Research Article

Design and Development of Chronomodulated System for Arthritis

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ABSTRACT

The main objective of the present study was to develop a single unit, directly compressible tablet pulsatile drug delivery system, for obtaining no drug release during lag time, followed by pulsed rapid drug release to achieve chronotherapeutic release of Indomethacin. The system developed consist of drug containing core tablet prepared by direct compression, which were then compression coated with mixture of erodible and swellable polymer to form Erodible pulsatile system. System shows swelling and erosion during lag time followed by pulsed release of drug. HPMC E10 was used as swellable and ethylcellulose used as erodible polymer for outer coating. Concentrtion HPMC E10 and Ethyl cellulose significantly affect the lag time and release of drug from pulsatile system.

INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration over the conventional dosage form[1]. Such systems release the drug with constant or variable release rates. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance[2]. The oral controlled release system shows the typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), there by sustained Therapeutic action [(2, 3)].

However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern can be achieved by modulating the chronobiologic system is known as chronomodulated system.

Chronomodulated system is also known as pulsatile system or sigmoidal release system. The word chronomodulated is related with Chronopharmaceutics and comes from Chronobiologic system. Chrobiology is the study of biological rhythms and their mechanism. There are three types of mechanical rhythms in our body[4].

a) Circadian Rhythm:-The Oscillation in our body that are completed in 24 hrs. are termed as circadian rhythm
b) Ultradian Rhythm: - the oscillation that are completed in a shorter duration of less than 24 hrs. are termed as Ultradian rhythm.
c) Infradium Rhythm: - the oscillations that are completed in more than 24 hrs are termed as Ultradian rhythm.

The Circadian rhythm is the main rhythm in the body which maintains all the physiological, Chemical, Biological and behavioral Processes. Thus Circadian rhythms causes the changes in the Pathophysiology of certain Disease states which may worsen the disease condition. Treatments of such type of disease require a Time controlled, Pre-programmed drug delivery which exactly matches the circadian changes in the body. Thus Chronomodulated or Pulsatile drug delivery system is a novel system which can be used for treatment of such diseases [5].

Pulsatile drug delivery system delivers the drug at specific time as per the pathophysiological need of the disease resulting in improved patient compliance and Patient therapeutic efficacy[6]. The purpose of the study was to develop Press coated tablet for pulsatile delivery of Indomethacin. The drug delivery system was design to deliver the drug at such time when it could be most needful to patient to the patient of rheumatoid arthritis[7]. RA is considered a systemic autoimmune disease that causes chronic inflammation of the joints[8]. Rheumatoid arthritis can also cause inflammation of the tissue around the joints, as well as in other organs in the body[9]. Inflammation is then driven either by B cell or T cell products stimulating release of TNF and other cytokines[10]. Rheumatoid arthritis typically manifests with signs of inflammation, with the affected joints being swollen, warm, painful and stiff, particularly early in the morning on waking or following prolonged inactivity[11]. Increased stiffness early in the morning is often a prominent feature of the disease and typically lasts for more than an hour[11]. Such disease needs the treatment with a pulsatile drug delivery system which release the drug at the time when the arthritis is more painful. Thus the press coated tablet containing Indomethacin in the core was formulated with an outer shell containing hydrophilic and hydrophobic polymer such as HPMC and ethyl cellulose respectively.

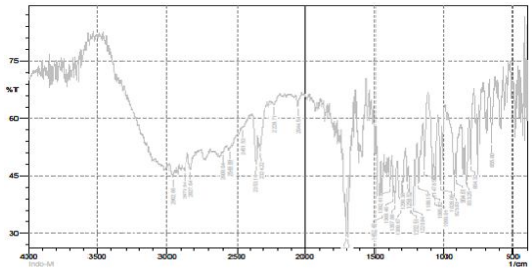
MATERIAL AND METHOD

Indomethacin was gift sample from Glen mark Pharmaceutical Ltd, Goa. Ethyl cellulose 45cps and hydroxy propylmethyl cellulose E10M were gift sample from Colorcon, Goa. Spray dried Lactose, Croscarmellose sodium (Ac-di-sol Microcrystalline cellulose and PVP K30 was Gift sample from Zydus Cadila, Ahmedabad.

