WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 10, 1890-1900. Research Article ISSN 2277– 7105

DESIGN, DEVELOPMENT AND IN VITRO EVALUATION OF INDOMETHACIN TABLET IN TABLET FORMULATION AS A PULSATILE DRUG DELIVERY SYSTEM

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Article Received on
02 Aug 2015,

Revised on 25 Aug 2015,
Accepted on 18 Sep 2015

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ABSTRACT

The objective of present investigation was to develop press coated indomethacin tablet in tablet formulation using hydrophilic polymers. The drug delivery system designed to deliver the drug at such a time it could be most needful to patient of rheumatoid arthritis. The press coated tablets containing indomethacin in the inner core was formulated with an outer shell by different weight ratio of hydrophilic polymers HPMC K4M and lactose. The release profile of press coated tablet exhibited a lag time followed by burst release. The optimized F3 batch gave drug release 99.62% which consisted of 35% HPMC K4M.

KEYWORDS: Press-coated tablet, lag time, HPMC K4M, rheumatoid arthritis, pulsatile drug delivery.

INTRODUCTION

Oral controlled drug delivery system represent the most popular form of controlled drug delivery system for the obvious advantages of oral route of drug administration over the conventional dosage form. Such system 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. 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. 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 chronomodulated system.[1] Pulsatile drug delivery system (PDDS) which releases drug in a programmed pattern i.e. at an appropriate time and/or appropriate site of action. The rapid and complete drug release occurs after predetermined lag time.[2] Diseases wherein pulsatile systems are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, attention deficit syndrome in children, allergic rhinitis and hypercholesterolemia.[3] The principle rationale for the use of pulsatile release is for the drug where a constant drug release i.e. zero order release is not desired.[4] PDDS designed according to circadian rhythm of the body.[5] Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 Hours. Interestingly, the term circadian is derived from the Latin circa which means "about" and dies which can be defined as "a day". Normally, circadian rhythms are synchronized according to internal biologic clocks related to the sleep-wake cycle. Our circadian rhythm is based on sleep-activity cycle and is influenced by our genetic makeup and thereby affects our body's function throughout day and night (24-hour period). Circadian rhythm regulates many body functions in humans like metabolism, physiology, behavior, sleep pattern, hormone production. Morning stiffness associated with pain at the time of awakening is a diagnostic criterion of the rheumatoid arthritis and these clinical circadian symptoms are supposed to be outcome of altered functioning of hypothalamic–pitutary–adrenocortical axis. Chronopharmacotherapy for rheumatoid arthritis has been recommended to ensure that the highest blood levels of the drug coincide with peak pain and stiffness. A pulsatile drug delivery system that can be administered at night (bed time) but that release drug in early morning would be a promising chronopharmaceutic system.[6] The press coating technique is a simple and unique technology used to provide tablets with a programmable lag phase. Followed by a fast, or rate controlled, drug release after administration. The technique offers many advantages, and no special coating solvent or coating equipment is required for manufacturing this type of tablet.[7] 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 different concentrations of hydrophilic polymers such as hydroxypropylmethyl cellulose and lactose.

MATERIALS AND METHODS

Materials

Indomethacin was obtained from Balaji drugs (Ahmadabad), Crospovidone obtained from FMC biopolymer (Mumbai), HPMC K4M obtained from Vishal Chem (Mumbai), Erythrosin obtained from Coral pharma (Ahmadabad), Lactose obtained from Concept pharma (Aurangabad). All other chemicals were of pharmaceutical grade.

METHODS

Fourier Transform Infrared (FTIR) spectroscopy

The FTIR spectrum was recorded using SHIMADZU FTIR-8400. The procedure consisted of, placing drug sample in FIIR cuvette. The drug sample was placed in the light path and scanned over the range of 4000 - 400 cm^{-1}. Obtained spectrum was recorded and analyzed.

