World Inventia Publishers

Journal of Pharma Research

http://www.jprinfo.com/

Vol. 6, Issue 2, 2017 ISSN: 2319-5622 USA CODEN: JPROK3

Research Article

FORMULATION AND EVALUATION OF CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEM FOR RHEUMATOID ARTHRITIS

Dr. Rama Bukka [1] *, Sujatha [2]

[1] Asst. Professor, Department of Pharmaceutics, Nargund College of pharmacy, Bangalore-85, Karnataka, INDIA.

[2] Department of Pharmaceutics, Nargund College of pharmacy, Bangalore-85 (Karnataka), INDIA.

Received on: 25-01-2017; Revised and Accepted on: 17-02-2017

ABSTRACT

Aim of the present work was to formulate and evaluate an oral pulsatile drug delivery system to achieve timed release of Ketoprofen, based on chronopharmaceutical approach for the treatment of Rheumatoid arthritis (RA). Pulsatile delivery system is capable of delivering drug when and where it is required most. Time-delayed capsule, designed to release drug after a predictable lag time, are intended for oral chronotherapy. The basic design of the project consists of insolubalization of capsule by exposing to formaldehyde vapors and coating of the capsule in order to lock cap and body which provides the required lag time. Core composition of capsule consists of Ketoprofen blend for burst release after lag time. Controlled release after lag time was achieved by inserting a Ketoprofen plug with various polymers. The prepared formulations were evaluated for various physical tests, lag time, in-vitro release profile, drug-excipients compatibility studies, etc. To maintain the required lag time for 6 hours, trials were carried out to achieve optimum E.C coating (5%). In order to achieve burst release after lag time Ketoprofen blend was added with various concentration of SLS and controlled release was obtained by using polymers like HPMC K4M, Polyox & HEC along with Ketoprofen, made as plug which exactly fits into the body of the formaldehyde treated capsule. Finally plug formulated with HPMC polymer, Ketoprofen blend with 16% SLS using 10% Formaldehyde treated capsule for 6h resulted in a formulation F10 with 6h lag time and continuous control release for 32hour.

Key words: *Pulsatile drug delivery; Lag time; Chronotherapeutics; Ketoprofen; Pulsincap.*

INTRODUCTION

Chronotherapy considers a person's biological rhythms in determining the timing and amount of medication to optimize a drug's desired effects and minimize the undesired ones. Study of influence of biological rhythm on the effects of medication is known as chronopharmacology while the science of study of biological rhythms is known as chronobiology [1].

Diseases presently targeted for chronopharmaceutical formulations are those for which there are enough scientific backgrounds to justify pulsatile drug delivery system (PDDS) compared to the conventional drug administration approach. They include:

Hypercholesterolemia, Asthma, Cancer, Duodenal ulcer, Arthritis, Diabetes, Neurological disorders, Cardiovascular diseases (e.g. Hypertension and acute Myocardial infarction) and Colonic delivery [2, 3].

Pulsincap is the one of the approaches for pulsatile drug delivery. Pulsincap system comprises of a water-insoluble capsule. The solubility of the formaldehyde treated capsule is depending on the concentration and time of exposure to the formaldehyde solution. Lag time increases as increasing the concentration and time of exposure to formalin vapours.

Rheumatoid arthritis is considered as a chronic disease which mainly causes destruction in the integrity of joints. In patients with rheumatoid arthritis, symptoms such as joint stiffness and functional disability mainly persist in the early morning hours. These symptoms are mainly characterized due to the diurnal variations in the levels of circulating pro-inflammatory cytokines, tumour necrosis factor-α and/or interleukin-6. It has been recommended to treat Rheumatoid arthritis by using the concept of chronopharmacotherapy to ensure that the highest concentration of drug should be present in the bloodstream when the excessive stiffness and pain of the disease persist. However, drug delivery system would be more effective and useful when taken during midnight for targeting morning symptoms of Rheumatoid arthritis than achieved by the same dose taken at early morning time [4-6]. But, having patients awake at each midnight is clearly not an acceptable treatment option. Therefore, present study planned to develop a Pulsincap of Ketoprofen formulation with chronotherapeutic treatment of rheumatoid arthritis, in which the delivery of treatment is coordinated with biological rhythms.

