CHAPTER 11

SUMMARY
With respect to tuberculosis, "Global Health Emergency" was declared by World Health Organization (WHO) in 1997. The management of tuberculosis has become complicated in monotherapy due to drug resistance development. Rifampicin, isoniazid, pyrazinamide and ethambutol were earlier used as separate formulations as the first line therapy. To overcome the problem of resistance, fixed dose combination therapy was suggested by WHO and International Union Against Tuberculosis and Disease (IUATLD). The major issue with TB therapy is the poor oral bioavailability of rifampicin. The main reason behind poor bioavailability of rifampicin was found to be the degradation of rifampicin in acidic media in presence of isoniazid.

In the present investigations, various formulations were fabricated to arrest the problem of degradation of rifampicin in acidic medium. Gastro-retentive rifampicin tablets (containing polymer hydroxypropyl methylcellulose K4M), enteric coated isoniazid capsule (coated with Eduragit L100-55), floating minitablets of rifampicin using hydroxypropyl methylcellulose K4M, gastro-retentive minitablets of rifampicin using polyethylene oxide WSR, enteric minimatrices of isoniazid coated with hydroxypropylmethylcellulose phthalate (HPMCP) and enteric sustained release microcapsules of isoniazid were fabricated.

Gastroretentive tablets of rifampicin were prepared by the wet granulation method using hydroxypropyl methylcellulose, calcium carbonate, and polyethylene glycol 4000. Hard gelatin capsules (size 4) containing a compacted mass of isoniazid and dicalcium phosphate were enteric coated using 2 % w/v of Eudragit L100-55). The minitablets of isoniazid were prepared using isoniazid, hydroxylpropylmethylcellulose phthalate (30 gm) and dibasic calcium phosphate by cold extrusion technique. The minitablets were coated using 2% w/v HPMC. Floating minimatrices of rifampicin were fabricated using rifampicin , hydroxypropylmethylcellulose K4M and calcium carbonate by cold extrusion technique. Gastro-retainentive minitablets of rifampicin were developed using rifampicin, polyethylene oxide WSR and calcium carbonate by cold extrusion technique. Enteric
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Microcapsules of isoniazid were formulated using isoniazid, sodium alginate and HPMCP by modified emulsification method. Calcium chloride solution was used for the crosslinking of sodium alginate to prepare microspheres which was coated by HPMCP upon evaporation of nonaqueous phase.

All the formulations were characterized for quality control. The flowability of granules/minitablets was estimated by Carr’s index, the Hausner ratio, and the angle of repose. The friability of granules/minitablets was determined by rotating the granules/minitablets in a friabilator (US Pharmacopeia [USP] XXIII, Electrolab, Mumbai, India) for 60 minutes at 25 rpm. The tablets were characterized by crushing strength (8M tablet-hardness testing machine, Dr Schleuniger Pharmatron, Solothurn, Switzerland), lag time to float, and duration of floating in 0.1N HCl. Particle size and particle size distribution were carried out by microscopical or sieving method. All the formulations showed acceptable pharmaceutical characteristics.

A biorelevant modified dissolution assembly was setup to overcome the problem of concentration dependent degradation of rifampicin in acidic medium in the USP XXIII dissolution apparatus. The comparative degradation study of rifampicin was carried out in both the dissolution apparatus and modified dissolution apparatus. It was found that the degradation of rifampicin was substantially reduced in case of gastro-retentive dosage forms when modified dissolution assembly was used.

Drug release mechanism was found to be zero order for all the gastro retentive dosage form when Bamba et al reported method was used for determining drug release mechanism. Due to the zero order drug release mechanism, the degradation of rifampicin was controlled through out in vitro drug release study. Similar results were found when combinations of rifampicin and isoniazid formulations were used for the invitro drug release study in modified dissolution assembly. Through out in vitro drug release and in vitro drug degradation study it was found that all the gastro-retentive rifampicin formulation showed less than 1% degradation of rifampicin in presence of isoniazid when
modified dissolution assembly used. The prevention of isoniazid release in acidic medium prevents exaggeration of degradation of rifampicin as well as gradual release of rifampicin (zero order) showed less degradation in presence of isoniazid. Under the short term stability study, all the formulations were also found to be stable.

The similarity in performance of all the formulations was studied by preparing three combination formulations of all the six formulations (Formulation A, formulation B and formulation C) Formulation A was capsule containing gastro-retentive rifampicin tablet and enteric coated isoniazid capsule. Formulation B was capsule containing floating minimatrices of rifampicin (HPMC K4 M) and enteric minitablets of isoniazid (coated with HPMCP). Formulation C was capsule containing floating minitablets of rifampicin (Polyethylene oxide WSR) and enteric sustained release microcapsules of isoniazid. The similarity factor ($f_2$) was determined for in vitro drug release profiles of all the three formulations by conventional method and using a new scheme of calculating weight. In both the method similarity factor was in the range of 50-100.

In the conclusion, the functionality of rifampicin can be improved by fabricating gastro-retentive dosage form of rifampicin and enteric dosage form of isoniazid in fixed dose combination therapy of tuberculosis. Hence, the oral bioavailability of rifampicin can be improved and drug resistance of antitubercular drug can be controlled by altering the degradation of rifampicin.