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Research Article

FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF FLURBIPROFEN

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ABSTRACT

Aim of the present work was to formulate and evaluate an oral pulsatile drug delivery system to achieve time release of flurbiprofen, based on Chronopharmaceutical approach for the treatment of antiinflammatory agent. Pulsatile delivery system is capableof delivering drug when and where it required most. Time-delayed tablets, designed to release drug after a predictable lag time, are intended for oral chronotherapy. The basic design consists of a core tablets prepared by wet granulation method. The tablets were coated with an inners well able layer containing karaya gum and sodium alginate. The entire device was enteric coatedwith 3% cellulose acetate phthalate solution, so that the variability in gastric emptying time can be overcome. The prepared pulsatile tablets were evaluated for the drug content, thickness and *in-vitro* release profile, etc. *In-vitro* release profiles of pulsatile device during six hours studies were found to have very good sustaining efficacy. During the first five hours it shows minimum drug release and at the end of six hours immediate release was observed. Increasing the level of the rupturable layer increased mechanical strength and retarded the water uptake and thus prolonged the lag time. Stability studies proved that coating of tablets seems to decrease the effect of temperature and moisture on the degradation of flurbiprofen. The programmable pulsatile release has been achieved from tablet overa 7-8 hr period, consistent with the demands of chronotherapeutic drug delivery.

Keywords: Flurbiprofen, chronotherapeutic drug delivery, Pulsatile delivery system.

INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for obvious advantages of oral route of drug administration. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuation, reduction in dose of drug, reduced dosage frequency, avoidance of side effects and improved patient compliance. In such systems the drug release commences as soon as the dosage form is administered as in the case of conventional dosage forms. However, there are certain conditions, which demand release of drug after alagtime. Such are lease pattern known as “pulsatile release”[1].

Due to advances in chronobiology,chronopharmacologyandglobalmarketconstraints,thetraditionalgoal of pharmaceutics (eg. design drug delivery system with a constant release rate)is becoming obsolete. However, the major bottle neck in the development of drug delivery Systems that match circadian rhythms (chronopharmaceutical drug delivery systems: ChrDDS)may be the availability of appropriate technology. The diseases currently targeted for chronopharmaceutical formulation or those for which there are enough scientific backgrounds to justify ChrDDS compared to the conventional drug administration approach. These include asthma, arthritis, duodenal ulcer, cancer, diabetics, cardio vascular diseases, hyper cholesterolemia, ulcer and neurological disorder[2].

THEEMERGING ROLE OFBIORHYTHMSIN OPTIMIZING DRUG THERAPY [17]

Thepresenceofcircadian rhythms inhuman health and illness has been alluded to since the time of Hippocrates. However, it was not until the 1960'sthatalarge variety of physiologic functions and biologic rhythms were described. Biologic variation shave now been reported for several physiologic processes and play an important role in the manifestation of many illnesses. The past decade has witnessed rapid advances in the field of chronobiology, which are now being incorporated into clinical medicine, pharmacology and pharmacy practice. A number of chronotherapeutics medications, aiming at synchronizing medications and the intrinsic biorhythms of disease have been developed by novel drug delivery technology. In some cases, conventional medications are being administered according to circadian rhythms[17].

Important findings from the new science of chronobiology-the scientific study of biological rhythms-clearly revealed that biological functions and processes are not static over time. Rather, they are variable in a predictable manner as rhythms of defined period. Some ofthe rhythms that affect our bodies include,

Ultradian, which are cycles shorter than a day(for e.g. the milli second it takes for a neuron to fire or a90-minute sleep cycle).

Circadian, which lasts about 24 hrs (such as sleeping and walking patterns).

Infradian, referring to cycles longer than 24 hrs (fore.g. monthly menstruation).

Seasonal, such as Seasonal Effective Disorder (SAD),which causes depression in susceptible people during the short days of winter[17,18].

Severalphysiological processes in humans vary in rhythmic manner, in synchrony with the internal biological clock**.** It represents the overview of most serious diseases displaying significant daily variations. Many of circadian dependent diseases display acute symptoms in early morning at awakening. Through a number of clinical trials and epidemiological studies, it has become evident that the levels of diseases activity of a number of clinical disorders have a pattern associatedwiththebody'sinherentclocksetaccordingtocircadianrhythms.

MATERIALS AND METHODS

Flurbiprofen, Potato starch, Magnesium stearate was obtained from Spectrum Labs Private Limited. Super disintegrants like croscaramellose Sodium and Crospovidone are obtained from Colorcon.Sodium Alginate, Karaya gum from S.D. fine chemicals Mumbai. Lycoat was obtained as gift sample from Central drug House Pvt Ltd. NewDelhi.

