



Development and Evaluation of Time Controlled Pulsatile Drug Delivery System of Ketoprofen.

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Accepted on: 30-11-2014; Finalized on: 31-12-2014.

ABSTRACT

Many disease conditions follow the circadian rhythm. In rheumatoid arthritis maximum pain observed early in the morning. So efforts have been done to delivery the drug, which is administered at the night, delayed the drug release for 6 hrs and release the drug early in the morning. An oral press coated tablet was developed by direct compression method to achieve the time controlled tablet with a distinct predetermined lag time. Press coated tablet containing ketoprofen in the inner core was formulated with outer shell by using hydroxy propyl methyl cellulose and ethylcellulose. The effect of outer coating on lag time was investigated and formulation was modified. The release profile of press coated tablet exhibit that hydroxyl propyl methyl cellulose have lesser effect on lag time, while ethylcellulose have lag time of up to 8 hrs. So formulation was developed by using combination of hydroxyl propyl methyl cellulose and ethylcellulose.

Keywords: Press coated tablet, lag time, Hydroxy propyl methyl cellulose, Ethylcellulose.

INTRODUCTION

Oral controlled release drug delivery system offer a number of advantages over the conventional immediate release delivery preparations. These systems are designed to deliver the drugs at a controlled and predetermined rate thus maintaining their therapeutically effective concentration in systemic circulation for prolonged periods. On the other hands, for certain therapies a pulsatile drug release pattern, where the drug is released after well defined lag time, exhibits significant advantages. It is well documented that most of the body functions display circadian rhythms, e.g. heart rate, stroke volume, blood pressure, gastric-pH¹.

Time controlled drug delivery system are dosage forms that are designed to mimic the circadian rhythm of the disease by releasing the drug at the appropriate time, by means of an internal pre-programmed clock that is initiated when the dosage forms come in contact with gastrointestinal fluids. TCDDS have been formulated as pellets², capsules^{3,4} and tablets⁵⁻¹¹ designed to release the drug only after defined lag time.

Particularly in the case of cardiovascular disease, bronchial asthma and rheumatoid arthritis, which mostly exhibit circadian manifestations in the early morning, the efficacy and tolerability of a therapy could notably be improved by delivery systems intended to timely release the drug few hours after bedtime administration, thus providing pharmacological protection when it is especially required without involving an unnecessarily extended patient exposure to the active molecule nor impairing the overall treatment compliance. In rheumatoid arthritis maximum pain observed between 6 A.M to 8 A.M¹². Ketoprofen [2-(3-benzoylphenyl) propionic acid] is a non-

steroidal anti-inflammatory and analgesic agent used to treat acute and chronic rheumatoid arthritis and osteoarthritis¹³ was used as model drug to develop pulsatile release system.

Because of the peculiar hydration behavior, both erodible and non-erodible swelling polymers exhibit generally high biocompatibility as well as susceptibility to being activated by physiological fluids¹⁴. Such inherent characteristics have drawn remarkable interest to swellable hydrophilic materials, which have widely been employed in the pharmaceutical area over the past decades. Ethylcellulose (EC) is a well-known water-insoluble polymer that has long been used as a rate-controlling membrane in medication dosage forms to regulate drug release. Recently, the unique suitability of EC powders to act as an outer shell has also been explored to directly prepare the press-coated tablet with a special time-controlled rupturing function¹⁵.

So, HPMC and EC were used alone and with different weight ratio for outer shell coating. The type of excipient used in inner core tablet also have significant effect on time controlled rupturing of press coated tablet, so in the present study the level of excipients were fixed to evaluate the effect of outer shell coating on lag time.

MATERIALS AND METHODS

Materials

Ketoprofen was gifted from Alembic Laboratories(India). HPMC K4M, HPMC K15M, HPMC K100M, L-HPC, Ethyl Cellulose, MCC were gifted from Zydus Cadila Ltd. Sodium Starch glycolate, Cross carmellose sodium, Crosspovidone, PVP K-30, Talc, Magnesium Stearate were purchased from National Chemical Laboratories (Mumbai).