Ketoprofen is a non-steroidal anti-inflammatory agent (NSAIA) with analgesic and antipyretic properties. The anti-inflammatory effects of Ketoprofen are due to inhibition cylooxygenase-2 (COX-2), an enzyme involved in prostaglandin synthesis via the arachidonic acid pathway. This results in decreased levels of prostaglandins that mediate pain, fever and inflammation. Ketoprofen is a non-specific cyclooxygenase inhibitor. It is rapidly absorbed after oral administration and maximal concentration in plasma are achieved within 1-2 hrs; food reduces the rate but not extent of absorption. The drug is extensively bound to plasma proteins (60 to 90%) and it has half life in plasma of about 2 hrs; slightly longer half life is observed in elderly patients [7].

MATERIALS AND METHODS

Materials:

Ketoprofen was received from BMR Pharma and Chemicals, Hyderabad. HPMC K4M, Polyox N60K, HEC/Natrosol 250HX, Avicel, Sodium Lauryl sulphate and all other ingredients used were either pharmaceutical or analytical grade.

***Corresponding author:**

Dr. Rama Bukka

Asst. Professor,

Department of Pharmaceutics,

Nargund College of pharmacy, Bangalore-85, Karnataka, INDIA.

E-Mail: ramabukka@gmail.com

Methods:

Preformulation studies:

Identification of Ketoprofen was carried out by Infra Red Absorption Spectrophotometry. Spectrum obtained was compared with that spectrum given in I.P. Solubility of the drug was checked in different solvents like Ethanol, Chloroform, Ether, and Water. Melting point of Ketoprofen was determined by Open Capillary Method. **λ**max was checked in 0.1N HCL, 6.8 and 7.4 pH buffer.

Standard calibration curve of the Ketoprofen were prepared in 0.1N HCL at 259nm, similarly standard curve prepared using 6.8 and 7.4 pH buffer at 260 nm.

Drug-Excipients Compatibility study was carried out by FTIR. Here weighed amount of drug or physical mixture of drug and polymer (1:1) was mixed with 100mg of potassium bromide (dried at 40-50^{0}c) the mixture was taken and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned by IR Spectrophotometer.

Formaldehyde treatment of empty capsules: [8]

50 hard gelatine capsule of size '1' were taken. 25 ml of 5% and 10% (v/v) formaldehyde solution was taken in two separate desiccators of 9 inches diameter and a pinch of potassium permanganate was added the solutions, to generate formalin vapours. The wire mesh containing the empty capsules separated into body and cap were then exposed to formaldehyde vapours. The desiccators were tightly closed. The reaction time was optimized by removing capsule at different time intervals and drying at 50°C for 30 min to ensure complete reaction between gelatine and formaldehyde vapours. The capsules were then dried at room temperature to facilitate removal of residual formaldehyde. These capsules were stored in double lined polythene bag.

Optimization of formaldehyde treated capsule: [9]

Capsules were optimized by conducting Disintegration test. The test was performed on both untreated and treated capsules. Formaldehyde treated bodies joined with caps and tested for disintegration. Disintegration test was carried out by using USP disintegration test apparatus in 0.1N HCL, pH 6.8 & pH 7.4 buffers maintained at 37°C throughout the experiment. The time at which the capsules disintegrate were noted (**table 3**).

Preparation of powder blends for pulsatile release:

As per information of Food and drug administration (FDA) Ketoprofen can be administered in divided dose of 25, 50 and 75 mg daily as immediate release, 100 to 200 mg as extended release for once daily. According to this information pulsatile delivery system and pulsatile controlled drug delivery system were formulated.

Formulation F1 to F5 trials were planned to get 6 hours of lag time using formaldehyde treated capsules by EC coating. 5% ethanolic solution of ethyl cellulose **(table 2)** was used to coat the 6hr formaldehyde exposed capsule which was previously contains 50mg of drug and 30mg of avicel. In F1 formulation the cap and body were locked by 1drop (it gives 1% increase of capsule weight after coating) of 5% EC solution between the clearance of cap & body using 23 gauge needle to 6hr formaldehyde exposed capsule. But from the dissolution study lag time was not observed. So in next trials coating was applied to whole capsule. Dip coating method was employed for coating the capsules. Capsule were dipped in the coating solution using a pointed forceps and then dried at room temperature until the coat was completely dry. Simultaneously dipping and drying was continued by changing the position of forceps to hold the capsule, till the required weight gain was achieved. After final coating it is dried at room temperature for about 5hrs and stored in a double lined polythene bags. Coating thickness was varied according to results from dissolution studies. Formulations F2, F3, F4 & F5 were coated to give 15%, 11%, 9% and 5% thickness respectively. Here % weight gain by EC coating is determined after filling, coating and drying Formaldehyde exposed capsule.

