

Formulation and Evaluation of Chrono Modulated Time Release Tablets of Metoprolol Tartrate

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Abstract

The aim of the present work is to design an oral time release tablet by press coating method to achieve a distinct predetermined lag time. In this study Metoprolol tartrate was selected as the model drug. The outer shell was formulated with different weight ratios of Hydroxy propyl methyl cellulose K100M and Ethyl cellulose to achieve a release profile with pre determined lag time. The lag time was the time period referring no release followed by complete drug release. The lag time was significantly dependent on weight ratios of Hydroxy propyl methyl cellulose K100M and Ethyl cellulose. The best suited time lag was found of 6 hrs for formulation CM4. The predetermined time lag prior to the drug release from press coated tablets prepared by using EC and HPMC as a combination of retarding coating layer and gelling layer can be successfully employed for the formulation of press coated tablets.

Keywords: Ethyl cellulose, Press coating, Hydroxy propyl methyl cellulose

INTRODUCTION

In the field of modified release there has been a rising interest in time specific oral delivery which is based on pre programmable release of drugs. Since living organisms are not zero order in their requirement or response to drug, there are predictable biological systems within the circadian cycle which alter the demand for drug. Hence the current research is preferred to formulate a dosage form which provides desired concentration of drug at particular point of time called Chrono drug delivery systems. Circadian rhythmic variation are observed in diseases such as bronchial asthma, attention deficit syndrome, rheumatic disease, angina pectoris and hypertension for which recurrence is mainly at night or at early morning. The present study was designed to formulate an oral press coated time release tablet for treatment of hypertension. Direct compression method was adopted to achieve the time controlled function with a distinct predetermined lag time [1, 2]. The press coated tablet was formulated containing Metoprolol tartrate (MT) as the model drug and different weight ratios of hydrophobic polymer EC and hydrophilic gel forming polymer HPMCK100M in the outer core [3]. EC is a well known water insoluble polymer effectively used for rate controlling membrane to regulate the drug release pattern. The water uptake capacity and release of drug from the dosage form depends on particle size and porosity of EC particles, whereas HPMC being a gelling polymer undergoes a glassy rubbery transition which is permeable to water. This mechanism is used in a different extent to delay drug release for a period of time depending on both physicochemical properties and amount of polymer added. The drug selected is Metoprolol tartrate (MT), Chemically it is 1-[4-(2-Methoxyethyl)phenoxy]-3-[(1-methylethyl) amino]-2-propanolol-tartrate. MT works by competing for β_1 receptor sites on cardiac muscle with no intrinsic sympathomimetic activity and membrane stabilizing activity is detectable only at plasma concentrations much greater than required for β -blockade.

MATERIALS AND METHOD

MT was a gift sample from Ranbaxy India, Microcrystalline cellulose; Lactose and Starch were purchased from JRS Pharma. EC and HPMC were gift sample from Signet Pharma. All other reagents are of analytical grade.

Preparation of core tablet

The MT core tablets were prepared using direct compression method. Powder mixtures of MT, MCC, Lactose and Talc were dry blended for 15 mins followed by addition of Magnesium stearate. The mixture was further blended for 10 mins and then compressed into tablets (average weight= 120 mg) using a rotary tablet machine equipped with 6mm flat faced punch. Table 1 lists core composition.

Preparation of Press coated tablets

Press coating of core was done using a hydraulic press. Different weight ratios (wt/wt) of rupturable polymer EC combined with swellable polymer HPMC were prepared in the following ratio: CM1(100%/0%), CM2 (0%/100%), CM3 (75%/25%), CM4 (60%/40%), CM5 (40%/60%), CM6 (25%/75%). All powder mixtures were passed through sieve no 60 and 100 mg of powder mixture was used for upper and lower shells. Half (100 mg) of mixture was first filled into the die to make a powder bed and the core tablet was placed manually in the center. The remaining half was poured on to the inner core and compressed 10mm in diameter to formulate the press coated tablet of average weight 320 mg [7].

EVALUATION OF PRESS COATED TABLET

Water uptake study [8]

Water uptake by the compression coated tablets (CM1-CM6) comprising of different weight ratios of HPMC and EC was determined. Each tablet was placed in the centre of a breaker containing 20 ml of water and the amount of water decreased with time was determined.

Swelling of Tablets [9]

Swelling behavior of tablet was determined in the dissolution media phosphate buffer, pH 6.8. Tablets were

immersed in the dissolution media. The % swelling was then calculated using the equations.

$$\% \text{ Swelling} = \frac{w_1 - w_0}{w_0} \times 100$$

Where w_0 is weight of original dry tablet, while w_1 is measured weight at time t

In vitro drug dissolution test [10]

The USP apparatus-1 was used to determine the amount of MT released from all compression coated tablets. The paddle rotation speed and temperature was set to 100 rpm and $37 \pm 0.5^\circ\text{C}$, respectively. The dissolution medium was 900 ml of the 0.1N HCl, pH 1.2 for initial 2 h subsequent in phosphate buffer pH 6.8 for up to rest period. Samples were withdrawn at time intervals and sink conditions were maintained throughout the test. The amount of dissolved drug was determined spectrophotometrically at 274 nm using the calibration plot of prepared earlier in the same media.

Table.1: Composition of core tablet

Ingredients	Quantity(mg)
Drug	50
Microcrystalline cellulose	43
Lactose	20
Starch	5.2
Talc	1.2
Magnesium stearate	0.6
Total(mg)	120

RESULT AND DISCUSSION

The press-coating technique is one of the novel methods and has been applied for many drugs to develop the site-and/or time-controlled release preparation. This technique was used to design a time-controlled press-coated tablet of MT by using hydrophobic ethylcellulose (EC) and hydrophilic HPMC K100M into the outer coating layer.