Table 1: Different Formulations of Flurbiprofen (core) Granules.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Flurbiprofen	50	50	50	50	50	50	50	50
Starch	125	135	135	135	125	135	135	135
Lactose	-	-	-	-	-	-	-	-
Potato starch	20	-	-	-	20	-	-	-
Lycoat	-	10	-	-	-	10	-	-
Croscarmellose sodium	-	-	10	-	-	-	10	-
Crospovidone	-	-	-	10	-	-	-	10
Magnesium stearate	5	5	5	5	5	5	5	5

Preparation of Standard Calibration Curve of Flurbiprofen

100mg of Flurbiprofen was accurately weighed and transferred into 100ml volumetric flask. It was dissolved and diluted to volume with 0.1N Hcl to give stock solution containing 1000µg/ml.

The standard stock solution was then serially diluted with 0.1N Hcl to get 2 to 10µg/ml of Flurbiprofen. The absorbances of the solution were measured against 0.1N Hcl as blank at 248 nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

PREFORMULATION STUDIES

It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies.

1. Determination of Melting Point

Melting point of Flurbiprofen was determined by capillary method. Fine powder of Flurbiprofen was filled in glass capillary tube (previously sealed atoneend). The capillary tube was tied to thermometer and the thermometer was placed in the Thaistube andthis tube was placed on fire. The powder at what temperature it melted was noticed .

2. Solubility

Solubility of Flurbiprofen was determined in pH1.2, pH6.8 and pH7.0 phosphate buffers. Solubility studies were performed by taking excess amount of flurbiprofen in different beakers containing the solvents. The mixtures were shaken for 24hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no.41. The filtered solutions were analyzed spectrophotometrically at 248 nm.

3. Compatibility Studies

Compatibility with excipients was confirmed by FTIR studies. The pure drug and polymers were subjected to FTIR studies. In the present study, the potassium bromide disc (pellet) method was employed.

4. Identification of Flurbiprofen[41]

Accurately about 0.25gm of Flurbiprofen dissolved in 50ml of carbondioxide-free water and titrated with 0.1M sodium hydroxide using phenol red solution as indicator. Repeated the operation without the substance under examination. The difference between the titrations represented the amount of sodium hydroxide required.

Formulation of Compressed Tablets of Flurbiprofen

The methodology adopted include

1) Preparation of core tablets of Flurbiprofen.
2) Coating of the core tablets

RESULTS AND DISCUSSION

Table 2:Standard Calibration Curve of Flurbiprofen at 248nm

S. No	Concentration (µg/ml)	Absorbance(nm)	
		pH 1.2	Phosphate buffer pH 6.8
1	2	0.084	0.065
2	4	0.187	0.121
3	6	0.267	0.185
4	8	0.365	0.241
5	10	0.459+8	0.297