A. Preformulation Study[12]

1. Characterization of Drug by FTIR

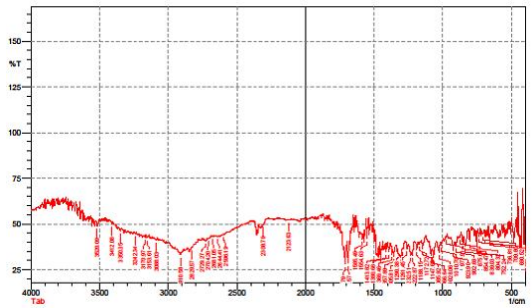
FTIR study was carried out for the characterization of drug ,the drug sample were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Scans were obtained at a resolution of 5 cm−1, from 4,000 to 500 cm−1.



IR of Indomethacin

B. Drug-Excipients Compatibility study By FTIR

The physicochemical compatibilities of the drug and the used excipients were tested by FTIR. FTIR spectra were obtained by using an FTIR spectrometer-Schemadzue. F5 formulation (40:60) was taken into consideration for FTIR study as a best batch. The Indomethacin and Formulation F4 (40:60) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Scans were obtained at a resolution of 4 cm−1, from 4,000 to 500 cm−1.



IR of Physical mixture of IM and (Drug + CCS + MCC + Eth.cellulose + HPMC E10M)

C. Precompression Parameter Study[12]

1. Precompression parameter study of Polymeric blend

The polymeric blend with different ratio of HPMC and ethyl cellulose were evaluated for various Precompression parameter such as bulk density, tap density, angle of repose, Hausner's ratio and cars index.

a. Bulk Density: it was calculated by following formula

Bulk density = Weight of powder / Bulk volume

b. Tapped bulk density

Tapped Density = Weight of powder / Tapped volume.

c. Carr's Index

Carr's Index (%) = [(TD-BD) x100]/TD

d. Hausner's Ratio

Hausner's Ratio = TD / BD

e. Angle of repose

tan □ = h/r

Formulation

1. Method of Preparation

Core tablet formulations by direct compression

The inner core tablets were prepared by using direct compression method. As shown in Table. Powder mixtures of Indomethacin, microcrystalline cellulose (MCC, Avicel PH-102), cross-carmellose sodium (Ac-Di-Sol) and Carmosin. Ingredients were dry blended for 20 min. followed by addition of Talc and magnesium Stearate. The mixtures were then further blended for 10 min., 100 mg of resultant powder blend was compressed using rotary tabletting machine (Fluidpack, India) with a 8mm punch and die to obtain the core tablet. Tablets were made in concave punch (100mg). The tablets were tested for hardness, Friability, Weight variation, Disintegration, Drug content and in vitro drug release.

Table : Composition of core tablets formulation

S. No	Ingredients	Quantity (mg)
1	Indomethacin	50
2	Microcrystalline cellulose	15
3	Lactose	17
4	PVP	1
5	Ac-di-sol	5
6	Talc	1
7	Magnesium stearate	10
8	Colour	1
	Total	**100**

b) Formulation of mixed blend for Coating layer

As given in the Table 2 the various formulation compositions containing HPMC and Ethyl cellulose. F1 to F7 different compositions were weighed and dry blended at about 10 min.1% magnesium Stearate used as lubricant and blend used as press-coating material to prepare press-coated pulsatile tablets (F1-F7) respectively by direct compression method.

Table: Composition of Coating layers (300mg)

Composition	Formulation						
Formulation Code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
HPMC : EC (Percent Ratio)	100:0	80:20	60:40	50:50	40:60	20:80	0:100
Magnesium Stearate	1%	1%	1%	1%	1%	1%	1%

Ec: Ethyl cellulose

C) Preparation of press-coated tablets

The core tablets were press-coated with 300mg of mixed blend as given in Table 3. 150 mg of barrier layer material was weighed and transferred into a 9mm die then the core tablet was placed manually at the center. The remaining 150 mg of the barrier layer materiel was added into the die and compressed using rotary tabletting machine (Fluidpack, India).Weight of each tablet was adjusted upto 400 mg.