Water uptake test

A comparison of water uptake by hydrophilic swellable polymer (HPMC K100M) and hydrophobic ethylcellulose (EC) of different weight ratios was done. The impermeability nature of EC reduces the water penetration, whereas the viscous gel forming nature of HPMC enhance the medium penetration. Least water uptake was found for CM1 with 100% EC composition and maximum water uptake was found for CM2 with 100% HPMC coat composition [8]. Results were shown in Fig.1

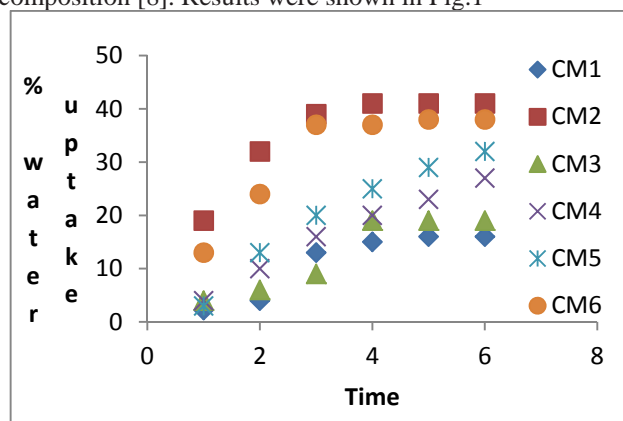


Fig.1: Showing water uptake characteristics of formulations CM1-CM6

Swelling studies

Swelling of polymer occurred owing to water uptake or hydration. Formulation CM1 and CM2 was taken for swelling study. For CM1 the swelling % is less in comparison to CM2, which is composed of 100% HPMC as coat polymer. After swelling of polymer, a rubber like state is formed so that ease of penetration of solvent occurred [9]. Graphical representation was given in Fig.2

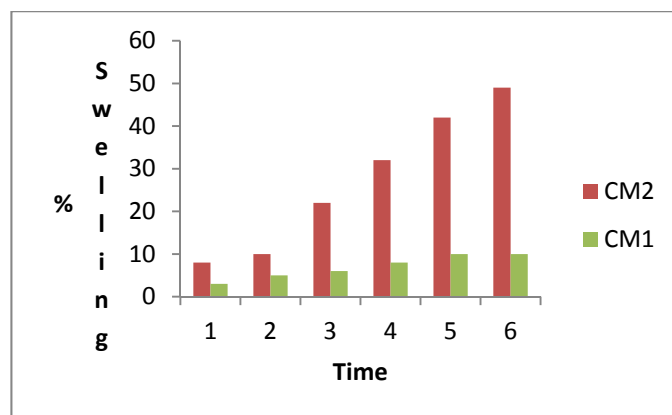


Fig.2: Comparison of Swelling behavior of formulation CF1 and CF2

In vitro drug dissolution test

All the press coated formulations were subjected to *in vitro* dissolution study. Through optimization of the proportions of EC and HPMC K100M in the press coat, it was desired to achieve a lag period of 6 h in the release initially followed by complete drug release. It was evident from the experiment that, when HPMC alone was used (CM2), it was unable to provide desirable lag period and sustainability. This might be due to the hydrophilic and swellable nature of HPMC which allow the penetration of water through the pores showing complete drug release. The release behavior of a press-coated tablet prepared by EC alone (CM1) in the outer shell might be due to the medium penetration from the lateral surface of tablet to destruct the outer shell, leading to a shorter time lag. The drug was rapidly released from the inner core after rupturing the surrounding outer shell, since an inner osmotic pressure caused by dissolving drug was built-up within the core system. After the time lag, the outer shell of the press coated tablet ruptured or broke into two halves to result in rapid drug release. Once combination of HPMC and EC was used into the formulation of the outer shell of the press-coated tablets, the dissolution profile was showing a distinctive induction lag followed by drug release. This might be due to the time lag prior to drug release was controlled by the combination of the thickness and the viscosity of the gel layer of HPMC and impermeable layer of EC. The time lag was gradually shortened with the increase of HPMC in the formulation of the outer shell. The maximum time lag of the press-coated tablets was found to be 6 hr for containing 60:40% EC and HPMC (CM4). The dissolution data's were shown in Fig. 3

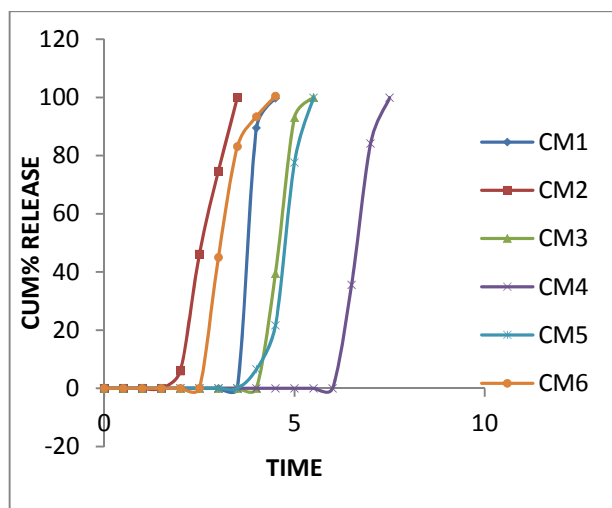


Fig.3: Comparative dissolution profile

CONCLUSION

The present study was designed to formulate time release tablet of Metoprolol tartrate indicating that the time lag of press coated tablet can be suitably modulated by formulating the outer shell with varying composition of EC and HPMC K100M.

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