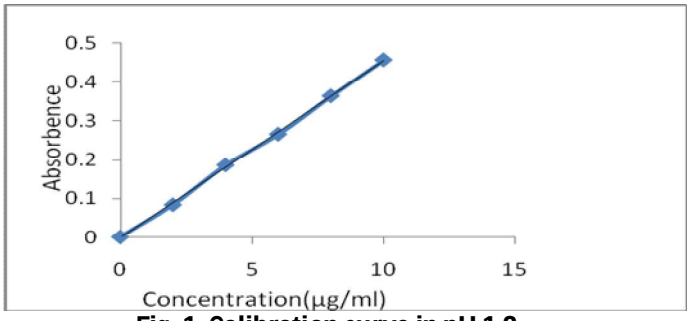

Fig. 1: Calibration curve in pH 1.2

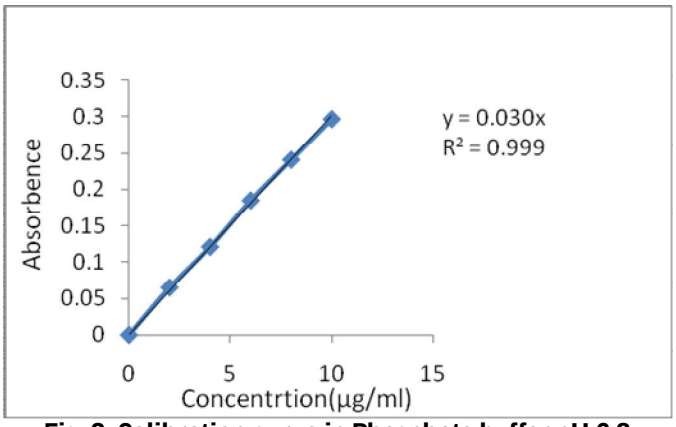

Fig. 2: Calibration curve in Phosphate buffer pH 6.8

Table 3:Data for Solubility Curve for Flurbiprofen

Sr.No.	Buffers	Solubility (mg/ml)
1	1.2	2.56
2	6.8	4.67

Table 4: Micromeretic properties of Granules of Flurbiprofen

Formula	Micromeretic properties of powder blend				
	Angleof Repose (θ) ±SD	BulkDensity (g/ml)±SD	Tapped Density (g/ml) ±SD	Carr's Index. (%)±SD	Hausner's ratio±SD
F1	26.54±0.36	0.375±0.018	0.420±0.019	10.90±0.15	1.11±0.021
F2	27.53±0.23	0.387±0.024	0.433±0.016	11.13±0.11	1.12±0.034
F3	25.31±0.22	0.365±0.032	0.421±0.026	13.10±0.25	1.13±0.033
F4	26.80±0.56	0.384±0.024	0.433±0.030	11.12±0.22	1.12±0.020
F5	25.43±0.27	0.376±0.017	0.434±0.026	13.43±0.16	1.14±0.014
F6	27.97±0.22	0.374±0.013	0.423±0.022	10.74±0.25	1.13±0.028
F7	29.43±0.22	0.367±0.012	0.423±0.018	13.16±0.13	1.15±0.032
F8	28.34±0.44	0.373±0.032	0.424±0.025	10.77±0.17	1.13±0.037

Table 5: Evaluation of Physical Parameters ofcompressed Tablets of Flurbiprofen

Formula	Weight variation (mean± SD,mg) (n = 20)	Hardness (mean± SD) (n = 3)	Friability (%) (n = 10)
F1	692.35±11.35	5.12±0.5	0.100
F2	693.25±9.68	5.23±0.18	0.572
F3	695.7±8.59	5.14±0.19	0.630
F4	692.9±8.36	5.19±0.18	0.060
F5	693.56±11.57	5.15±0.5	0.140
F6	696.9±7.23	5.20±0.19	0.153
F7	695.14±8.52	5.12±0.5	0.473
F8	694.9±10.42	5.16±0.19	0.130

Table 6: Thickness of core and coated Flurbiprofen Tablets

Formulation code	Thickness(mm)± SD	
	Core tablets	CotedTablets
F1	5.02±0.023	5.54±0.022
F2	5.12±0.024	5.71±0.015
F3	5.04±0.036	5.60±0.011
F4	5.13±0.005	5.61±0.024
F5	5.10±0.012	5.69±0.005
F6	5.01±0.018	5.59±0.015
F7	5.06±0.040	5.55±0.022
F8	5.14±0.005	5.71±0.016

Table 7: Content uniformity of different formula(F1 toF8)

Formulation code	pH 1.2	pH 6.8
F1	98.75±2.92	98.77±1.71
F2	98.16±2.10	98.06±2.75
F3	100.05±2.84	99.80±3.10
F4	100.31±2.41	100.20±2.16
F5	98.35±2.50	98.08±3.12
F6	99.39±1.14	99.09±1.33
F7	97.53±1.66	97.33±1.96
F8	100.68±2.50	100.43±2.15

Table 8: Disintegration time ofcoated Flurbiprofen tablets

Formulation code	Disintegrationtime Of coated(minutes)±SD	Disintegrationtime Ofcore(minutes)±SD
F1	225.5±4.91	9.46±13
F2	176.5±2.13	4.30±14
F3	196.5±3.51	5.35±13
F4	171.5±4.91	3.06±8
F5	173.5±2.13	3.25±8
F6	172.5±3.48	3.30±11
F7	187±2.78	5.05±12
F8	180.±2.81	3.47±11

Table 9:Cumulative percent drug release of core Flurbiprofen tablets of different formulations. (F1toF8)

TIME	Cumulative%drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
5	7.32	23.24	26.69	17.87	13.45	11.91	14.25	15.56
10	13.41	41.28	33.68	31.46	21.81	23.12	20.69	24.56
15	19.74	56.32	34.58	42.78	34.26	42.23	37.42	42.84
20	26.86	73.81	49.68	58.41	43.84	55.06	53.59	57.62
25	33.21	84.45	59.85	66.46	52.46	65.52	64.35	68.78
30	37.72	94.89	74.44	75.85	63.53	77.16	78.16	78.59
40	45.81	99.78	92.89	84.60	73.49	86.46	88.23	92.86
50	51.74	100.14	99.46	97.34	86.56	98.68	98.77	99.06
60	59.89	99.73	101.24	99.32	98.49	98.39	99.59	100.14
75	68.80	99.36	101.61	100.08	98.25	98.68	99.32	100.15
90	79.56	99.81	101.56	99.58	97.79	98.34	99.56	–
105	90.86	–	–	–	–	–	–	–
120	99.26	–	–	–	–	–	–	–

