DESIGN AND EVALUATION OF CHRONOPHARMACEUTICAL DRUG DELIVERY SYSTEMS OF ANTIHYPERTENSIVE DRUGS

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Drugs that are used to treat cardiovascular diseases are suitable candidates for achieving chronological delivery owing to the circadian rhythm in physiological and pathological conditions such that a greater plasma concentration of drug must be attained at a point in circadian cycle when symptoms of disease intensify. Aforementioned concept was applied to design compression coated core tablet formulations of two important cardiovascular drugs; Metoprolol Tartrate (MT) ($\beta_1$ adrenoreceptor blocker), and Carvedilol (CRV) ($\alpha$ and $\beta$ adrenoreceptor blocker).

Firstly, a chronopharmaceutical drug delivery system of MT was prepared by using hydroxypropyl cellulose (HPC) as a coat polymer. Two grades of HPC were used in the outer coat of tablets such that the optimized formulation contained HPC-L and HPC-M in ratio of 1:2. This formulation was further modified in order to achieve extended delivery of drug upto 24 h after a lag time of 6 h in the onset of drug release. This was achieved through dissolution-guided optimization of proportion of different grades of hydroxypropyl methylcellulose (HPMC) polymer in the outer coat of tablets such that the optimized formulation contained methocel K4M and methocel K15M in ratio of 2:1. A chronopharmaceutical drug delivery system of Carvedilol was also formulated and evaluated. It was formulated through optimization of proportion of hydroxypropyl methylcellulose (HPMC) and ethyl cellulose (EC) polymers in the outer coat of tablets. The optimized formulation contained EC and HPMC (methocel K4M) in a ratio of 3:1

Apart from physical evaluations, compressibility and compactibility of tablets, in vitro dissolution test, in vitro core erosion test, effect of rotation speed of paddle, effect of pH of dissolution media, fitness of dissolution data, water uptake test, swelling studies, pharmacokinetic studies, in vitro-in vivo correlation studies and stability studies have also been carried out. The optimized formulation of MT prepared using HPC as coat polymer produced a lag phase of 6 h followed by complete release of 99.02±0.82% in 12 h. Core erosion ratio was greater than 55% thereby showing steady release of the drug after the lag time until complete dissolution. The present system of MT exhibited pH independent behaviour.
The results from the chronopharmaceutical system of MT using HPMC as coat polymer showed core erosion ratio greater than 50% thereby showing steady release of the drug. The optimized formulation produced a lag phase of 6 h followed by a complete release of $98.7 \pm 2.1\%$ in 24 h. Water uptake study revealed that methocel K15M has lower water uptake ($30 \pm 1.2\%$) than methocel K4M ($40 \pm 1.7\%$) after 24 h. The axial swelling of polymers was higher than swelling in the radial direction. Drug-polymer interaction study precludes any interaction between drug and polymer. In vivo evaluation of this system involved determination of bioavailability parameters of tablets vis-a-vis drug solution thereby, revealing $C_{\text{max}}$, $T_{\text{max}}$ and $AUC_{0-\infty}$ of $36.42\pm1.96$ ng/ml, 12 h and $1158.65 \pm 148.77$ ng h/ml respectively in case of tablets and $159.32\pm2.64$, 0.5 h, $1263.15\pm69.96$ ng h/ml in case of aqueous solution. The IVIVC ($R^2$) of 0.8986 indicated a good correlation of absorption with the amount of drug released. There was no significant change in physical appearance, % drug content, % drug release and DSC thermogram and FTIR spectra of optimized formulation during stability studies.

The chronopharmaceutical system of CRV showed a lag time of 6 h before releasing $99.65\pm1.08\%$ in 24 h. Dissolution of optimized tablets at different pH and rotation speed of paddle showed a pH-independent release with no effect of rotation speed of paddle on the amount released. In vivo evaluation of this system involved determination of bioavailability parameters of tablets vis-a-vis drug suspension thereby revealing $C_{\text{max}}$, $T_{\text{max}}$ and $AUC_{0-\infty}$ of $52.30\pm1.86$ ng/ml, 12 h and $1285.67\pm100.21$ ng h/ml respectively in case of tablets and $176.56\pm2.89$, 0.5h, $1419.23\pm56.69$ ng h/ml in case of aqueous suspension. The IVIVC ($R^2$) of 0.9309 indicated a good correlation of absorption with the amount of drug released. There were no significant change in physical appearance, % drug content, percentage drug release and DSC thermogram and FTIR spectra of optimized formulation during stability studies. Thus, it can be assumed that such formulations can be stored for minimum six months without considerable change in its characteristics.

Thus, through this work we propose to attain delayed onset extended release (DOER) for a hydrophilic drug by using hydrophilic swellable polymer and for a hydrophobic drug
using blend of hydrophilic (HPMC) and hydrophobic polymers (EC) in the press-coat. Such drug delivery system will be able to provide a viable alternative for effective management of hypertension and other related disorders.