F5 formulation success could maintain 6 hour lag time but after lag time, complete drug release took more than 2hour. So next trial were planned to release the drug as burst manner after lag time by adding SLS in different concentration, formulation F6 consist of 8mg (10%), F7 consist 9.6mg (12%), F8 consist 11.2mg (14%) and F9 consist 12.8mg(16%) of SLS respectively.

Blend formulations of Ketoprofen, Avicel, SLS were accurately weighed (as per **table 1**) and mixed well using a poly bags and triturated finely using glass marter then passed through the mesh No.40 and weighed, required quantity of prepared blend was filled into the Pulsincap.

Formulation of pulsatile controlled drug delivery system:

Here the powder blend consists of same composition as F9 formulation for pulsatile delivery and additionally plug was prepared in such a way that it should fit into the internal diameter of body of the capsule. Plug of three polymers HPMC K4M, Polyox and HEC were used in the F10, F11and F12 formulations respectively. Accurately weighed quantity of drug and polymer were passed through sieve no.40 & mixed in poly bag. Then magnesium stearate was added to the above blend and passed through sieve no.80. Weight of blend equivalent to 100mg of Ketoprofen was taken and it was compressed using 6mm shallow concave punch and this plug was inserted into the formaldehyde exposed capsule body which previously contained 50mg of Ketoprofen powder blend for pulsatile delivery**.** So these three formulations were used as pulsatile controlled release.

Then all the three formulations (F10, F11 & F12) were coated until 5% increase the weight of filled capsule using EC as described in the above procedure.

Evaluation of pulsincap:

Pre-compression parameters: [8, 10]

Various pre-compression parameters such as bulk and tapped density, Carr's compressibility index, Hausner's ratio and angle of repose were evaluated for the prepared powder blend for both immediate release and for controlled release plug blend.

Post-compression parameters: [11, 12]

Various post-compressional parameters such as hardness, thickness, weight variation, and friability were evaluated for the prepared Ketoprofen plug**.**

In-vitro dissolution profile: [8]

Dissolution studies were carried out by using USP XXIII dissolution test apparatus (basket method). Capsules were placed in a basket so that the capsule would be immersed completely in dissolution media and would not float. In order to simulate the pH changes along the GI tract, three dissolution media with 0.1N HCL, 6.8pH and 7.4pH buffer were sequentially used as per sequential pH change method. When performing experiments, the 0.1 N HCl (1.2 pH) was first used for 2 hrs (since the average gastric emptying time is 2 hrs) then removed and the fresh pH 6.8 phosphate buffer was added. After 3 hrs (average small intestinal transit time is 3 hrs) the medium was removed and fresh pH 7.4 dissolution medium was added for subsequent hours. 900ml of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.5°C. 5 ml of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed by UV absorption spectroscopy.

RESULTS AND DISCUSSION

The IR spectrum of pure drug was found to be similar to the standard spectrum of Ketoprofen, which was in compliance with I.P. standards [13].

Solubility of Ketoprofen shows that it is freely soluble in ethanol, slightly soluble in chloroform, ether and insoluble in water which was in accordance with literature in I.P [13].

The melting point of Ketoprofen was found to be 94^o C, which complied with I.P standards thus indicating purity of the drug sample [13].

An absorption maximum was found to be at 249nm in 0.1N HCL & 250nm in pH 6.8 & 7.4 buffer which is accordance with I.P [13].

Standard graph was plotted between the range of 2-14 µg/ml at 259nm in 0.1N HCL and 260nm in 6.8 and 7.4 buffer shows linearity **(Fig. 7, 8 & 9)**.

Drug-Excipients compatibility study was carried out by FTIR technique and it shows that there is no interaction between Ketoprofen and other Excipients used as all the characteristic peak of the drug are remained unchanged when mixed with Excipients (**Fig1. 2 & 3**).