Drug-excipient compatibility study

The Drug-excipient compatibility study was carried by DSC with their physical mixture in ratio 1:1. The mixtures were prepared by triturating the drug with excipients and the mixtures were stored for 24 hours at room temperature. The mixtures were then filled in aluminum pan specially made for DSC sampling and the DSC thermogram was recorded.

Characterization of indomethacin core granules and polymeric blend of coating material

Indomethacin core granules and polymeric blend of coating material were evaluated for various precompression parameter such as bulk density, tapped density, angle of repose, carr's index, hausner's ratio.

Preparation of indomethacin core tablets

Core tablet containing 50 mg of indomethacin per tablet was prepared as shown in table 1. Wet granulation method was used to prepare the granules for the core tablet. Indomethacin, starch and lactose were sifted separately through sieve no.60 then geometrically mixed them. Then weighed quantity of PVP K30 and erythrosine was dissolved in sufficient amount of IPA to prepare binder solution. To geometrically mixed blend, binder solution was added to prepare granules. Granules was dried at 30-40 ^{0}C for 10-15 min. Dried granules were passed through sieve no.22. Then added 60 mesh sifted crospovidone in the dried granules. Sifted granules were transferred to polythene bag and magnesium stearate and talc sifted through sieve no.60 and added to above granules, mixed for 10 minutes. 150 mg of lubricated blend

was compressed using rotary tablet machine with 9mm standard concave punch to obtain the core tablet. The tablets were tested for hardness, thickness, friability, weight variation, disintegration, drug content and in vitro drug release

Table 1 : Composition of indomethacin core tablet

Sr.No.	Ingredients	Quantity (mg)
1	Indomethacin	50
2	Starch	44.25
3	Lactose	44.25
4	PVP K30	4.75
5	Crospovidone	3
6	Erythrosin	1.5
7	Magnesium stearate	0.75
8	Talc	1.5
9	IPA	q.s
	Average weight	**150**

Press-coating of core tablets

HPMC K4M, lactose, PVP K30 and crospovidone were sifted separately through sieve no. 60 then dry mix them, to mixture magnesium stearate added, mixture were dry blended for 10 min. The core tablets were press coated with 300mg blend as given in table 2. 150mg of coating layer was weighed and transferred into 12mm FFBE die then core tablet was placed manually at the centre. The remaining 150 mg of coating layer material was added into the die and direct compressed using rotary tablet machine.Weight of each tablet was adjusted upto 450 mg.

Table 2: Composition of coating layers (300 mg)

Sr.No.	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
1	HPMC K4M	45	75	105	120	135	150	165	180
2	Lactose	240.06	210.06	180.06	165.06	150.06	135.06	120.06	105.06
3	PVP K30	6.72	6.72	6.72	6.72	6.72	6.72	6.72	6.72
4	Crospovidone	6.72	6.72	6.72	6.72	6.72	6.72	6.72	6.72
5	Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Evaluation[1,8,9,10]

General Appearance: The general appearance of a tablet, its visual identity and overall "elegance" is essential for consumer acceptance. These include tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking. Cross section of press coated tablet was also examined. For the ease of identification colored core tablet were prepared.

Tablet dimensions: Thickness and diameter were measured by using Vernier caliper. Tablet thickness should be controlled within a ± 5% variation of standard value.

Hardness (Mechanical strength): The resistance of tablets to capping, abrasion or breakage under storage, transportation and handling before usage depends on its hardness. Tablet hardness has been defined as the force required to breaking a tablet in a diametric compression test. Hardness of tablet determined by using Monsanto hardness tester.

Friability: The ability of the tablet to withstand abrasion in packaging, handling and shipping. Friability was determined by the using friabilator apparatus. Take the 10 tablets and dedust it carefully before testing. The tablet sample was accurately weighed, and place the tablets in the drum. Rotate the drum 100 times. Remove the tablets, remove any loose dust from the tablets and accurately weigh. A maximum loss of weight not greater than 1.0 per cent is acceptable for most tablets.

