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Formulation and evaluation of ibuprofen pulsion cap technique for controlled release

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ABSTRACT

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the advantages of oral route of drug administration. In certain conditions conventional drug release pattern is not suitable like Diabetes mellitus, Asthma, cardiovascular diseases Arthritis, Peptic ulcer etc. In such conditions pulsatile drug delivery system is used in which release drug on programmed pattern especially at appropriate time and at appropriate site of action. In PDDS a pulse is designed that a complete and rapid drug release is achieved after the lag time so as to match body's circadian rhythms with the release of drug which increases the efficacy and safety of drugs by proportioning their peak plasma concentrations during the 24 hours in synchrony with biological rhythm. In this present study an attempt was made to formulate and evaluate ibuprofen as pulsing cap technique. The prepared capsules were evaluated for uniformity of weight, drug content and in vitro release. Promising results indicated the usefulness of the pulsion cap technique for controlled release of ibuprofen.

Keywords: Pulsatile Drug Delivery system, Ibuprofen, Hard gelatin capsules, Hydroxyl propyl methyl cellulose K 100 M,

INTRODUCTION

The most of therapeutic agents are, generally effectual when the release is at a fairly constant rate or near the absorption sites. The absorption of active pharmaceutical ingredients produced results in required plasma concentrations leading to minimum toxic side effects and maximum efficacy [1]. Pulsatile delivery is desirable for drugs acting locally or having an absorption window in the gastro-intestinal tract or for drugs with an extensive first pass metabolism, for e.g. β -blockers or for drugs, which develop biological acceptance, where the constant presence of the drug at the site of action diminishes the pharmacological effect, or for drugs with special pharmacokinetic characteristics designed according to the circadian rhythm of human. Controlled drug delivery technology emerged as most virtuous drug delivery systems mainly to enhance the drug therapy [2], the Controlled drug delivery technology offer many advantages when compared to conventional dosage forms; include increasing therapeutic activity compared to the intensity of side effects, reducing the frequency of drug administration thereby increasing the patient compliance, or eliminating the need for specialized drug administration (e.g., repeated injections). Controlled release systems show a typical release pattern of drug release for a prolonged period of time by maintaining the drug concentration within the therapeutic window where the rate of drug release matches the rate of drug elimination [3-6].

On the other hand, such release patterns where constant blood levels of drug, may not be applicable for certain conditions. These conditions involve release of drug after definite lag time. Such a release pattern is known as pulsatile release. Pulsatile drug delivery system also known as time-controlled systems are capable of providing rapid or transient release of drug molecules at predetermined lag times or at site specific sites, results in better drug absorption and effective plasma drug concentration-time profile[4-6].

Presently, the concept of chronotherapeutics [7] has come out, where a therapeutic agent is released at a rhythm that ideally matches the biological conditions of a given disease therapy. In other words, it delivers the drug in higher concentration in the time of greatest need and lower concentrations when the need is less. Several biological processes and disease states have been shown to be influenced by circadian rhythm[8]. Circadian rhythm regulates many body functions like sleep pattern, hormone production, bio-transformation especially in cardiovascular diseases. In case of arthritis patients will experience disease related symptoms based on circadian rhythm. Rheumatoid arthritis patients complain of prolonged morning stiffness for a period lasting an hour or more and these clinical circadian symptoms are supposed to be outcome of altered functioning of hypothalamic–pituitary–adrenocortical axis. A pulsatile drug delivery system that can be administered at night (bed time) but the release of the drug in the early hours of the day would be a propitious chronopharmaceutic system[9,10].

Ibuprofen (iso-butyl-propanoic-phenolic acid) is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties used for remedy of arthritis, fever. The study aims attention at developing pulsatile capsules of ibuprofen which are the single unit systems where the lag time is controlled by a plug. Polymers used for designing of the plug are hydroxyl propyl methyl cellulose, polyethylene oxide, which are erodible compressed polymers. The main constituent of capsule is gelatin, formaldehyde is used to retard the rate of hydrolysis. In the present investigation capsule body was hardened by formaldehyde vapours to prevent dissolution of capsule body. The main intention of this work was to formulate a single unit pulsatile capsules of ibuprofen which releases the drug after a definite lag time and provides required concentration of drug at regular intervals of time[11,12].