Table 6 .11: Formulations of press coated tablets (400mg)

Composition	Formulation code						
CL : Core tablet 300 : 100	F1 Tab	F2 Tab	F3 Tab	F4 Tab	F5 Tab	F6 Tab	F7 Tab
HPMC : EC (Percent Ratio)	100:0	80:20	60:40	50:50	40:60	20:80	0:100

Ec: Ethyl cellulose, CL: coating layer

Evaluation parameter

1. Drug content [13]

20 tablets were weighted and its average weight was taken which was crushed in mortar and pestle. The powder weight equivalent to single tablet i.e.50 mg was dissolved in 10 ml water in a 100 ml volumetric flask and allowed to stand for 10 minute. To that 75 ml of methanol was added initially followed by addition of sufficient methanol to produce 100 ml which was then filtered through whatman filter paper. 5 ml of this resulting solution was further diluted to 50 ml with 7.4 pH phosphate buffer: methanol (1:1).again ml was diluted to 50ml by the same solvent. The absorbance of each of the standard and sample solution were taken in UV-visible spectrophotometer at 320 nm using equal volume of 7.4 PH phosphate buffer and methanol as blank[15].

7. In-vitro drug release studies

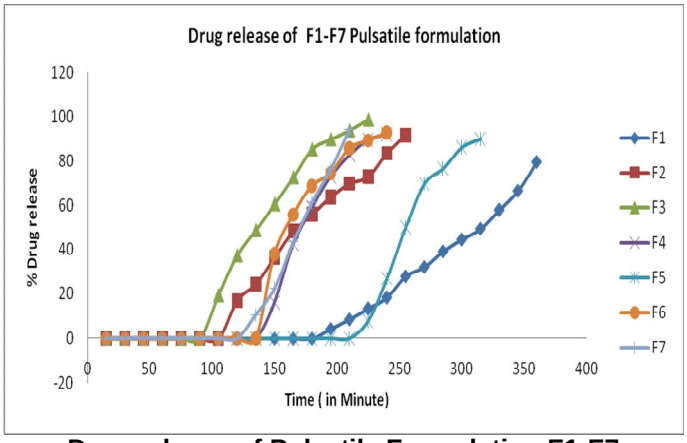
Conducting in vitro drug release studies assessed the tablet coating of Indomethacin to remain intact in the physiological environment of stomach and small intestine.

1. In vitro drug release study of core tablets

In vitro dissolution studies of core tablet were carried out using USP Type II (paddle method) apparatus (Electrolab TDT-06T). 6.8 Phosphate Buffer was used as a dissolution medium. Release pattern was studied visually by taking sample of 5 ml at the specific time intervals 2min, 4min…….24min. Also the sample was analyzed at 320 nm using a UV spectrophotometer.

2. In vitro drug release study of press-coated tablets

In vitro dissolution studies were carried out using USP Type II (paddle method) apparatus (Electrolab TDT-06T). In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 6.8 and 7.4 were sequentially used. When performing the experiment, 0.1 M HCL pH 1.2 medium was used for 2 h (since the average gastric emptying time is 2 h), Then removed and fresh pH 6.8 phosphate buffer was added. After 2 h (average small intestinal transit time is 2 h), the medium was removed and fresh pH 7.4 Phosphate buffer saline (PBS) dissolution medium was added for subsequent hours. 900 ml of the dissolution medium was used at each time. Rotation speed was 50 rpm and temperature was maintained at 37 ± 0.5^{o} C. 5ml of dissolution media was withdraw at predetermined time interval and fresh dissolution media was replaced. The withdrawn samples were analysed at 320nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times.



Drug release of Pulsatile Formulation F1-F7

RESULT AND DISCUSSION

Present study was done to formulate time-release drug delivery of Indomethacin by coating with blend of water insoluble polymer ethyl cellulose and water soluble polymer HPMC. Due to this coating Tablet will show lag time and drug will not release during lag time. Aim of this formulation was to get effect of drug in early morning for the treatment of Rheumatoid Arthritis, Time- release Indomethacin tablet was evaluated for various parameters.

1. Preformulation Study

Characterization of Drug

IR spectrum of Indomethacin is characterized by the following groups

Frequency cm^{-1}	Assignment
655.8	C-Cl stretching
1028.06	C—O—C stretching
1712.79	C=O stretching
2962, 2873.94, 2827.64	Aliphatic C-H stretching

It also shows presence of aromatic C-H group and OH group. Thus .the presence of all the functional group indicates that the drug is indomethacin.