% Friability = Initial wt-Final wt/Initial wt X 100

Weight variation: Twenty tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with average weight. Tablet meet the USP test if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Disintegration test of core tablet: In vitro disintegration time of six tablets from was determined by using disintegration test apparatus. To test for disintegration time, 1 tablet was dropped in each glass tube and the basket rack assembly was set in a 1 L beaker of water at 37 ± 2^{0} C.

Drug content: 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 100ml volumetric flask and allowed to stand for 10 min. To that 75ml 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 50 ml 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.

Water uptake study (% swelling): In this study tablet of each batch was separately placed in the basket of dissolution apparatus by using water as immersion medium at 37 ± 2 ^{0}C. Tablets were withdrawn at a time of 3 hr and bottled with tissue paper to remove the excess water. The weight of tablet after swelling was measured on an analytical balance. The initial and final weights of the tablets were used to calculate % swelling or water uptake of the tablet as follows

$$\% \, Water \; uptake = \left(\frac{W_t - W_0}{W_0} \right) \times 100$$

Where, W_t and W_o are final weight after swelling and initial dry weight of the tablet respectively.

In vitro dissolution study

a) For core tablet: The in vitro dissolution study of core tablet was performed using USP type II (Paddle) dissolution testing apparatus. Dissolution studies were carried out in 900 ml of pH 6.8 phosphate buffer for 30 min at 50 rpm. 5 ml sample was withdrawn at 5, 10, 15, 20, 25 and 30 min. Same volume of dissolution medium was replaced at every time interval and absorbance of sample solution was measured at 320 nm.

b) For press coated Indomethacin tablet in tablet: The in vitro dissolution study of press coated pulsatile tablet was performed using USP type II (Paddle) dissolution testing apparatus. Dissolution studies were carried out in 900 ml of 0.1 N HCl for 2 hr then it is replaced by 6.8 buffer for 2 hr then it is replaced by 7.4 buffer for 3 hr at 50 rpm. 5 ml sample was withdrawn at 1,2,3,4,5,6,7 hours. Same volume of dissolution medium was replaced at every time interval and absorbance of sample solution was measured at 320 nm.

RESULTS AND DISCUSSION

The descriptions of the observed peak are given in the following table.

Table 3: FTIR characteristic peaks of indomethacin

Assignment	Wave number cm^{-1} (Recorded)
Aromatic C-H stretching carboxylic acid	30.72
C=O Stretching	1704.17
O-CH_3 deformation	1463.06
Aromatic C=C Stretching	1599.04
C-O Stretching plus O-H deformation	1239.31
Carboxylic O-H out of plane deformation	918.15
C-Cl stretching	833.28

Fourier Transform Infrared (FTIR) spectroscopy

FTIR spectrum of indomethacin was recorded and characteristic peaks were observed.