Formaldehyde treatment of empty capsules: Exposure to formalin vapours results in an unpredictable decrease in solubility of capsule. Disintegrate test were carried out in different media such as 0.1N HCL,

6.8 & 7.4 pH buffer for normal capsules and formaldehyde treated capsules. It was observed that in untreated capsules, dissolved within 15 min where as in case of formaldehyde treated capsules, the solubility of capsule shell decreased as increasing the concentration and time of exposure.

Optimization of formaldehyde treated Capsules: Capsules exposed to 5% formaldehyde for 12 hrs softened in 10hr, whereas with 10% treated for 6hr, the capsule were found to be intact up to 8hr.As the treatment time increased solubility is comparatively decreased. Hence finally 10% of formaldehyde treatment for 6 hour was considered as optimised treatment for empty HGC **(Table 3)**.

Formulation of pulsatile drug delivery system: Here in F1 to F5 formulation, EC coating thickness was varied but contains same physical mixture of Ketoprofen and Avicel **(Table 1)**.

The aim of the formulation was to maintain the lag time of up to 6Hrs. So in F1 formulation the gap between cap and body was filled with drops of E.C solution. But lag time was not observed as 14% of drug release seen in second hour. In F2 formulation, whole formaldehyde treated capsule was given coating by dip coating method until it gained weight up to 15% but it shows long lag time of 12 hours, so in F3 formulation coating was reduced from 15% to 11%, here drug release time was reduced from 12hrs to 10hrs. Again in F4 formulation coating was reduced from 11% to 9%, showed a lag time of 8 hours but required lag time was 6 hour. So in F5 formulation, coating was reduced from 9% to 5% and it shows the lag time of 6hrs and this formulation is considered as optimized formulation for treatment of HGC.

In F5 formulation required lag time were maintained but after lag times the release of drug taken more time i.e. about 4hrs. So in F6 formulation 10% SLS were added to release the drug as burst manner. The release of drug took 3hrs so this formulation fails to release as burst manner after lag time. In F7 Formulation SLS concentration was increased from 10% to 12%, the drug released taken up to 3hrs. In F8 formulation concentration of SLS increased to 14% and the drug release was observed up to 2 hrs after lag time. In F9 formulation the concentration of SLS is increased to 16%, it shows within 2Hrs releases the entire drug as a burst manner. So this formulation is taken as better formulation and used for pulsatile delivery of Ketoprofen.

Formulation of pulsatile controlled drug delivery system:

Ketoprofen can be administered at a dose levels of 100mg & 200mg for once a day dosing, so in order to maintain pulsatile controlled release till the next dose, the drug release has to be controlled up to 30hrs(6hr lag time + 24hr control release).

In formulation F10, F11 & F12 different polymers were used to control the drug release after the burst release (pulsatile control delivery). Here the aim was to maintain 24hrs drug release after lag time (6+24hr) so totally 30hrs dissolution test is performed. F10 formula containing HPMC K4M releases 99.5% drug in 30hrs where as F11 formula containing Polyox WSR N60K releases 100% drug with in 24 hrs. In case of F12 formula containing HEC at the end of 30hrs releases 86.24% drug, & 98.24% drug release was observed after 34hrs. So it concluded that F9 formula containing HPMC is better polymer to control the drug release to required period of time.

Pre and post compression result (**Table 4, 5 & 6)** shows that all formulations pass the pharmacopoeial limits [13].

Table No. 1: Composition of Ketoprofen

Composition (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ketoprofen	50	50	50	50	50	50	50	50	50	50+100	50+100	50+100
Avicel pH 102	30	30	30	30	30	30	30	30	45	45	45	45
SLS	-	-	-	-	-	8 [10%]	9.6 [12%]	11.2 [14%]	12.8 [16%]	12.8 [16%]	12.8 [16%]	12.8 [16%]
HPMC	-	-	-	-	-	-	-	-	-	49	-	-
Polyox	-	-	-	-	-	-	-	-	-	-	49	-
HEC	-	-	-	-	-	-	-	-	-	-	-	49
Mg. Stearate	-	-	-	-	-	-	-	-	-	1	1	1
Total	80	80	80	80	80	88	89.6	91.2	107.8	257.8	257.8	257.8
Avg. Wt gain by 5% EC coating	1	15	11	9	5	5	5	5	5	5	5	5