MATERIALS AND METHODS

Ibuprofen (I.P), Hydroxyl propyl methyl cellulose and Hard gelatin capsules (size '0') were purchased from Yarrow Chemical Limited. Polyethylene oxide was purchased from Oxford laboratory. Formaldehyde was purchased from Fischer. Magnesium stearate was purchased from Otto Chemical Limited. Aerosol was purchased from Loba chemie.

Insolubilization of capsule body by formaldehyde vapor treatment

Hard gelatin capsules were taken and the bodies were separated from caps of the capsule. Formaldehyde was taken in a petri dish and placed in a dessicator, this bodies of the capsules are dipped in the formaldehyde and then the lid of dessicator is closed and kept aside for 24hrs.

Procedure

The selected size '0' of hard gelatin capsules (blue cap with orange body) were taken, that capsules bodies and caps were separated. The bodies were placed on a wire mesh spread as a single layer. They were placed in a desiccator containing formaldehyde liquid at the bottom in equilibrium with its vapour. The bodies of capsule were exposed for varying periods of time viz., 6, 12 and 24 hrs. The capsule bodies were removed from the desiccators after the required exposure time and air-dried for 4 hrs. Later they were dried in a desiccators for 12 hrs and stored in an air tight container.

Test for the solubility of capsules

Disintegration test was performed on both untreated and treated capsules. The formaldehyde treated body joined with untreated cap and was tested for disintegration. Disintegration test was carried out by using Hiccon disintegration test apparatus. Purified water was used as medium and was maintained at 37°C through the experiment.

Preparation of blend for filling in to capsules

Different blend formulations were prepared for filling into capsules are given in Tables 1 and 2. In each formulation accurately weighed quantity of drug, polymer along with other ingredients the used in were passed through mesh No. 60. All the ingredients were mixed together in a mortar to obtain a homogeneous mixture by using geometric dilution technique. HPMC K100M and polyethylene oxide were selected as two polymers for controlling the release of drug. The polymer was used at weight of 10, 20, 30, 40 and 50 mg per unit in different formulations and studied the effect of polymer concentration. In these formulations polymer was used in two different methods. In one case (Formulation F1 to F10) the polymer was blended with other excipients and filled in to capsules. In other case (Formulation F10 to F20) the blend was prepared without polymer and filled in to capsules, and then the polymer was placed over the filled blend to form a slug over the filled material.

Preparation of modified pulsincaps

Bodies of the gelatin capsules of size '0' hardened with formaldehyde for 12 hours were taken for preparing the modified pulsincaps. In case of formulation F1 to F10, drug-excipient blend equivalent to 400 mg ibuprofen was weighed and filled into the hardened capsule body. Then the soluble cap was locked into the body to form the modified pulsincap.

In case of formulation F11 to F20, drug-excipient blend equivalent to 400 mg ibuprofen was weighed and filled into the hardened capsule body. The remaining volume of the capsule body was covered with PEO and HPMC. Then the soluble cap was locked into the body to form the modified pulsincap.

Uniformity of weight

From each batch 20 pulsincaps were selected at random, weighed together and individually. The mean and standard deviation were determined.

Estimation of drug content

From each batch of the prepared pulsincaps of ibuprofen ten pulsincaps were randomly selected and the contents were removed and powdered. From this sample 100 mg powder was accurately transferred into a 100 ml volumetric flask. Added 10 ml of methanol to dissolve ibuprofen. The solution is made up to volume with pH 7.2 phosphate buffer. The resulted solution was filtered through 0.45 μm filter paper and suitably diluted and the drug content was estimated spectrophotometrically by measuring the absorbance at 265 nm. The results are shown in Table 3.

In vitro dissolution studies

In vitro drug dissolution studies were conducted by using the dissolution rate test apparatus (M/s. Electro Lab Dissolution Tester USP). For in vitro dissolution studies of ibuprofen pulsincaps, phosphate buffer of pH 7.2 was used as the dissolution medium. The in vitro dissolution studies were carried out by using USP XXIV Type-I dissolution rate test apparatus (basket system). The stirring rate was 100 rpm. 900 ml of the dissolution medium was used and was maintained at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ throughout the experiment. 5 ml samples of dissolution fluid were withdrawn at predetermined time intervals with a pipette fitted with a filter. The volume withdrawn at each time interval was replaced with 5ml of fresh dissolution medium maintained at the same temperature. The filtered samples were suitably diluted whenever necessary and assayed for ibuprofen by measuring absorbance at 265 nm. All the dissolution experiments were conducted in triplicate and the mean values are reported.