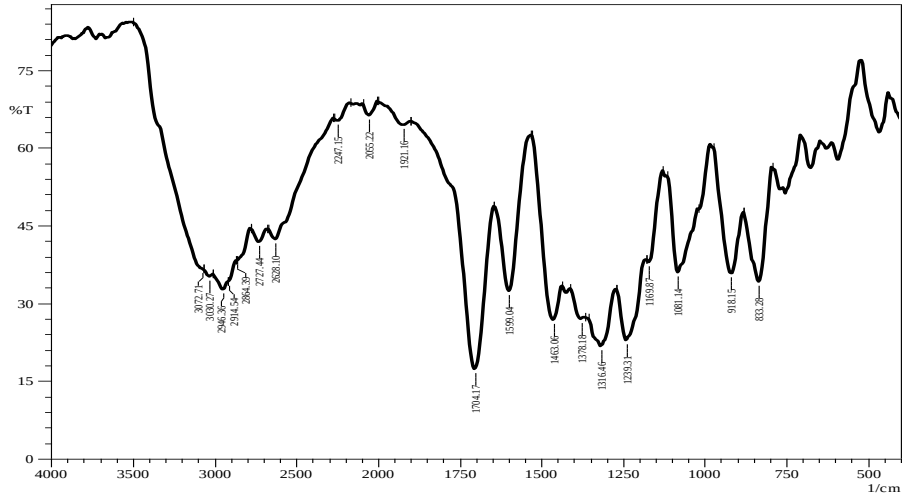

Fig. 1: FTIR spectrum of indomethacin

Drug-excipient compatibility study

The possible interaction between the drug and the polymers was studied by differential scanning colorimeter (DSC). There was no considerable change in DSC endothermic values, comparing pure Indomethacin and with excipient (HPMC K4M, lactose, PVP K30, crospovidone) which indicated the absence of any interaction between drug and excipients used in preparation. Peak values obtained at 159.86 ^{0}C which is very much nearer to pure drug i.e. 161.61 ^{0}C. DSC thermogram is shown in Fig.2. and Fig.3.

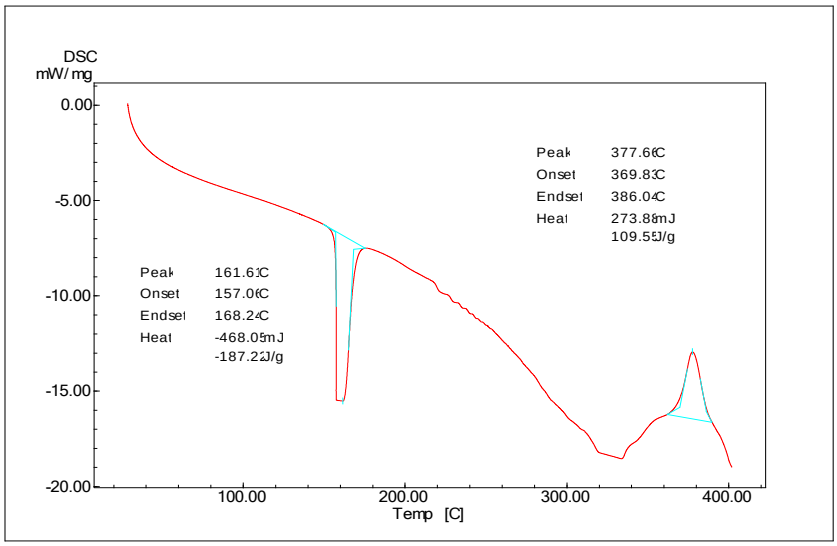

Fig.2: DSC thermogram of indomethacin

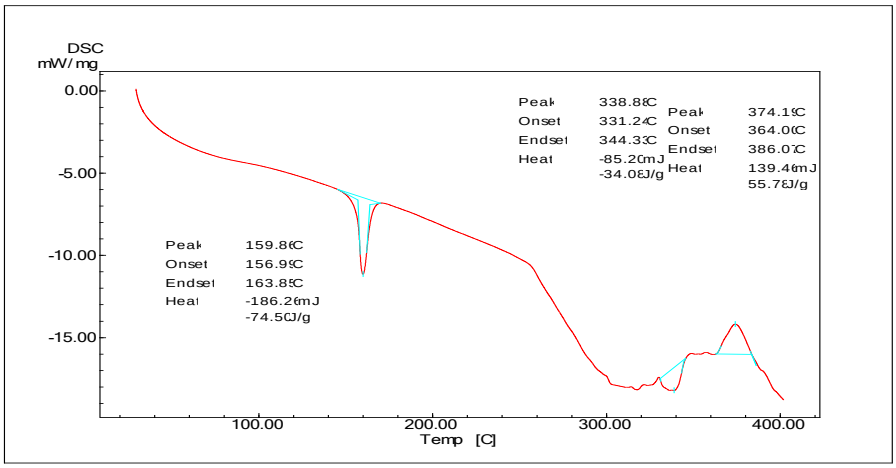

Fig. 3: DSC thermogram of indomethacin + excipients

Precompression evaluation of granules

Table 4: Evaluation of indomethacin core granules

Formulation	Parameters				
	Angle of repose (degree)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio
Core tablet	28.30±0.03	0.29±0.01	0.33±0.02	11.94±0.03	1.13±0.02