2. Drug-Excipients Interactions

The IR spectra of Formulation F5 (40:60) was compared with the standard spectrum of Indomethacin (Fig.6.10). In spectra of Formulation F5, this band was same absorption pattern as that of pure drug (Fig.6.5). Mentioned evidences thus lead to the conclusion that changes are not seen as there is no physical interaction between the drug and polymers.

3. Precompression Parameter

8.2.1. Evaluation of Polymeric blend

The core material and polymeric blend for outer coating was evaluated for various Precompression parameter such as Bulk density, tap density, angle of repose, Hausseners ratio and compressibility index. The values of pre-compression parameters evaluated were within prescribed limit and indicated a good free flowing property.

Pre-compression parameter for Core material and Polymeric Blend

Formulations Code	Bulk Density g/cc	Tap density g/cc	True Density g/cc	Angle Of Repose (Θ)	Hausseners ratio	Carrs index
F1	0.378	0.456	1.25	34^0	1.206	17.10
F2	0.475	0.534	2.50	31 º	1.124	11.048
F3	0.445	0.525	1.68	30º	1.177	15.10
F4	0.448	0.573	2.50	27º	1.279	21.81
F5	0.470	0.571	2.47	28º	1.210	17.36
F6	0.443	0.532	3.36	29º	1.198	16.57
F7	0.496	0.556	1.98	30º	1.118	10.63

Evaluation of pulsatile tablet

Table 8.2: Post-compression parameter for Core tablet

Formulation	Thickness (mm)	Diameter (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight variation (mg)	Disintegration time (min)	Drug content (%)
Core tablet	2.14	8.315	2.2	0.785	95.5± 9.55	2min10 sec	96.5

Table 8.3: Post-compression parameter for Press coating tablet

Formulation code	Thickness (mm)	Diameter (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	Weight variation (mg)
F1	3.29	12.135	5.8	0.185	94.74	403.5 ± 20.17
F2	3.17	12.14	6.2	0.283	93.40	406.0 ± 20.30
F3	3.20	12.20	6.4	0.247	96.88	404.5 ± 20.22
F4	3.20	12.42	6.6	0.125	97.84	400.5 ± 20.025
F5	3.12	12.28	6.8	0.149	95.78	402.5 ± 20.125
F6	3.18	12.23	6.8	0.187	94.88	399 ± 19.95
F7	3.21	12.21	6.8	0.111	95.48	402.5 ± 20.125

In-vitro dissolution study

In Vitro dissolution of core tablets

The core tablet of indomethacin is a Fast disintegrating tablet. When the tablet comes in contact with dissolution medium it get rapidly disintegrated. Thus it shows 85 % of drug release within 20 minutes upon contact with dissolution medium.

In present study croscarmellose sodium used in core tablets formulation and it gave release after disintegration of tablet. In 5 % concentration of cross carmellose Tablet disintegration is fast and thus drug release is fast.

Croscarmellose sodium (Ac-di-Sol) in concentration of 2% gave slow disintegration and complete disintegration is occur in 4 min.32 sec. Crosscarmellose in concentration of 3.5% shows complete disintegration in 3 min 48 sec. which was unacceptable. Therefore 5% concentration is used as a final concentration in core formulation.

Table 8.4: Percent Drug Release of Optimised Core Tablet

S. No.	Time (min)	%Drug Release
1	2	13.42
2	4	29.9
3	6	32.46
4	8	41.4
5	10	49.46
6	12	59.46
7	14	63.36
8	16	70.56
9	18	76.02
10	20	85.26
11	22	93.36
12	24	99.04