Calibration Curve for Ketoprofen

Calibration curve of Ketoprofen was prepared in pH 1.2 HCL and in pH 6.8 phosphate buffer using UV visible spectrophotometer (UV 1700, Shimadzu) at 260 nm.

Procedure: An accurately weighed quantity of Ketoprofen was taken in 100 ml volumetric flask and sufficient quantity of pH 1.2 HCL & pH 6.8 Phosphate Buffer solutions were added and diluted to 100 ml with the same solvent so as to get the concentration of 100µg/ml. For various concentration of drug solution, appropriate aliquots were pipette out from standard stock solution into the series of 10 ml volumetric flask and the volume was made up to the mark with respective buffers to get concentration of 10-50 µg/ml of Ketoprofen¹⁶.

Preparation of Core Tablets using Direct Compression

A direct compression method was used to prepare core tablet. All the ingredients like Ketoprofen, superdisintegrants, and directly compressible agent were sieved through no. 40 mesh screen and mixed uniformly using tumbler mixer. Magnesium stearate and Talc was introduced into the blend and mixed properly then compressed into tablets using flat faced punches (Rotary tablet press, Karnavati Engineering) by keeping hardness 4 to 6 kg/cm². The core tablets were evaluated for

thickness, content uniformity, friability and disintegration. Formulation containing different amount of super disintegrating are given in Table 1.

Table 1: Composition of Core Tablet

Batch (All weights in mg)	F1
Ketoprofen	80
Cross Carmelose Sodium	2
Sodium Starch Glycolate	2
MCC	20
PVP k-30	3
Mg. Stearate	2
Talc	1
Total Wt.	110

Preparation of Compression-Coated Tablets

The core tablets were compression coated with different hydrophilic polymers and hydrophobic polymers (Formulation Table 2). Half the quantity of outer coating material was transferred into the die and core tablet was placed manually in the centre of the die. Then the remaining half quantity of outer coating material was added into the die and compressed using rotary tablet punching machine.

Table 2: Composition of Outer Shell Coating

Batch	PR1	PR2	PR3	PR4	PR5	PR6	PR7	PR8	PR9	PR10	PR11
Core tablet	110	110	110	110	110	110	110	110	110	110	110
HPMC K4M	240	300	-	-	-	-					
HPMC K 15M	-	-	240	300	-	-					
HPMC K-100M					240	300			125	125	125
Ethyl cellulose (10cp)	-	-	-	-	-	-	240	300	125	150	175
PVP K-30	5	5	5	5	5	5	5	5	5	5	5
Mg. Stearate	3	3	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2	2	2
Total	360	420	360	420	360	420	360	420	370	395	420

Table 3: Lag Time of the Coated Tablet of Ketoprofen Batch PR1-PR11

Lag Time of the Coated Tablet of Ketoprofen Batch PR1-PR11											
Batch	PR1	PR2	PR3	PR4	PR5	PR6	PR7	PR8	PR9	PR10	PR11
	195±7	213±5	255±1	280±1	275±5	335±9	455±7	460±2	320±7	350±5	370±12

