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Study the effect of polymer on lag time in the development of timed release ketoprofen press coated tablet

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ABSTRACT

The aim of the current study is to prepare the press coated tablet and to investigate the effect of polymer on lag time. Press coated tablet were prepared by direct compression technique, containing rapidly disintegrating core and outer barrier layer containing hydrophilic polymer like hydroxy propyl Methyl Cellulose, HPC, NaCMC and hydrophobic polymer like Ethyl cellulose. The study reveal that as the amount and viscosity grade of polymer in outer coating increases the lag also increases. The in vitro drug release study shows that HPC and NaCMC have lesser effect on lag time, while HPMC and Ethylcellulose gives 4-8 hrs of lag time followed by rapid release of the drug.

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

1. INTRODUCTION

Oral controlled release drug delivery systems offer a number of advantages over the conventional immediate release delivery preparation. 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 hand, for certain therapies a pulsatile drug release pattern, where the drug is released after well defined lag time, exhibits significant advantages[1]. The symptoms for number of diseases, such as bronchial asthma, myocardial infarction, angina pectoris, hypertension, rheumatic diseases, etc follow a circadian rhythm [2].

Chronobiology is the study of biological rhythms and the mechanisms of biological timekeeping. Chronobiology is clearly relevant to the fields of medicine, pharmacology, and drug delivery [3]. The daily pain profile must be used to determine the best time to administer an analgesic drug to a patient. The circadian rhythm of arthritic pain is well known to physicians as patients with rheumatoid arthritis typically report the presence of greatest pain in the morning [4]. So for such type of condition pulsatile drug delivery system is used, which taken at the nighttime and delayed the drug release for fix time and release the drug at early morning.

Pulsatile drug delivery systems are gaining a lot of interest and attention these days. These systems have a peculiar mechanism of delivering the drug rapidly and completely after a "lag time," i.e., a period of "no drug release [5]. Delayed release dosage forms can be classified into site-specific and time controlled systems. Drug release from site-specific systems relies on the gastrointestinal environment such as pH and/or presence of enzymes which trigger drug release. On the other hand, drug release from a time-controlled system, such as a single or multiple unit, is influenced by the system itself. Therefore, attempts were made to prepare simpler pulsatile tablet dosage forms by incorporating materials with unique swelling properties that allow for a distinct drug release pattern[6]. Over a period, many different approached have been used for delivering the drugs as time and/or site specific which includes, Timeclock®[7] system, Chronotropic®[8] system, Pulsincap®[9] system, Port®[10] system, TimeRx®[11] system and Geomatrix®[12] system. These systems are developed with intention to meet the needs of chronopathologies with symptoms mostly recurring at night time or early morning hours.

Direct compression is an accepted pharmaceutical manufacturing technique because of its many advantages such as low equipment costs, short processing time and limited steps, low

labor and energy requirements, and use of nonsolvent processes [13]. So direct compression is followed in this study. Ketoprofen [2-(3-benzoylphenyl) propionic acid] is a non-steroidal anti-inflammatory and analgesic agent used to treat acute and chronic rheumatoid arthritis and osteo-arthritis[14] was used as model drug to develop pulsatile release system.

This study focused on the development of press coated pulsatile release tablets to treat rheumatoid arthritis. The press coated tablet investigated in current study consist of rapid release core tablet which is press coated with Hydrophilic polymer like Hydroxy Propyl Methyl Cellulose, Na CMC, HPC and hydrophobic polymer like EC. The purpose of this study was to investigate the effect of type and amount of hydrophilic and hydrophobic polymer as outer coating on lag time.

2. MATERIALS AND METHODS

2.1. 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 gycolate, Cross carmellose sodium, Crosspovidone, PVP K-30, Talc, Magnesium Stearate were purchased from National Chemical Laboratories(Mumbai).

2.2. 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.