Analysis of Dissolution data

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated problem and is practically evident in case of modified release dosage form. The dissolution data obtained was fitted to zero order [13], first order [14,15], Higuchi [16] and erosion [17] to understand the order and mechanism of drug release from the Pulsincaps.

Zero order release kinetics

It defines a linear relationship between the fraction of drug released versus time.

$$Q=k_0t$$

Where Q is the fraction of drug released at time t and k_0 is the zero order release rate constant.

A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First order release kinetics

Wagner [18] assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process, suggested that drug release from most slow release tablets could be described adequately by apparent first order kinetics. The equation used to describe first order kinetics is $\ln(I-Q) = -k_1t$

Where, Q is the fraction of drug released at time, (t) and k_1 is the first order release rate constant.

Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi equation

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$$Q = k_2t^{1/2}$$

Where, k_2 is the release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation.

Erosion equation

This equation defines the drug release based on erosion alone.

$$Q = 1 - (1 - k_3t)^3$$

Where, Q is the fraction of drug released at time (t), k_3 is the release rate constant. Thus, a plot of between $[1 - (1 - Q)^{1/3}]$ against time will be linear if the release obeys erosion equation.

RESULTS AND DISCUSSION

Formaldehyde reacts with gelatin forming an irreversible complex. The primary amine group present in gelatin reacts with formaldehyde making it irreversibly bound. In the present investigation the bodies of the hard gelatin capsules were exposed to formaldehyde vapours for different periods of time in a closed desiccator in which vapour is equilibrated with formaldehyde liquid containing approximately 38% w/v formaldehyde.

The hardened capsules were tested for their dissolution using disintegration tester in purified water medium. The hardened bodies of the capsules which were exposed to formaldehyde vapours for 6 hours were did not disintegrate for more than 24 hours. However the bodies of the capsules, which were exposed to 12 and 24 hours formaldehyde vapour were softened and became very sticky masses on exposure to the formaldehyde vapours. Hence in the present study the capsule bodies exposed to formaldehyde vapours for 6 hours were used in further studies.

Drug content

The drug content of the prepared capsules was found to be in the range 97.76 to 101.81%. The drug content values for all the capsules were within the acceptable limits indicating that there was no loss of drug during the process of filling.

Dissolution studies

The results of in vitro dissolution studies indicated that the release of the drug ibuprofen from the all the pulsatile capsules was uniform and extended for a period of 12 hours (shown in Tables 4 & 5, Fig. 1-5). This may be due to hardening of the capsule body extending the release of the drug. The drug release from the capsules prepared by using Hydroxy propyl methyl cellulose and Polyethylene oxide showed extended release over a period of 12 hours. In our present study the polymer in both the cases of Hydroxy propyl methyl cellulose and Polyethylene oxide were used in two methods. In one case (Formulation F1 to F10) the polymer was blended with other excipients and filled in to capsules. In other case (Formulation F10 to F20) the blend was prepared without polymer and filled in to capsules, and then the polymer was placed over the filled blend to form a slug over the filled material. In both the

methods for Hydroxy propyl methyl cellulose and Polyethylene oxide the drug release from the capsules was well controlled and extended over a period of time.

Formulation F1 to F5 contains Hydroxy propyl methyl cellulose K100M in different concentrations in the range of 10, 20, 30, 40 and 50 mg per unit. The invitro dissolution data showed that increasing the polymer concentration decreased the drug release. The results are same even in the case if the polymer was used as a slug over the filled materials (formulations F11 to F15).

Formulation F6 to F10 contains Polyethylene oxide in different concentrations in the range of 10, 20, 30, 40 and 50 mg per unit. The in vitro dissolution data showed that increasing the polymer concentration decreased the drug release. The results are same even in the case if the polymer was used as a slug over the filled materials (formulations F16 to F20).