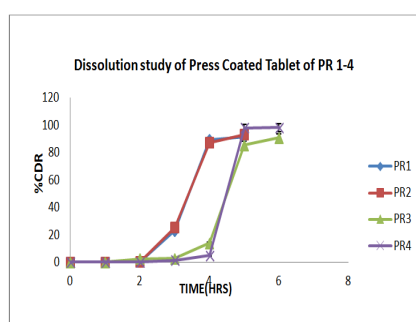


Figure 1: Dissolution study of press coated tablet of PR 1-4

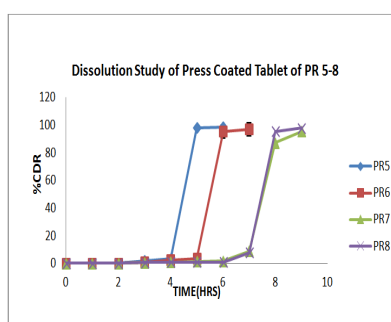


Figure 2: Dissolution study of press coated tablet of PR 5-8

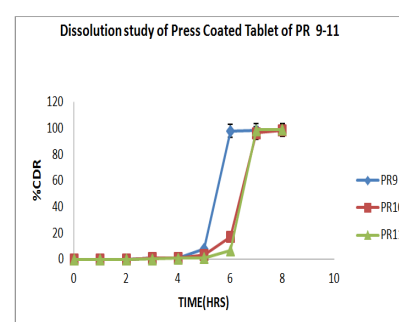


Figure 3: Dissolution study of press coated tablet of PR 9-11

Lag Time Study

The Rupture test on coated tablets was carried out using USP paddle apparatus. Here all other Parameters were same as *In-Vitro* Dissolution Method. The time at which the outer coating layer starts to rupture is called as lag time.

In Vitro Release Studies

Dissolution of ketoprofen tablets were performed in a USP dissolution tester (Lab India), paddle method with 900 ml of 0.1 N HCL for 2hrs and then with pH 6.8 Phosphate buffer for 6 hrs, as a medium at 37 ± 0.5 °C. The speed of the paddle was adjusted 50 RPM. At predetermined time intervals an aliquot of the samples were collected, filtered and analyzed under UV spectrophotometer at 260 nm. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

RESULTS AND DISCUSSION

Lag Time Study

Lag time investigation shows that when HPMC used alone, as the concentration and viscosity grade of HPMC increases lag time also increases (Table 3). Same result observed with the EC. But EC has more significant effect on lag time as compared to the HPMC. Different weight ratio of HPMCK100M and EC fulfilled our required lag time of 6 hrs.

In Vitro Release Studies

All the press coated tablets showed pulsatile release behavior with distinct lag time. Fig. 1-3 shows the dissolution profile of the press coated tablets. The release profile composed of an induction (lag time) followed by a rapid release phase.

The sudden splitting of the outer shell of press coated tablet after lag period is a key factor to achieve the time controlled delivery. The drug was immediately released from a core tablet after rupturing the surrounding outer shell, caused by a pressure build up within the core system.

Three different viscosity grades of HPMC were used as outer shell coating. The lag time for HPMCK4M observed was 195-213 min (PR1 and PR2). Similar results were obtained for medium and higher viscosity grade HPMC.

The mechanism by which hydrophilic cellulosic barriers delay release depends on the progressive hydration, dissolution and erosion phenomena they undergo when exposed to the aqueous medium, thus preventing the drug from being delivered until the inner core is reached by the solvent.

Higher polymer viscosity reflects a stronger ability of the polymer chains to produce entanglements and consequently matrices with slower erosion. As the amount of outer shell polymer increases lag time also increases.

The maximum lag time was observed for PR6 of 335 min. In all batches from PR1-PR4 of low and medium viscosity grade HPMC, the rate of hydration and erosion was fast so initial drug release occur before immediate drug release.

The release behavior of a press-coated tablet prepared by EC alone in the outer shell might be attributed to the slower medium penetration from the lateral surface of tablet to destruct the barrier shell, leading to a longer time lag. This is because of the hydrophobic nature of the EC.

To optimize the release pattern different weight ratio of EC/HPMC were used. For drug release from the press-coated tablets prepared by using EC/HPMC in the outer shell, the eroded flocculates were observed in the dissolution medium after rupturing the press coated tablet, suggesting that both erosion and destruction mechanisms might be responsible for the time-controlled release mechanism.

However, the water-soluble function of HPMC might also increase the permeability of medium and therefore reduce the lag time.

In formulation PR9-PR11, as the amount of EC increases, the lag time also increases. Formulation F11 shows desirable lag time of 6 hrs with burst release for pulsatile drug delivery of ketoprofen.

CONCLUSION

In press coated tablet, hydrophobic polymer was found to be the major factor affecting lag time, while hydrophilic polymer has lesser effect.

Lag time can be programmed with different weight ratio of HPMCK100M and EC with immediate burst release of ketoprofen after lag time.

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Source of Support: Nil, **Conflict of Interest:** None.

