ABSTRACT

Oral route is the most common and preferred route for the delivery of most therapeutic agents due to its ease of administration, patient compliance and cost effective manufacturing methods. Oral controlled drug delivery systems have received much attention of the researchers during the past two decades. The rationale for developing a controlled release formulation is to enhance its therapeutic benefits, reducing its side effects and improving the management of diseased condition. A number of strategies have been developed to obtain controlled release of the drug in the body. These include a simple matrix tablet to more technologically sophisticated products which are introduced to the market place.

Studies have been carried out for developing oral controlled release matrix tablet formulations of verapamil hydrochloride and losartan potassium by using polymeric materials like polyox WSR 301, polyox WSR 303, polymethacrylates, ethylcellulose, xanthan gum, guar gum, karaya gum and sodium alginate. These are selected as matrix forming polymers for controlled release as these were reported to have matrix forming property.

Studies were conducted to investigate the influence of poly (ethylene oxides) level and type on the controlled release of the drugs from matrix tablets by in vitro methods. The influence of nature of fillers in the matrix tablets on drug release rate and mechanism was studied.
Studies were undertaken to evaluate the influence of binary polymeric systems on the controlled release of the drugs from the matrix tablets. For this purpose a combination of hydrophilic polymer like poly (ethylene oxides) with hydrophobic polymers like methacrylates and ethyl cellulose were used in the matrix tablets. A combination of synthetic and natural polymers like poly (ethylene oxides) and various natural gums were also used in the matrix tablets to study their influence on controlling the drug release.

The prepared matrix tablets were evaluated for weight uniformity, hardness, friability and drug content. The matrix tablets were then evaluated for the influence of polymer concentration, polymer type and nature of diluents on the drug release from matrix by \textit{in vitro} dissolution studies.

I.R Spectral studies were carried out on some selected matrix tablet formulations of verapamil hydrochloride and losartan potassium by using Bruker Fourier Transfer Infrared Spectrometer. These studies on matrix tablets were performed before they are subjected to dissolution studies to check any interactions between the drug and excipients used in the formulation of matrix tablets.

The selected matrix tablets of verapamil hydrochloride and losartan potassium were subjected to \textit{in vivo} pharmacokinetic studies. Rabbits were used as animal model for the study. The pharmacokinetic parameters such as $C_{\text{max}}$, $t_{\text{max}}$, $t_{1/2}$, MRT, $\text{AUMC}_{(0-t)}$ and $\text{AUC}_{0-t}$ were
estimated from serum concentrations of the drug versus time profiles. The serum concentrations of the drug were determined by HPLC method.

Selected formulations of verapamil hydrochloride and losartan potassium were subjected to accelerated stability studies. The formulations were stored at 40°C ±2°C, 75% ± 5% RH for 6 months. After the accelerated storage conditions, the tablets were evaluated for physical parameters such as weight uniformity, hardness, friability, drug content and for drug release. No significant changes were observed from the prepared tablets during the study period.

The results of present research work clearly indicated that the nature and level of poly (ethylene oxides) in the matrix tablets greatly influenced the drug release properties. Both the Polyox WSR 301 and Polyox WSR 303 were suitable for preparing the matrix tablets of verapamil hydrochloride and losartan potassium. Among the two polymers used, high molecular weight polymer, POLYOX WSR 303 effectively extended the drug release for prolonged period of time than low molecular weight POLYOX WSR 301. Insoluble diluents like microcrystalline cellulose, dicalcium phosphate and slightly soluble diluent like starch 1500 can be used as release rate modifiers in the formulation of controlled release matrix tablets. The formulations containing these diluents along with poly (ethylene oxides) enhanced the drug release over a period of 20 hrs than with the formulations containing lactose as diluent.
A combination of hydrophilic gums, hydrophobic eudragits and ethylcellulose with high molecular weight poly (ethylene oxides) led to prolonged release of drug up to 22 hrs. An important feature of these systems is potential for generating constant controlled drug release. The matrix tablets exhibited good controlled release characteristics both in vitro and in vivo. As such these formulations with a combination of poly (ethylene oxides) with polymethacrylates and ethylcellulose, poly(ethylene oxides) and gums like xanthan gum, guar gum and karaya gum can be recommended for oral controlled drug delivery of verapamil hydrochloride and losartan potassium. Thus present research work fulfilled the objective of developing once a day formulations of verapamil hydrochloride and losartan potassium as matrix tablets employing poly (ethylene oxides). The steady state plasma level of the drugs for prolonged period of time was also achieved.