Table 1: Formulae for the preparation of blend for filling of Ibuprofen pulsatile capsules

S.No.	Ingredients	Qty (mg)									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Ibuprofen	400	400	400	400	400	400	400	400	400	400
2	HPMC K100M	10	20	30	40	50	-	-	-	-	-
3	Polyethylene Oxide	-	-	-	-	-	10	20	30	40	50
4	Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
5	Mg Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Table 2: Formulae for the preparation of blend for filling of Ibuprofen pulsatile capsules

S.No.	Ingredients	Qty (mg)									
		F11	F12	F13	F14	F15	F16	F17	F18	F19	F20
1	Ibuprofen	400	400	400	400	400	400	400	400	400	400
2	Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
3	Mg Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
4	HPMC K100M*	10	20	30	40	50	-	-	-	-	-
5	Polyethylene oxide*	-	-	-	-	-	10	20	30	40	50

**Used to cover the filled material as powder slug*

Table 3: drug content in various Ibuprofen pulsatile capsules

Pulsatile capsules	Drug content (%)
F1	99.85
F2	98.56
F3	99.46
F4	99.32
F5	100.64
F6	101.49
F7	98.32
F8	98.64
F9	100.19
F10	99.45
F11	100.09
F12	98.29
F13	99.23
F14	98.89
F15	98.72
F16	97.76
F17	100.12
F18	98.42
F19	101.81
F20	99.46

The release of ibuprofen from pulsatile capsules followed first order kinetics which is indicated by the correlation coefficient values shown in Table 6. Among all the formulation F3, F8, F13 and F17 showed well controlled and pulsatile release of ibuprofen over a period of 12 hours. Hence these formulation are considered as best formulation. The mechanism of drug release was established by constructing plots of cumulative percent drug released versus square root time (Higuchi diffusion) and cube root of fraction of drug remained to be released versus time (erosion). The linear correlation coefficient of the slopes for the plots as shown in Table 6. The correlation coefficients for both diffusion as well as erosion are near to 1 indicating good correlation for both the mechanisms of drug release.

The causes for diffusion may be due to the swollen insoluble matrix, which entrapped the drug. The diffusional path length increased with increase in the size of the swollen matrix there by leading to good correlation for diffusion. The cause for good correlation for erosion may be due to the rupture and breakdown of the swollen matrix.

The results of the present study clearly indicated the usefulness of pulsatile capsule technique in delivering ibuprofen in well controlled and pulsatile manner.

Table 4: Dissolution data of various Ibuprofen pulsatile capsules(F1-F10)

S.No.	Time (h)	Cumulative percent drug released (%)									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	1	8.23	11.12	26.07	17.54	14.9	6.5	14.6	13.7	13.8	6.3
2	2	38.45	40.52	40.25	20.99	19.8	22.9	17.9	22.4	29.5	18.0
3	3	56.76	58.67	38.64	18.41	20.6	53.3	47.8	32.7	27.3	22.7
4	4	77.43	71.70	45.72	22.91	14.8	68.9	63.4	43.2	25.8	24.4
5	6	98.89	85.54	60.96	22.88	30.7	81.0	80.5	52.8	54.4	33.3
6	8	98.72	100.09	74.36	30.01	40.3	95.7	96.3	100.2	63.9	34.0
7	10	97.76	98.29	76.68	45.43	40.2	100.1	100.2	92.3	78.8	48.5
8	12	100.00	99.23	100.16	60.95	45.2	99.8	84.5	97.3	100.0	52.1

Table 5: Dissolution data of various Ibuprofen pulsatile capsules (F10-F20)

S.No.	Time (h)	Cumulative percent drug released (%)									
		F11	F12	F13	F14	F15	F16	F17	F18	F19	F20
1	1	19.60	21.15	7.91	12.17	8.9	24.0	11.4	11.4	10.1	13.3
2	2	32.98	37.34	9.91	15.34	16.9	37.1	21.3	20.1	24.3	22.2
3	3	39.84	28.67	14.59	17.47	10.5	56.2	18.7	25.9	21.8	24.0
4	4	49.80	35.96	17.41	16.12	10.2	61.3	27.4	28.4	25.6	25.6
5	6	81.97	77.36	29.99	14.49	11.5	70.4	38.1	30.0	25.6	26.1
6	8	90.02	83.65	90.12	45.76	22.0	74.0	45.1	57.1	41.3	29.1
7	10	96.98	88.83	94.88	41.38	23.4	100.5	84.8	56.2	49.9	31.3
8	12	100.99	100.15	98.91	48.05	25.0	98.0	98.7	61.3	39.1	32.1