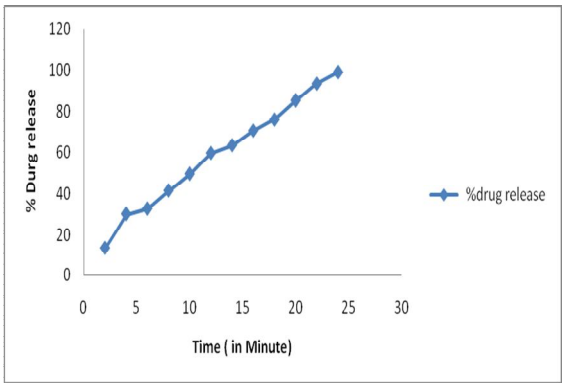


Fig. 8.1: Drug release profile of core tablet

In Vitro dissolution of press coated tablets

All press coated tablet showed pulsatile release behavior with distinct lag time. Incorporation of core tablet into press coated tablet produce a lag time prior to drug release. When dissolution medium reaches the core after eroding or rupturing the outer barrier layer rapid drug release was observed.

In vitro drug release profile for individual as well as combination of two polymers was shown in fig.2 and fig.3

Formulation F1 containing HPMC alone in outer coating. HPMC is a hydrophilic and water soluble polymer. It was observed that outer coat of HPMC formed the viscous gel like structure which resulted in delay drug release. On exposure to the dissolution fluids, the HPMC get hydrated and forms a viscous gel layer that slows down further seeping-in of dissolution fluids towards the core tablets. The lag time achieved with HPMC alone used as a outer coating polymer is 3 hr 10 min.

In case of Formulation F7 Ethylcellulose is alone used as a coating polymer, as it is a hydrophobic polymer, Ethyl cellulose in the form of coat is capable of protecting the drug from being released completely in the physiological environment of stomach and small intestine. The hydration of Ethyl cellulose seems not to be affected by the pH of the dissolution medium. The Drug release profile of formulation F7 containing Ethyl cellulose as outer coating polymer shows the lag time of 2 hr 11 minute.

When the combination of HPMC and the Ethyl cellulose is used, as a result of solubility of HPMC upon contact with dissolution medium HPMC hydrated and form compact with ethylcellulose. The Hydrophobicity of the ethyl cellulose retard the hydration of HPMC therefore dissolution medium did not penetrate the outer coating layer but the coating erode slowly.

Amongst the various combinations the Drug release profile of Formulation F5 containing combination of HPMC and Ethylcellulose in ratio of 40:60 showed desirable lag time of 3 hr 43 minute with desirable drug release in comparison of other combination used. Thus this formulation is considered as best formulation combination to achieve the pulsatile release of indomethacin after suitable lag time.

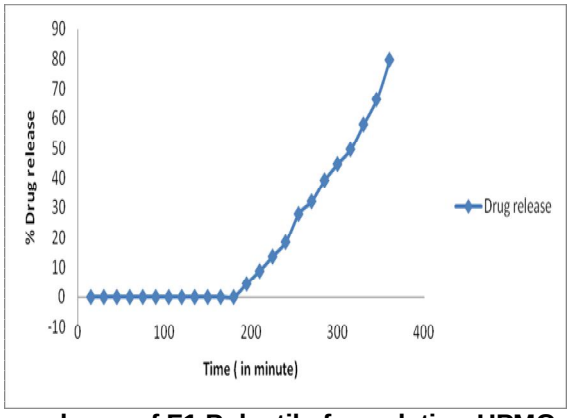
The drug release profile varied as concentration ratio of polymers was changed. Formulation F1 (100:0) showed slow drug release. This might be due to the time lag prior to drug release was controlled by the thickness and the viscosity of the gel layer of HPMC. After erosion or dissolution of the HPMC gelling layer a distinct onset for drug release was observed. Thus with this polymer the drug release is insufficient ie.90 percent over 6 hrs.

It was also observed that the formulation containing high ratio of HPMC shows decreasing lag time that may be due to the solubility of HPMC in medium as seen in Formulation F1,F2,F3. As the