Table 5: Evaluation of polymeric blend of coating layer

Formulation	Parameters				
	Angle of repose (degree)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio
F1	25.90±0.03	0.32±0.03	0.36±0.02	11.41±0.04	1.12±0.01
F2	29.51±0.02	0.32±0.01	0.37±0.01	13.63±0.04	1.13±0.01
F3	25.85±0.03	0.32±0.01	0.35±0.07	8.93±0.09	1.09±0.04
F4	28.30±0.02	0.32±0.04	0.37±0.01	13.58±0.20	1.15±0.01
F5	27.97±0.01	0.30±0.02	0.35±0.03	13.03±0.11	1.14±0.03
F6	27.65±0.02	0.31±0.03	0.35±0.05	12.64±0.39	1.14±0.02
F7	27.49±0.03	0.33±0.04	0.38±0.06	14.21±0.34	1.16±0.01
F8	28.28±0.02	0.32±0.04	0.36±0.01	11.35±0.02	1.12±0.02

Evaluation of press coated Indomethacin tablet in tablet.

Table 6: Post compression parameter for indomethacin core table.

Evaluation parameter	Core tablet
Appereance	Pink coloured round shape uncoated tablet
Weight variation (mg)	156.73
Thickness (mm)	2.80
Hardness (kg/cm^2)	2.5
Friability (%)	0.37
Disintegration (sec)	58
Drug content (%)	98.80

Table 7: Evaluation of press coated Indomethacin tablet in tablet.

Evaluation Parameter	Batches							
	F1	F2	F3	F4	F5	F6	F7	F8
Appearance	White colored press coated tablet containing pink colored inner core							
Weight variation (mg)	486.15	469.19	467.46	471.81	467.72	471.87	465.78	471.11
Thickness (mm)	3.05	3.10	3.12	3.08	3.04	3.11	3.10	3.04
Hardness(kg/cm^2)	4.4	4.3	4.2	4.4	4.3	4.2	4.2	4.4
Friability (%)	0.47	0.59	0.49	0.45	0.63	0.82	0.74	0.52
Drug content (%)	98.23	97.66	99.10	98.46	97.45	98.80	97.99	98.95

Table 8: Water uptake study (% swelling).

Batches	F1	F2	F3	F4	F5	F6	F7	F8
Swelling index (%)	68.88	70.66	76.66	66.22	55.11	57.33	62.22	60.00