2.2.1. Procedure

An accurately weighed quantity of about 10 mg Ketoprofen was taken in 100 ml volumetric flask, dissolved in sufficient quantity of pH 1.2 HCL & pH 6.8 Phosphate Buffer solutions 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 Ketoprofen.

2.3. Preparation of core tablets using direct compression

A direct compression method was used to prepare core tablet. All the ingredients like Ketoprofen, superdisintigrants, 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 no. 1.

2.4. Preparation of compression-coated tablets

The core tablets were compression coated with different hydrophilic polymers (HPMC, HPC, Na.CMC) and hydrophobic polymers (Formulation table no.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.

2.5. Disintegration time for core tablet

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in Electrolab USP disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top, and held against a 10 mesh screen, at the bottom end of the basket rack

Table-1. Formulation of the core tablet

Batch (weight in mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ketoprofen	80	80	80	80	80	80	80	80	80
Cross Carmelose Sodium	3			4			2		2
Cross Povidone		3			4		2	2	
Sodium Starch Glycolate			3			4		2	2
MCC	20	20	20	20	20	20	20	20	20
PVP k-30	3	3	3	3	3	3	3	3	3
Mg. Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	1	1	1	1	1	1
Total Wt.	110	110	110	110	110	110	110	110	110

Table - 2: Formulation of press coated tablet

Batch	PR1	PR2	PR3	PR4	PR5	PR6	PR7	PR8	PR9	PR10	PR11	PR12	PR13	PR14
Core tablet(F_9)	110	110	110	110	110	110	110	110	110	110	110	110	110	110
Coating composition of the press coated tablet														
HPMC K4M	240	300	-	-	-	-	-	-						
HPMC K 15M	-	-	240	300	-	-	-	-						
HPMC K-100M					240	300								
Na –CMC	-	-	-	-			240	300						
Ethyl cellulose (20cp)	-	-	-	--	-	-		-	240	300				
EC N10											240	300		
HPC--L	-	-	-	-	-	-	-	-	-	-	-	-	240	300
PVP K-30	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mg . Stearate	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total	360	420	360	420	360	420	360	420	360	420	360	420	360	420

assembly. To test the disintegration time of tablet, one tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker containing pH 6.8 Buffer solution at 370C ± 100 C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

2.6. Lag time study

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

2.7. *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±0.5ºC. 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.

3. RESULT AND DISCUSSION

3.1. Disintegration time for core tablet

The test for disintegration carried out in Electrolab USP disintegration test apparatus in pH 6.8 buffer. The time taken for the complete disintegration of the tablets were noted and present in table 3. For this study different types and concentration of Super disintegrants like cross carmellose sodium, cross povidone and sodium starch glycolate were taken. Only F9 shows fast disintegration then others formulations. F9 formulation was taken for Press coating to evaluate the effect of different polymer on lag time (table 4).

Table – 3: Disintegration Studies of core tablet of Ketoprofen for F1-F9. (Time in second)

Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9
Time	28±2	38±3.5	34±0.57	26±1.52	36±2.0	30±1.15	30±3.57	42±2.5	22±1.5

Table - 4: Lag time of the coated tablet of Ketoprofen Batch PR1-PR7. (Time in minutes)

Batch	PR1	PR2	PR3	PR4	PR5	PR6	PR7	PR8	PR09	PR10	PR11	PR12	PR13	PR14
Time	195 ±7.65	213 ±5.4	255 ±12.58	280 ±10.0	275 ±5.0	335 ±12.58	310 ±5.0	235 ±5.4	455 ±7.63	460 ±2.88	405 ±5.0	410 ±10.0	190 ±2.9	205 ±5

3.2. *In vitro* release studies

Drugs used for the ideal treatment of diseases should be administered only at the required time to maintain a therapeutic blood level. This reveals that the drug release behavior should be controlled by time rather than by rate. In order to achieve the development of chronopharmaceutical dosage forms, currently, the site and/or time-controlled release preparation with a designated initial lag time phase without drug release followed by a rapid release phase has been investigated (Fgure -1).

