CHAPTER 1

AIM OF THE PRESENT WORK
1. Aim of present work

Tuberculosis (TB) has been a scourge of mankind for thousands of years and remains one of the deadliest diseases in the world today, with an estimated eight million new cases and at least two million deaths every year (Bloom, 1992; Dye, 1999).

Tuberculosis has been declared a public health emergency by the World Health Organization (WHO). The emergence of multi-drug resistance TB (MDR-TB) has threatened the efforts of TB control. World Health Organization and International Union Against lung and tuberculosis diseases (IUATLD) recommend the use of fixed-dose combination (FDC) formulations of the essential antitubercular drugs as one further step to ensure adequate treatment of patients (Maher, 1997).

Rifampicin, isoniazid, pyrazinamide and ethambutol were earlier used as separate formulations as the first line therapy. The major issue with TB therapy is the poor oral bioavailability of rifampicin. The reasons for poor oral bioavailability are listed below:

1.1 Poor solubility/permeability of rifampicin
Gallo and Radaelli found that rifampicin is more soluble at low pH (1 in 5 of 0.1M HCl) and it is less soluble in alkaline medium (1 in 100 of phosphate buffer of pH 7.4 at 37°C) (Gallo, 1976). Prankerd and co-workers reported that solubility of rifampicin at 25°C is 1 in approximately 10, 250, and 360 parts of water at pH 2, 5.3, and 7.5 respectively (Prankerd, 1992).

1.2 Stability of rifampicin in gastro-intestinal fluid
Gallo and Radaelli found that in solid state rifampicin is stable up to 5 years at 25°C. In aqueous solution, degradation is catalyzed by both acid and base (Gallo, 1976). Rifampicin is hydrolyzed to 3-formyl rifampicin SV (3FRSV) and 1-amino 4 methyl piperazine under acidic pH and oxidizes to rifampicin quinone in phosphate buffer (Gallo, 1976).
Maggi and co-workers concluded that rifampicin is converted to rifampicin quinone at pH 8. The quinine formation can be prevented by adding ascorbic acid, which reduces rifampicin quinone to rifampicin (Maggi, 1968). At pH 8.2, rifampicin forms 25-desacetyl rifampicin, which is insoluble in the alkaline medium (Maggi, 1968). Pranker and co-workers reported that rifampicin show maximum stability at pH 5 (Pranker, 1992).

Shishoo and co-workers reported that isoniazid triggers the degradation of rifampicin in acidic medium (Shishoo, 1999). Singh and co-workers reported that the increased decomposition of rifampicin in the presence of isoniazid is due to the formation of hydrazone (Singh, 2000). Savale and co-workers reported the presence of isoniazid enhances degradation of rifampicin in acidic environment which is reflected in impairment of bioavailability of rifampicin from rifampicin plus isoniazid fixed dose combination formulation as compared to rifampicin capsule (Savale, 2006). Singh and co-workers reported that rifampicin is well absorbed from stomach due to its high solubility at pH 1-2 and isoniazid from intestine due to its high solubility in intestine (Singh, 2003). Singh and co-workers further reported that a delivery system is required to release rifampicin in the gastric medium and isoniazid in intestine (Singh, 2003).

1.3 Miscellaneous reasons

Henwood and co-workers found that crystalline form II and amorphous form of rifampicin rapidly dissolves in gastric fluid (Henwood, 2000). Pelizza and co-workers suggested that polymorphism of rifampicin is also a reason for variable bioavailability (Pelizza, 1977). Boman and co-workers reported that adsorption of rifampicin on excipient like bentonite may affect bioavailability of rifampicin (Boman, 1974).

Khalil and co-workers reported that antacids decrease oral absorption of rifampicin (magnesium trisilicate> aluminium hydroxide>sodium bicarbonate) (Khalil, 1984). Panchagnula and co-workers reported that oral absorption of rifampicin is decreased in
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presence of food (Panchagnula, 2003). Loos and co-workers examined the influence of enzyme induction by rifampicin on its presystemic metabolism (Loos, 1985).

Devani and co-workers discussed kinetics of hydrazone formation from isoniazid in presence of reducing sugars (Devani, 1985).

It is well known to those skilled in art that the drug degradation in any medium is concentration dependent.

The following objectives were kept in mind:

1. To develop novel formulations of rifampicin and isoniazid with improved patient compliance and better clinical efficacy
2. To arrest degradation of rifampicin in stomach
3. To extend release of rifampicin at the absorption site (stomach)
4. To segregate rifampicin and isoniazid to arrest degradation of rifampicin
5. To prevent release of isoniazid in stomach
6. To release isoniazid at the site of absorption, i.e. intestine
7. To develop biorelevant dissolution testing
8. To use the Quality by Design concept of USFDA.
1.4 References


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