In vitro dissolution study

a) For core tablet

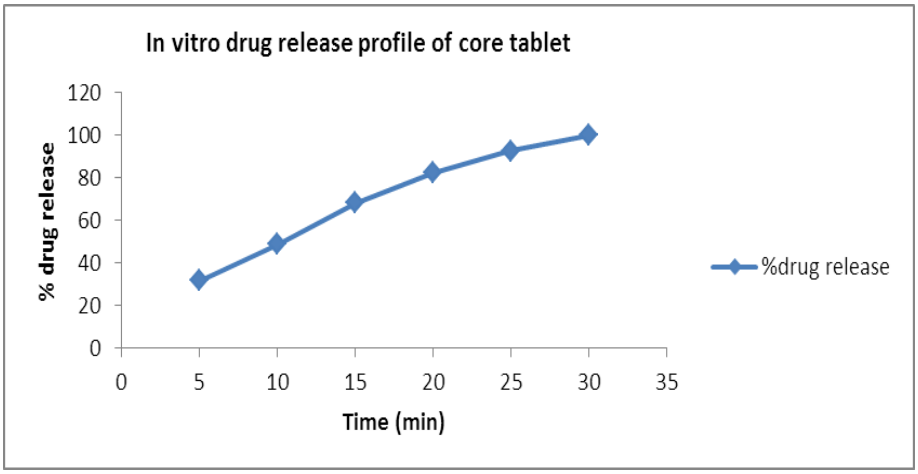

Fig. 4: In vitro drug release profile of core tablet

b) For press coated Indomethacin tablet in tablet

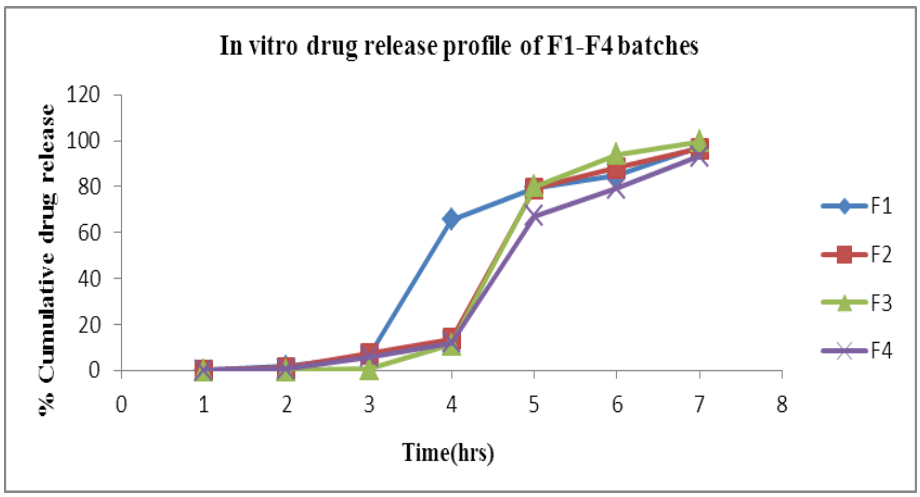

Fig. 5: In vitro drug release profile of F1-F4 batches

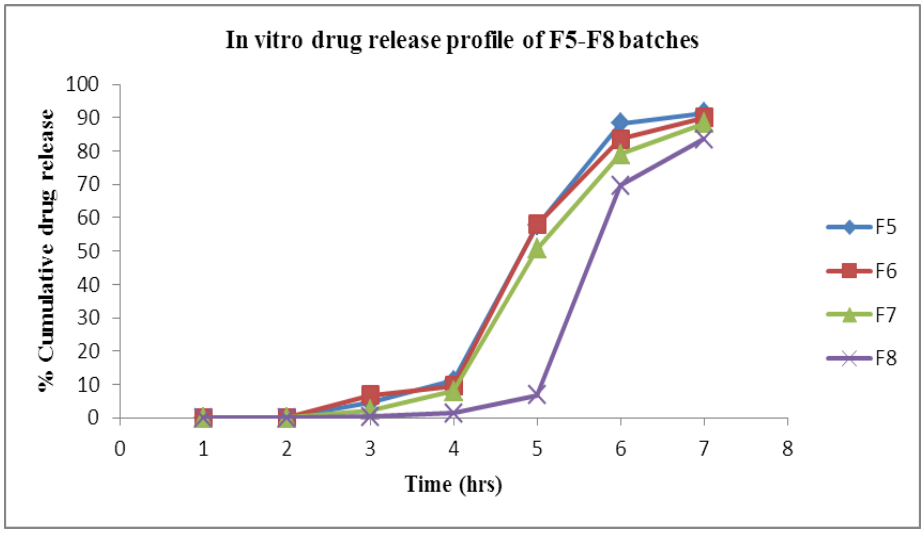

Fig. 6: In vitro drug release profile of F5-F8 batches

The HPMC K4M in 35 % concentration in press coated Indomethacin tablet shows the better drug release. The % drug release of press coated Indomethacin tablet was found to be 99.64 % in batch F3 shows the better release after predetermined lag time of 4 hrs and 5 min. Among all the formulations, the formulation F3 has been selected as best formulation. All the parameters of formulation F3 are good and within the specification limits as well as it shows the better drug release.

