, reduce the dose dependent side effects of the drugs and also minimize the dosing frequency of the formulations.

➢ To evaluate the system for intestinal antitubercular activity.

➢ To evaluate the system for *in vitro* drug release using *in vitro* release apparatus.

➢ To evaluate the possibility of drug-polymer (excipients) interference and interaction by interference and interaction studies.

➢ To perform the *in vivo* studies of the formulation on animals.

➢ To determine the physicochemical stability and shelf life of the formulations.
3.3. RESEARCH ENVISAGED

In an attempt to develop particulate drug delivery system of antitubercular drugs, the following plan was envisaged.

➢ Physicochemical characterization and identification of drugs
  • Organoleptic properties
  • Melting point
  • Solubility
  • pH
  • Identification by fourier-transform infrared spectroscopy (FTIR)
  • Identification by differential scanning calorimetry (DSC)
  • Identification by ultraviolet (UV) spectral analysis

➢ Analytical methodology
  • Ultraviolet (UV) spectrophotometry
  • High performance thin layer chromatographic (HPTLC) method development for isoniazid and rifampicin

➢ Drug polymer interference study

➢ Drug polymer interaction study

➢ Formulation and optimization of microparticles

➢ Evaluation of optimized microparticles
  • Morphological characterization of microparticles
  • Particle size determination of microparticles
  • Drug entrapment efficiency study
  • In vitro bioadhesion test
  • Study of swelling behaviour of microparticles
  • Drug polymer interaction study in microparticles
  • In vitro drug release study in simulated gastric fluid as well as in simulated intestinal fluid
  • Release kinetics study

➢ In vivo studies

➢ Assessment of antibacterial efficacy of optimized formulation

➢ Assessment of antmycobacterial efficacy of optimized formulation for intestinal tuberculosis

➢ Stability study of optimized microparticles according to various guidelines

➢ Formulation and evaluation of oral prolonged release drug delivery system