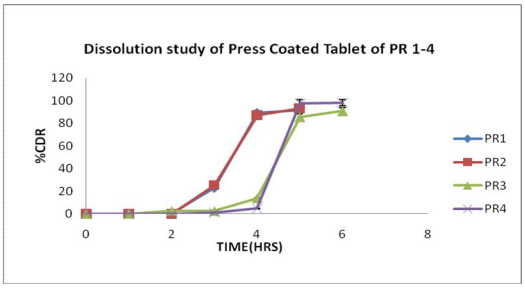

Figure - 1a: Dissolution study of press coated tablet of PR 1- **4**

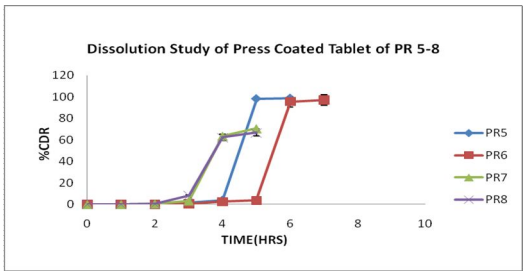

Figure – 1b: Dissolution study of press coated tablet of PR 5- **8**

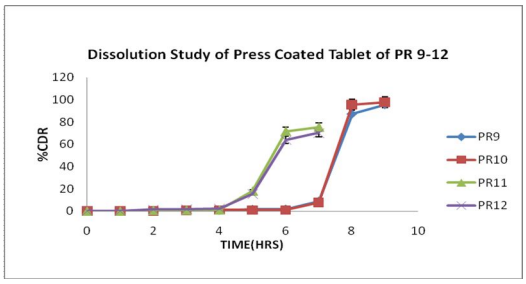

Figure - 1c: Dissolution study of press coated tablet of PR 9-12.

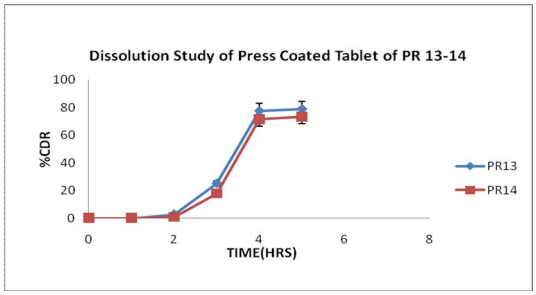

Figure - 1d: Dissolution study of press coated tablet of PR 13-14.

Many polymers have been investigated in this study to evaluate the effect on lag time. Generally viscosity and amount of polymer greatly affect the lag time and release of the drug. From the dissolution graph, it is observed that as the viscosity grade and amount of HPMC increases the lag time also increases and also affect the rate of gelation. Drug release is due to the swelling and erosion of the gelling layer. In lower viscosity grade rate of gelation is high and water penetrates through the gel layer, drug dissolution and swelling of superdisintegrant takes place afterwords. Due to the erosion and swelling of superdisintegrant, initial drug release was observed followed by burst of the tablet.

For NaCMC initial lag time of 3 hrs was observed for low and high level of concentration, but after lag time it release the drug in sustained manner rather than burst release. NaCMC generally solubilize at pH 6.8, gel layer slowly hydrate and eroded due to this sustained might be observed.

When EC used as a barrier coating layer in press coated tablet in PR9 and PR10, it shows higher lag time and outer shell ruptured in two halves to permit rapid drug release. Sudden explosion of system is due to the pressure build up into the core tablet. Particle size of the EC also affect the lag time, as the particle size increases the lag time decreases. Sustained release effect was in case of HPC.

4. CONCLUSION

Hydrophilic polymer used has less effect on lag time, while hydrophobic polymer (EC) considerably delays the lag time. As the viscosity grade and amount of polymer increases, the lag time also increases.

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