Table No. 2: Composition of coating solution

Ethyl cellulose	5g
Ethanol	100ml (q.s)

Table No. 3: Disintegration of Formaldehyde treated empty capsule

Formaldehyde %	Time of exposure (hr)	Observation in Dissolution Media		
		0.1 N HCl	6.8 Phosphate buffer	7.4 Phosphate buffer
5 %	4	Soften in 2hrs	Soften in 2hrs	Soften in 2hrs
	6	Soften in 4hrs	Soften in 4hrs	Soften in 4hrs
	12	Soften in 10hrs	Soften in 10hrs	Soften in 10hrs
10%	4	Intact up to 5hrs	Intact up to 5hrs	Intact up to 5hrs
	6	Intact up to 8 hrs	Intact up to 8 hrs	Intact up to 8 hrs
	12	Intact more than 12 hrs	Intact more than 12 hrs	Intact more than 12 hrs

Table No. 4: Pre compression parameters of powder blend

Formulation	Angle of repose	Bulk density (wt/vl)	Tapped density (wt/vl)	% compressibility	Hausner's Ratio
F1-F5	26.79	0.377	0.437	11.52	1.15
F6	29.29	0.392	0.425	7.76	1.08
F7	30.11	0.384	0.434	11.52	1.13
F8	24.32	0.392	0.454	13.65	1.15
F9	23.07	0.377	0.437	13.72	1.15
F10	26.47	0.377	0.437	13.72	1.15
F11	25.64	0.384	0.434	11.52	1.13
F12	28.41	0.392	0.425	7.76	1.08

Table No. 5: Post compression parameters

Formulation	Weight variations (mg)* n=20	Hardness(kg/cm^2) n=3	Friability (%)	Thickness(mm) * n=10
F10	148.6±1.174	4 to 5	0.196	4.73±0.01
F11	152.3±1.247	4 to 5	0.467	4.70±0.05
F12	150.8±1.895	4 to 5	0.398	4.72±0.04

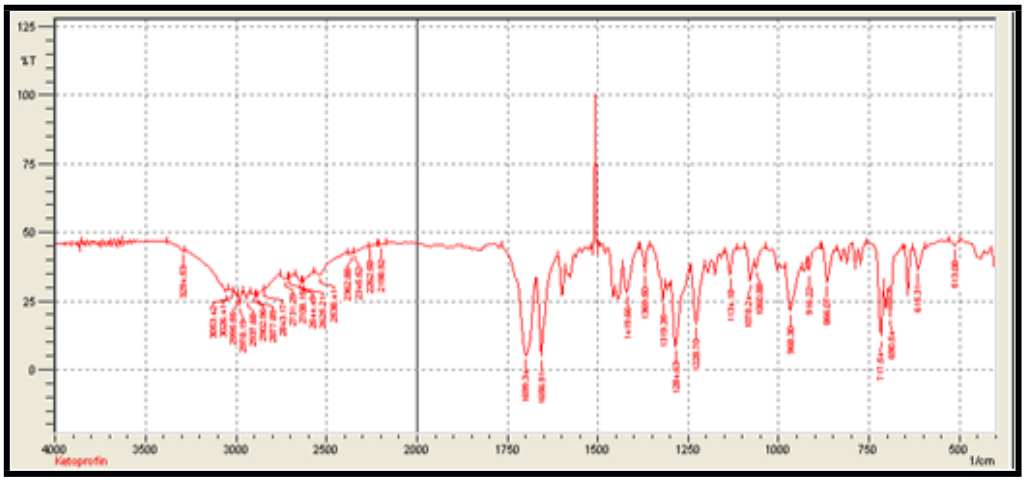

Fig. 1: FTIR Spectra of Ketoprofen (Pure drug)