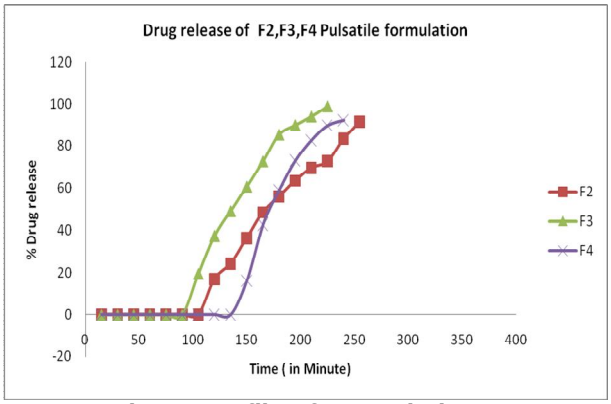
Concentration of Ethyl cellulose increases the lag time further goes on increasing as seen in F4, F5 .Formulation F5 (40:60) showed longer lag time of 3hrs.43 minute with require release rate in comparison with other formulation .Thus, this study , clearly indicated that the 40:60 ratio is more suitable among the polymers combinations used in the formulations to design pulsatile release formulations of Indomethacin.

Table 8.5: Lag time of Pulsatile Formulation

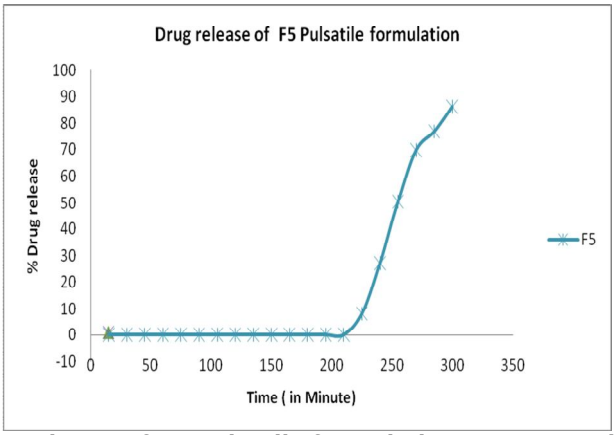
S.no.	Formulation code	Lag time
1	F1	3 hrs. 10 mins.
2	F2	2 hrs. 16 mins.
3	F3	1 hrs. 32 mins.
4	F4	2 hrs. 28 mins.
5	F5	3 hrs. 43 mins
6	F6	2 hrs.18 mins.
7	F7	2 hrs. 11 mins.



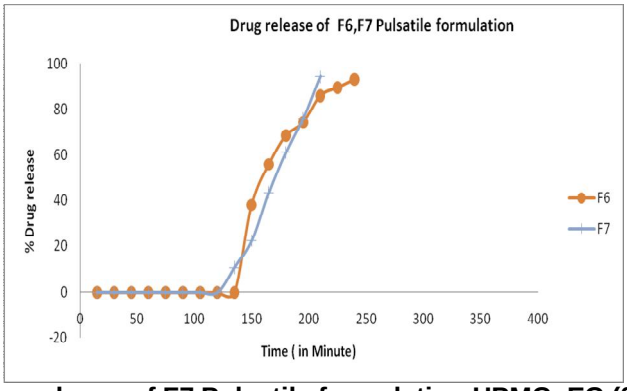
1. Drug release of F1 Pulsatile formulation HPMC: EC (100:0)



2. Drug release profile of Formulation F2, F3, F4



3. Drug release of F5 Pulsatile formulation HPMC: EC (40:60)



4. Drug release of F7 Pulsatile formulation HPMC: EC (0:100)

CONCLUSION

Ethyl cellulose and HPMC was outer coating polymer used in pulsatile tablet formulation. When HPMC alone used as outer coating polymer (in F1 Formulation) it gives long lag time more than 3 hrs. But slow disintegration and drug release was found in this formulation. So HPMC alone can not be used as an outer coating polymer to achieve lag time. Ethyl cellulose alone used in F7 formulation as an outer coating polymer which shows good lag time upto 2 hrs 11min. The blend of HPMC and Ethyl cellulose was used in different ratio to achieve desired lag time. Amongst all ratio, 40:60 ratio showed desired lag time of 3 hrs 43 min. it was longer lag time as compared to other ratio used.

Thus combination of HPMC and Ethyl cellulose in the ratio of 40:60 found tobe best possible combination for achieving desired lag time.

Conclusion was that croscarmellose sodium (Ac-di-sol) in 5% conc. was suitable disintegrating agent for core tablet in time pulsatile drug delivery system, which gave complete drug release after coating was ruptured.

It was also concluded that HPMC and Ethyl cellulose in 40:60 ratio are the best polymer to be used in pulsatile formulation.

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