Table 10: Cumulative %drug release of coated different formulation (F1 toF8)

Time (Hrs.)	Cumulative%drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
IN pH1.2								
1	0.78	0.62	0.36	0.63	0.39	0.31	1.06	0.84
2	1.56	2.12	0.94	1.51	0.59	1.19	1.75	1.31
IN pH6.8								
3	7.25	8.27	7.45	16.68	6.34	8.85	7.42	9.52
4	17.56	16.09	14.32	21.48	15.94	16.32	18.56	19.57
5	24.89	32.07	25.86	42.24	31.51	31.24	33.51	34.85
6	36.32	71.73	78.59	79.45	67.86	82.09	74.51	84.01
7	48.25	84.12	86.42	99.42	87.21	95.35	97.72	99.21
8	64.89	96.42	99.46	–	99.00	100.64	–	–
9	76.18	–	–	–	–	–	–	–
10	87.78	–	–	–	–	–	–	–
11	98.74	–	–	–	–	–	–	–

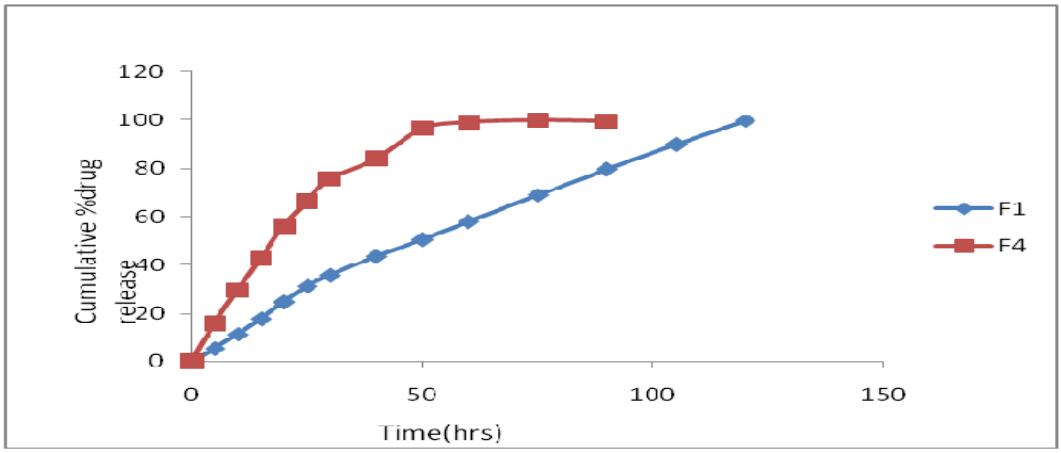