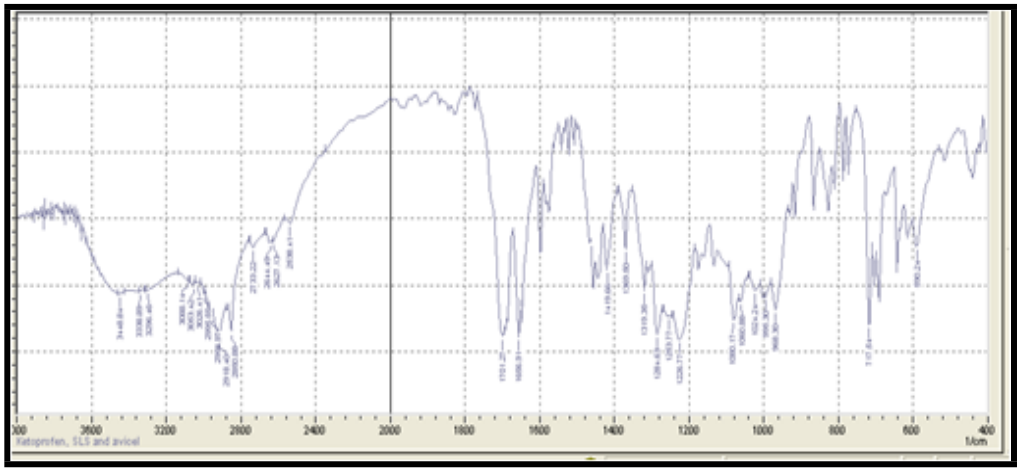

Fig. 2: FTIR Spectra of Ketoprofen + Avicel + SLS

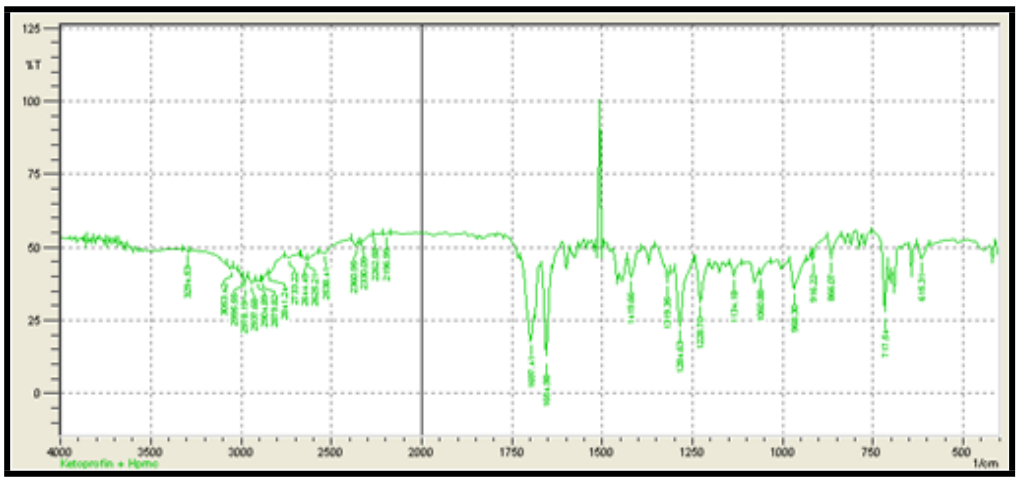

Fig. 3: FTIR Spectra of Ketoprofen + HPMCK4M

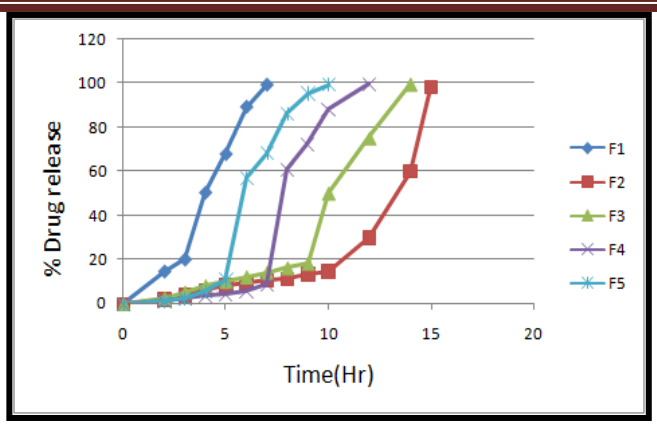

Fig. 4: *In-Vitro* dissolution profile of F1 to F5

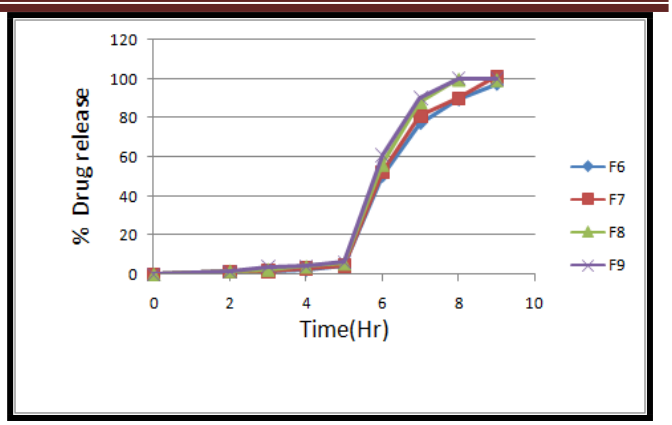

Fig. 5: *In-Vitro* dissolution profile of F6 to F9

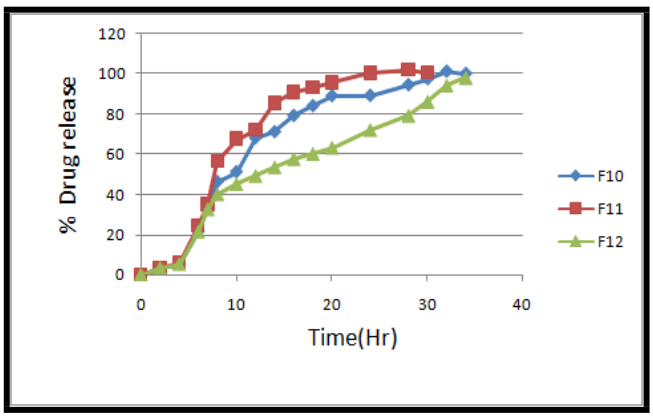

Fig. 6: *In-Vitro* dissolution profile of F10 to F12

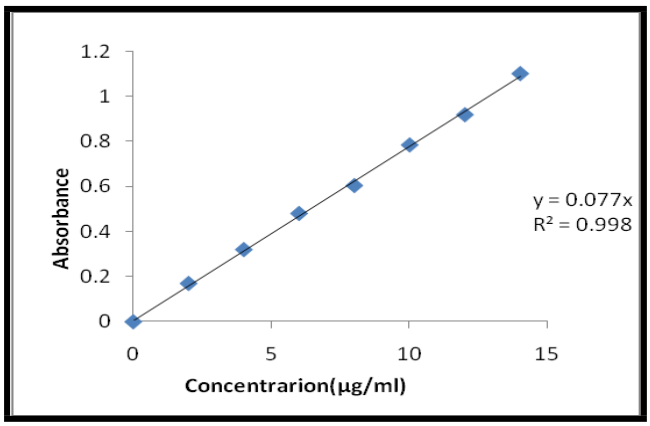

Fig. 7: Standard graph in 0.1N HCL

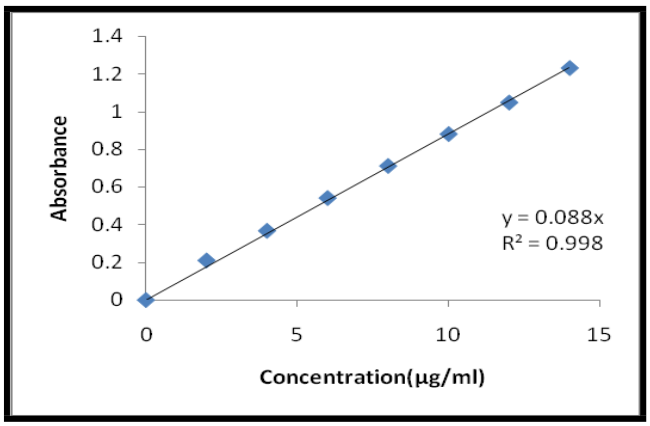

Fig. 8: Standard graph in pH 6.8 buffer

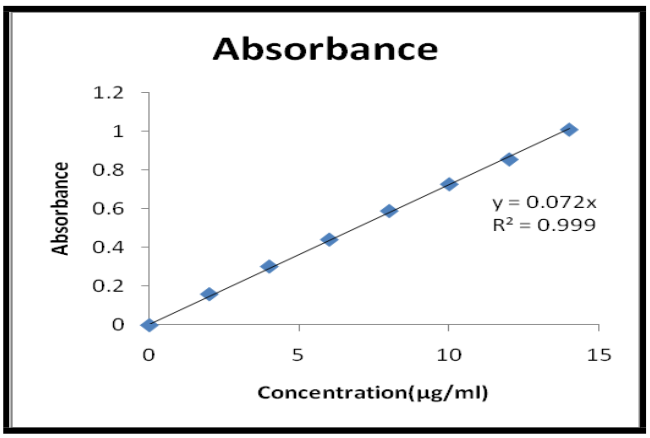

Fig. 9: Standard graph in pH 7.4 buffer

Fig. 10: Release of drug from E.C coated capsule

CONCLUSION

The drug-SLS ratio was found to influence the release of drug from the formulation after the lag time in burst manner. As the SLS concentration was increased, the drug release rate was found to be rapid. Formulation F9 containing 16% SLS selected as better formulation for burst release of drug after a lag time, F9 formulation selected as optimized for pulsatile delivery. Different drug- polymer combination like HPMC K4M, Polyox & HEC was used in F10, F11 & F12 formulations