Table 6: The Correlation coefficient of various Ibuprofen pulsatile capsules (F1-F20)

Formulation	Correlation coefficient			
	Zero order	First order	Higuchi	Erosion
F1	0.9097	0.9076	0.9531	0.9339
F2	0.9330	0.9909	0.9725	0.9091
F3	0.9465	0.9846	0.9909	0.9779
F4	0.9027	0.9083	0.9247	0.9080
F5	0.9288	0.9425	0.9456	0.9387
F6	0.9505	0.9726	0.9605	0.9720
F7	0.9649	0.9789	0.9638	0.9696
F8	0.9708	0.9469	0.9350	0.7942
F9	0.9773	0.9714	0.9523	0.9785
F10	0.9654	0.9736	0.9743	0.9723
F11	0.9760	0.9755	0.9778	0.9925
F12	0.9556	0.8920	0.9479	0.9690
F13	0.9390	0.8694	0.8391	0.9087
F14	0.8905	0.8813	0.8622	0.8849
F15	0.8289	0.8360	0.8608	0.8333
F16	0.9469	0.9678	0.9843	0.8666
F17	0.9546	0.9734	0.8947	0.9003
F18	0.9618	0.9723	0.9531	0.9601
F19	0.9462	0.9556	0.9561	0.9540
F20	0.8218	0.8484	0.9504	0.8394

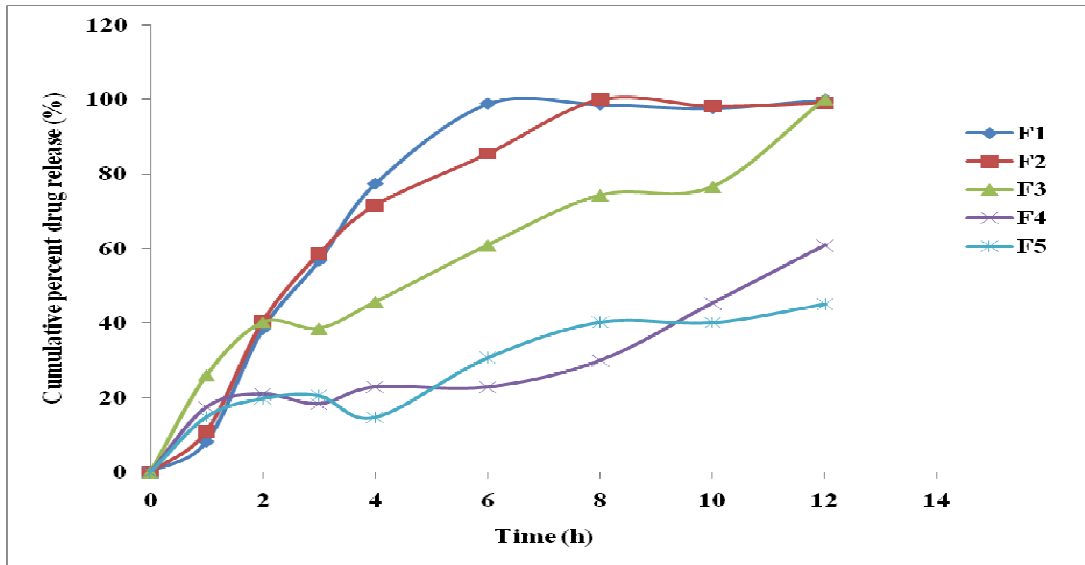


Fig. 1. Dissolution plots of Ibuprofen pulsatile capsules (F1-F5)

