Tuberculosis is a global public health threat. The antitubercular regimen containing rifampicin and isoniazid is the keystone of effective treatment, and should be initiated once conclusive evidence of active tuberculosis is found.

Successful strategy against TB should include not only the adequate chemotherapy but also management of patients, constant monitoring for undesirable effects, evaluating bacteria eradication and most important of all, ensuring patient compliance, since patient compliance contributes significantly to successful cure rate, as well as cost-effectiveness. The consequences of patient non-compliance results in treatment failure, additional treatment, additional expenses, development of the MDR-TB and death.

Although the most important determinant of the outcome of TB treatment is the patient compliance, the current administration of antitubercular drugs is generally inconvenient and further increases the tendency of patient non-compliance. Therefore, a “dosage-friendly’ microsphere formulation containing anti-TB drugs like rifampicin and isoniazid is the key factor of improving tuberculosis treatment in many ways.

In chapter one, the risk caused by tuberculosis is fully reviewed as this disease is infectious and life-threatening. The evolution of anti-tubercular drug treatment and the emergence of new challenges like MDR-TB, XDR-TB and HIV + TB, further reinforce the need for design of an efficient drug delivery system like microspheres.

Chapter two consisting of detailed review of the literature concludes that the microsphere drug delivery system can provide the sustained and controlled delivery of anti-TB drugs like isoniazid and rifampicin over prolonged duration. Herbal bioenhancers proved effective in enhancing the bioavailability / efficacy of several categories of drugs may be effective in case of anti-TB drugs like INH and RIF.

In the present study, we attempted an innovative approach to overcome the above-mentioned problems of TB therapy by combining both these approaches of microspheres and bioenhancers. Microspheres of Isoniazid were prepared using several methods of which modified emulsification method and complex coacervation method were found to be the most effective. Small amounts of herbal extract of *Piper nigrum* and *Carum carvi*, alone and in combination were incorporated in them as bioenhancers.
CHAPTER 6. CONCLUSIONS

In microspheres containing isoniazid prepared by modified emulsion and complex coacervation method, the drug polymer interaction study using DSC and FT-IR did not reveal any significant drug interactions. The microspheres were cross-linked with calcium chloride and Na-TPP in modified emulsion and complex coacervation method respectively. The particle size was uniform and was found to be less than 135 micron in size. The drug encapsulation efficiency of prepared microsphere was found to be in the range of 54.80-78.40%, it was increased on incorporation of bioenhancer in the formulations. The percentage bioadhesion of the microsphere where bioenhancers were used was found to increase by 12-15% as compared to basal value (upto 65% from 50-52%). The *in-vitro* release study by USP paddle apparatus and the most important results from the *in-vitro* release study relates to the very significant enhancement in drug release (43 to 92% for microspheres prepared by modified emulsion method and 42 to 88% complex coacervation method), due to co-administration of bioenhancer alone and in combination.

Sodium tripolyphosphate (Na-TPP) could be an interesting cross-linking agent in complex coacervation method and allows the use of this formulation for controlled release of isoniazid.

In microspheres containing rifampicin prepared by modified emulsion and complex coacervation method, the drug polymer interaction study using DSC and FT-IR and did not reveal any significant drug interactions. The microspheres were cross-linked with calcium chloride and Na-TPP in modified emulsion and complex coacervation method respectively. The particle size was uniform and found to be less than 130 micron in size; the particle size may alter (decreased by 5-10 micron) on addition of bioenhancer extract to the formulations. The drug encapsulation efficiency was found to be in the range of 43.30-66.50% (increased on addition of bioenhancer in the formulations). The percentage bioadhesion of the microsphere where bioenhancers were used found to increase by 20% as compared to basal value (upto 67% from 42%). The *in-vitro* release study by USP paddle apparatus and the most important results from the *in-vitro* release study relates to the very significant enhancement in drug release (45 to 90% for microspheres prepared by modified emulsion method and 47 to 90% complex coacervation method), due to co-administration of bioenhancer alone and in combination.
In microspheres containing isoniazid and rifampicin in combination prepared by modified emulsion and complex coacervation method, the drug polymer interaction study using DSC and FT-IR did not reveal any significant drug interactions. The microspheres were cross-linked with stearic acid and Na-TPP in modified emulsion and complex coacervation method respectively. The particle size was uniform and was found to be less than 115 micron in size. The drug encapsulation efficiency of prepared microsphere was found to be in the range of 48.10-82.50%, it was increased significantly on incorporation of bioenhancer in the formulations. The percentage bioadhesison of the microsphere where bioenhancers were used was found to increase by 15-22% as compared to basal value (upto 80% from 58-65%). The in-vitro release study shows very significant enhancement in drug release of isoniazid microsphere (from 46 to 92% prepared by modified emulsion method and from 43 to 90% complex coacervation method) and it was more than double (from 43 to 88% for modified emulsion method and from 46 to 89% for complex coacervation method) in case of rifampicin due to co-administration of bioenhancer alone and in combination.

Stearic acid was used as cross-linking agent in complex coacervation method and found to be interesting to allowing the use of this formulation for controlled release of isoniazid.

The intestinal sac method was used to evaluate intestinal permeability of all the formulations. The purpose of the study was to see that the drug release from microspheres in intestinal environment is smooth and continuous over a period of time i.e. to characterize whether microspheres affect the drug release. The intestinal permeability of all the microsphere formulations was found to be satisfactory and there was noteworthy increase in intestinal permeability in the formulations where bioenhancers were incorporated (single or in combination).
RECOMMENDATIONS:

- Use of bioenhancers for Fixed Dose Combinations (FDC’s) recommended by WHO will help in reducing the dose of anti-tubercular drugs.

- Better permeation and availability of drugs using microsphere entrapment of anti-TB drugs will also help in overcoming resistance of tubercle bacilli.

- The combined approach using microspheres and bioenhancers might result in reduction of drug dosage, with accompanying reduction in dose related adverse effects and toxic effects; thus leading to better patient compliance.

- Well designed animal studies and clinical studies need to be conducted to confirm the potential of the approach suggested in our research work.