respectively to control the delivery after pulsatile release. In this HPMC K4M shows 99.5% drug release so formulation F10 with HPMC K4M was selected as best formulation for pulsatile controlled delivery.

REFERENCES:

1. Brahma CK, G. Vidya Sagar Gali. Chronotherapeutics drug delivery systems challenges to pharmaceutical field. J Glob Trends Pharm Sci **2012**;3(3):1077–87.
2. Sharma GS, Srikanth MV, Uhumwangho MU, Kumar P, Ramana Murthy. Recent trends in pulsatile drug delivery systems - A review. Int J Drug Delivary **2010**;2(2010):200–12.
3. Rajput M, Sharma R, Kumar S, Jamil F, Sissodia N. Pulsatile Drug Delivery System : A Review. Int J Res Pharm Biomed Sci **2012**;3(1):118–24.
4. Verma M, Maity T, Gupta AK, Sharma V, Mittal A, Nandy BC, et al. An overview of Chrono-pharmaceuticals drug delivery systems: Recent advances. J Drug Discov Ther **2014**;2(16):11–26.
5. Choy E. Understanding the dynamics : pathways involved in the pathogenesis of rheumatoid arthritis. **2012**;3–11.
6. Hadi MA, Guggilla N, Rao R, Rao AS. Formulation and evaluation of mini-tablets-filled-pulsincap delivery of lornoxicam in the chronotherapeutic treatment of rheumatoid arthritis. Pak J Pharm Sci **2011**;28(1):185–93.