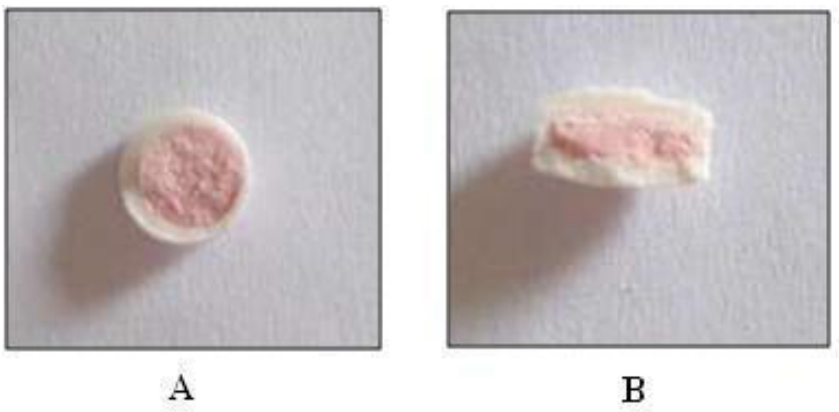

Fig. 7: Photograph of A) Transverse and B) Longitudinal section view of press coated Indomethacin pulsatile

CONCLUSION

A chronotherapeutic dosage form was formulated by press coating technique. The lag time and time-controlled release behavior of indomethacin from press coated tablets could be modulated by varying the concentration of polymer in outer coating layer and thickness of the compression coating. The HPMC K4M in 35 % concentration in press coated Indomethacin

tablet shows the better drug release. The % drug release of press coated Indomethacin tablet was found to be 99.64 % in batch F3 shows the better release after predetermined lag time of 4 hrs and 5 min. The dosage should be timed to ensure that the higest blood levels of the drug coincide with peak pain.

REFERENCES

1. Bhasakaran S, Moris S, Sheikh A. Design and developmemt of chronomodulated system for arthritis. Int. J. Pharm. and Chem. Sci., 2012; 1(4): 1350-61.
2. Patil ND, Bari MM, Barhate SD. A review on novel approach pulsatile drug delivery system. Int. J. Pharm. Sci. Rev. Res., 2013; 21(1): 209-22.
3. Keraliya RA, Patel MM. Chronopharmaceutical: A critical review of pulsatile drug delivery system. PhTechMed., 2013; 2(2): 256-64.
4. Avani S, Doshi N, Patel D, Badmanaban R, Patel CN. Footsteps of pulsatile drug delivery system in pharmaceutical sciences. Res. J. Pharm. and Tech., 2010; 3(2): 385-89.
5. Shidhaye S, Dhone A, Budhkar T, Surve C. Technologies in pulsatile drug delivery system. Int. J. Adv. Pharm. Bio. and Chem., 2012; 1(4): 438-45.
6. Moon A, Kondawar M, Shah R. Formulation and evaluation of press-coated indomethacin tablets for pulsatile drug delivery system. J. Pharm. Res., 2011; 4(3): 564-66.
7. Shan YL, Yoshiaki K. Current status and approach to developing press-coated chronodelivery drug system. J. Cont. Rele., 2012; 157: 331-53.
8. Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy. 3rd ed, Mumbai., 1991; 293-344.
9. Gennaro AR. Remington the Science and Practice of Pharmacy. 21st ed. Vol. 1 Philadelphia: Lippincott Williams & Wilkins: 916-17.
10. Nawle RB, Tadvee AA. Formulation and evaluation of time-release compression coated tablet containing acebrophylline for chronotherapy of asthma. Int. J. Pharm. and Pharm. Sci., 2014; 6(9): 231-37.