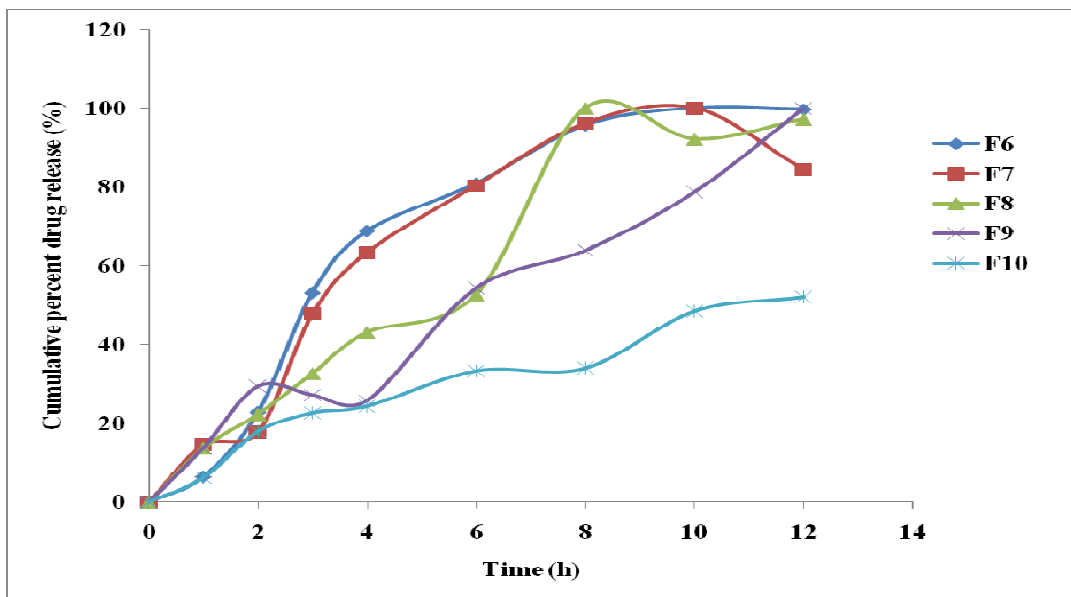


Fig. 2. Dissolution plots of Ibuprofen pulsatile capsules (F6-F10)

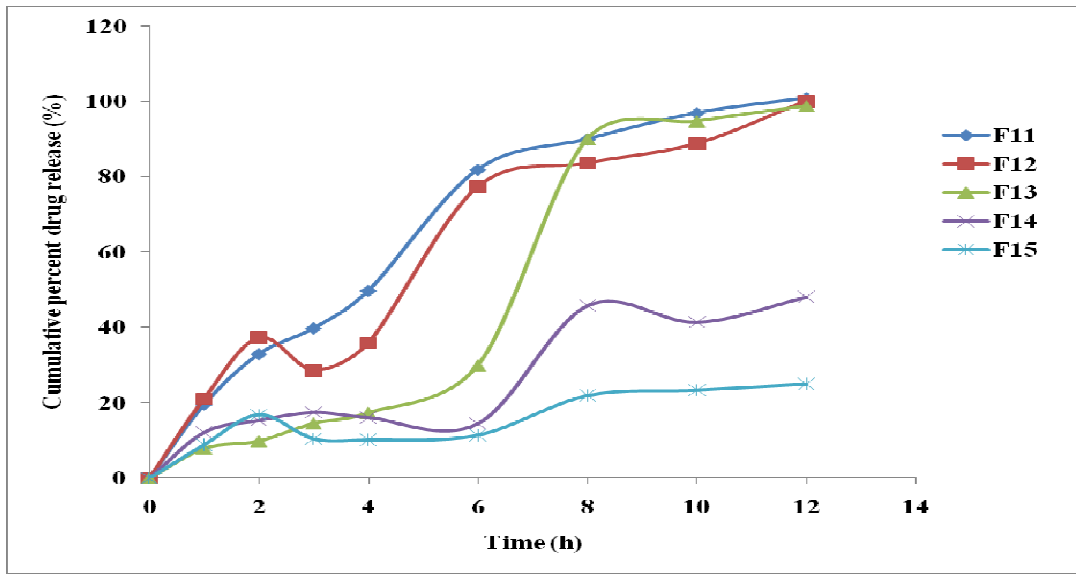


Fig. 3. Dissolution plots of Ibuprofen pulsatile capsules (F11-F15)