7. Borse RD, Derle D V., Saptarshi D. Formulation and in vitro evaluation of pulsatile drug delivery system of Ketoprofen. Asian J Pharm Res Dev **2013**;1(4):204–16.
8. Modi P, Patel G, Shah R. Design and evaluation of modified pulsincap of Tramadol HCL according to circadian rhythm. Int J Pharm Innov **2013**;3(3):1–14.
9. Reddy g. S, B.sirisha, Umamaheshwar R, Lakshmi p. V, Ajitha A. Formulation and in vitro evaluation of colon specific drug delivery of Naproxen sodium by using pulsincap technology. An Int J Adv Pharm Sci **2014**;5(1):1751–60.
10. Lachman L, Lieberman HA. Theory and Practice of Industrial Pharmacy. **2009** ed. CBS Publishers & distributers PVT. LTD.
11. Rowe RC, Sheskey PJ, Owen SC. Handbook of Pharmaceutical Excipients. 5th editio. Landon: pharmaceutical press; **2005**.
12. Pavia DL, Lampman GM, Kriz GS. Introduction to Spectroscopy. Third edit. Wahington: Harcourt College Publishers;
13. Pharmacopoeia. I. Government of India Ministry of Health & Family Welfare. **2010**.

How to cite this article:

Dr. Rama Bukka, Sujatha. FORMULATION AND EVALUATION OF CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEM FOR RHEUMATOID ARTHRITIS. J Pharm Res 2017;6(2):10-15.

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil