ABSTRACT

Tuberculosis (TB) is a chronic infection and is the major cause of mortality and morbidity throughout the world. In spite of the sustained efforts of World Health Organization (WHO), the number of new cases of TB, as well as the mortality related to it are on the rise, due to the emergence of drug resistance, and reduced patient compliance due to dose-related side effects and toxic effects.

Rifampicin and isoniazid are model drugs and used as first-line drugs treatment of tuberculosis and are included in the list of WHO as a recommended drug regimens for treatment of latent *M. tuberculosis* infection in adults.

Microsphere drug delivery consists of small particles of solids or small droplets of liquids surrounded by walls of natural and synthetic polymer films of varying thickness and degree of permeability acting as a release rate controlling substance and have a diameter upto the range of 0.1 to 200 μm. It is one of the processes to provide the sustained and controlled delivery of drug for long periods of time.

Bioenhancers are the ‘bioavailability enhancers’; they themselves do not show any typical drug activity, but when used in combination, they enhance the activity of drug molecule in several ways, including increasing bioavailability of the drug across the membrane, potentiating the drug molecule by conformational interaction, acting as receptors for drug molecule and making target cells more receptive to drugs.

In this research work entitled “Micro Particulate Delivery System for Anti-Tubercular Drugs”, we have attempted a combined approach for the most popular anti-tubercular agents viz. isoniazid and rifampicin, consisting of microsphere drug delivery system and bioenhancers. The microspheres having particle size in the range of 50-150 μm were designed to achieve both the sustained release of drugs as well as their successful entrapment in macrophages. The herbal bioenhancers viz. *Piper nigrum* and *Carum carvi* were for the first time used for increasing the bioavailability of selected anti-tubercular drug both singly and in-combination. The rationale behind their use was to improve the release performance of drugs from microspheres and ultimately to maximize their effectiveness.
The microspheres of the anti-tubercular agents were prepared by various methods of which the modified emulsion method and complex coacervation method were found to be most appropriate for our work. Variables like polymer concentration, drug-polymer ratio, concentration of cross-linking agent and time required for crosslinking were considered in the optimization of the formulation.

Hydro-alcoholic extract of *Piper nigrum* (Black pepper) and *Carum carvi* (Caraway) used as herbal bioenhancer were prepared and piperine was isolated from black pepper extract. Constant weight of bioenhancer extract (5 to 15 mg, singly or in combination) was incorporated into the drug loaded microspheres.

The prepared microspheres loaded with drug and bioenhancer/s were evaluated for various parameters including drug-excipient incompatibility, particle size, percentage yield, percentage entrapment efficiency, percent bioadhesion and intestinal permeability using intestinal sac method. Selected formulations were kept for stability studies as and no significant variation was found in physicochemical parameters of microspheres such as particle size, % drug entrapment efficiency (% drug content) and *in-vitro* drug release (% drug release in 12 hr.) was detected.

The microsphere were evaluated for *in-vitro* release and about 10% of the isoniazid or rifampicin was released in the SGF in first 2 hr and released about 85% upto 12 hr in SIF.

The most important finding of this study relates to the very significant enhancement in drug release from 48% (without bioenhancer) to 85% (with single bioenhancer) i.e. up to 70-80% increase in release rate and to 92% (with combination of bioenhancer) i.e. up to 80-95% increase in release rate of the anti-tubercular agents.

This research work has potential for application in the further advancement of anti-tubercular therapy. Our novel approach comprising of the twin mechanisms of microsphere and bioenhancers might pave the way for significant reduction in the dosage of first-line anti-tubercular agents thereby reducing their dose related side effects and toxic effects and improving patient compliance, without compromising with the efficacy of the formulation.