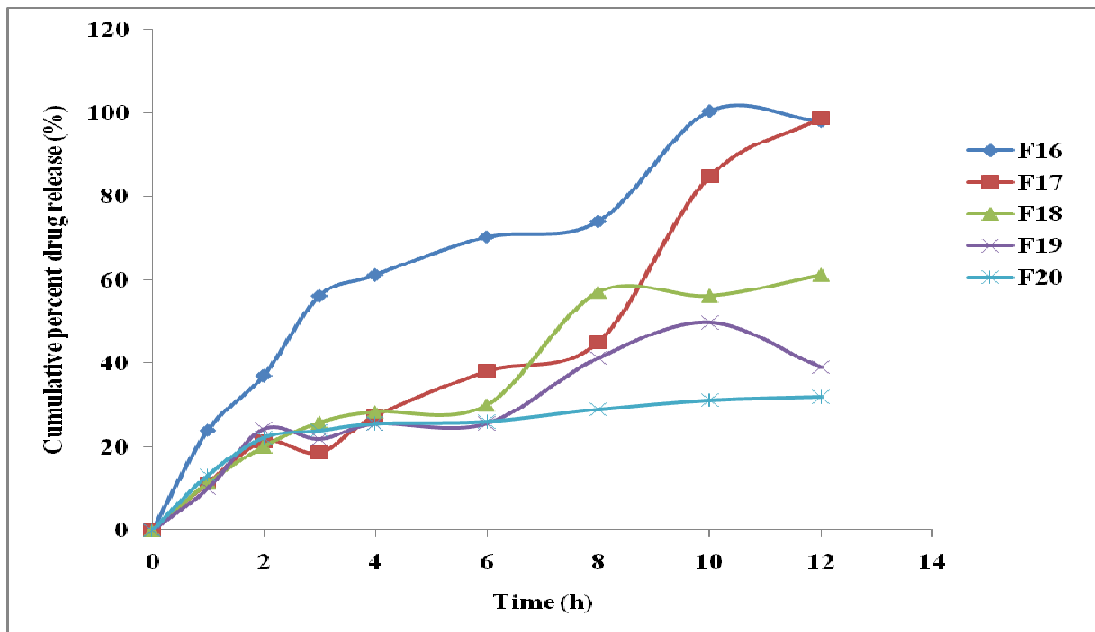


Fig.4. Dissolution plots of Ibuprofen pulsatile capsules (F16-F20)

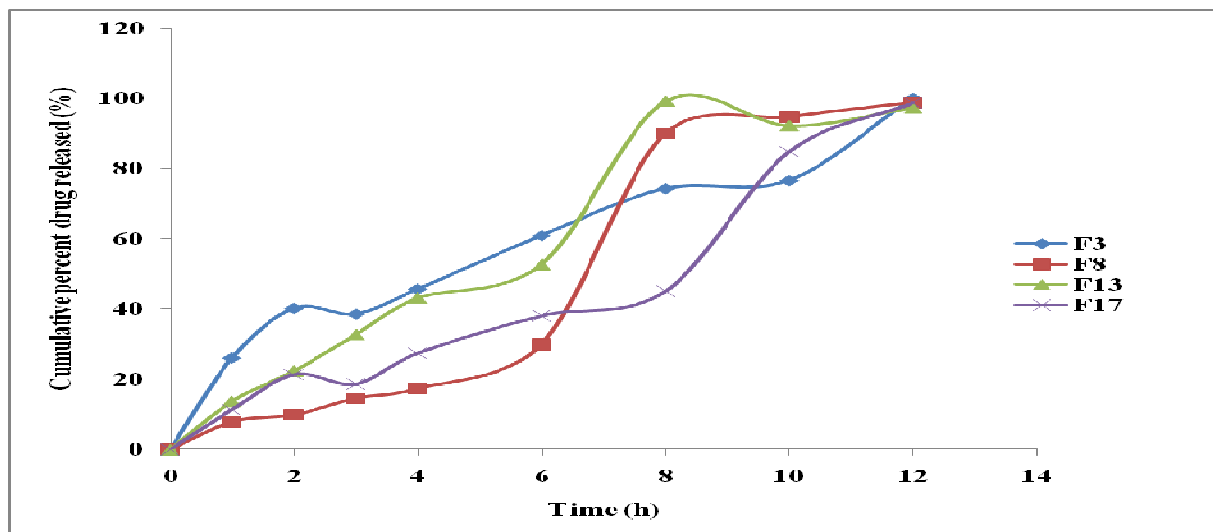


Fig.5. Dissolution plots for various Ibuprofen pulsatile capsules

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