Fig. 3: Cumulative percentage drug release of coated formulation F1 &F4

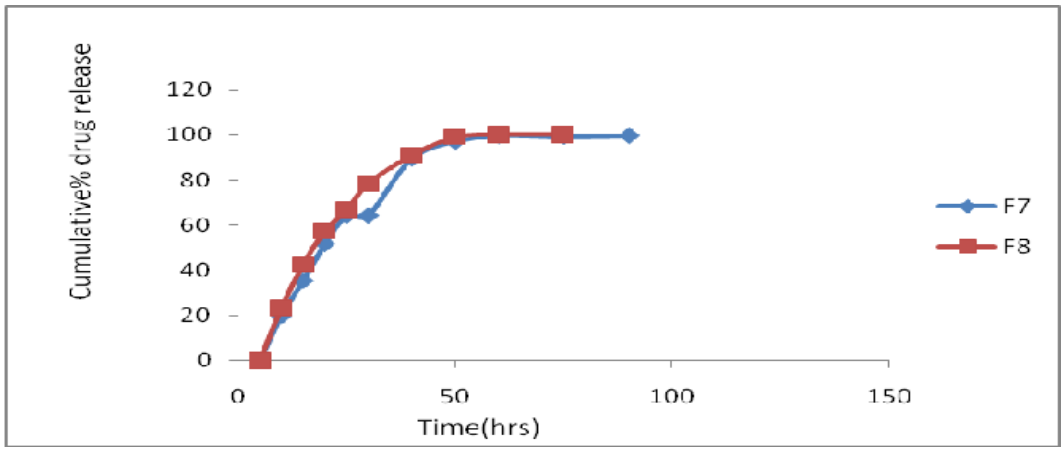

Fig. 4: Cumulative percentage drug release of coated formulation F7 &F8

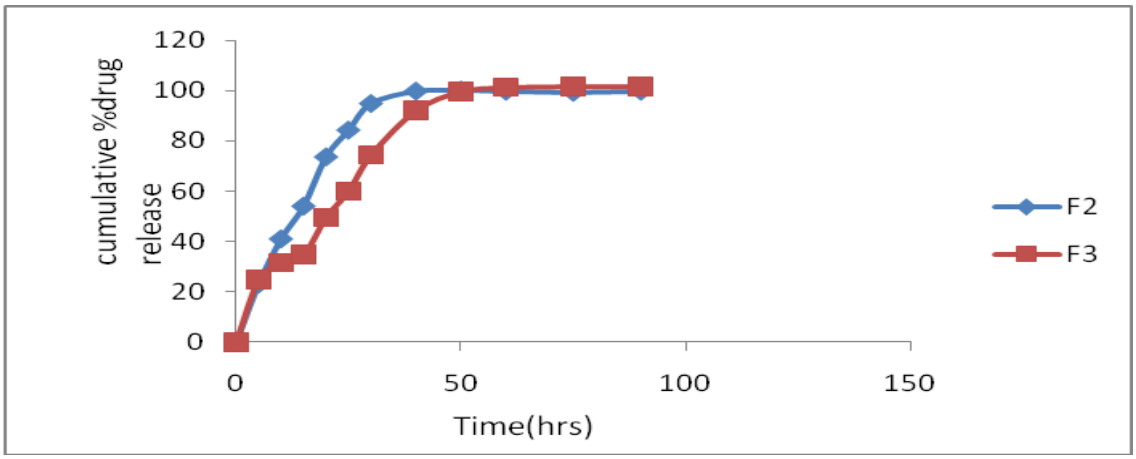

Fig. 5: Cumulative percentage dug release of coated formulation F2 &F3

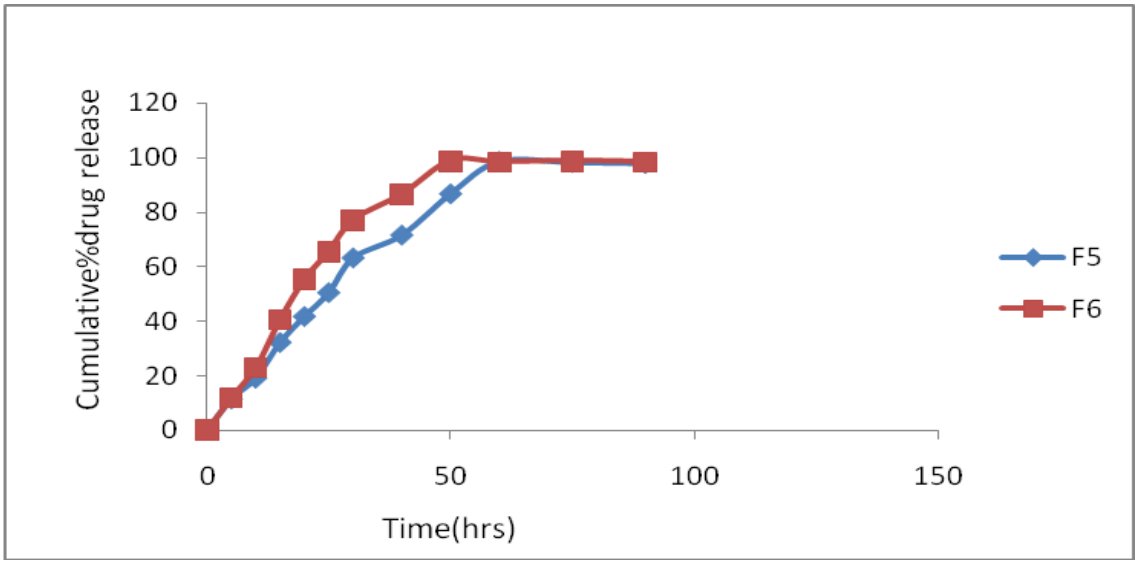

Fig. 6: Cumulative percentage drug release of coated formulationF5 &F6

Table 11: Effect of Outer Polymer Concentration on %Water Uptake

TIME (hrs)	F-3			F-6			F-8		
	4%	6%	8%	4%	6%	8%	4%	6%	8%
1	6.9	5.43	4.77	6.66	5.57	4.52	6.84	5.34	4.61
2	14.34	8.29	6.21	14.57	8.41	7.41	14.46	8.37	6.30
3	18.72	9.48	7.34	18.44	10.55	7.54	18.50	10.44	7.46
4	-	14.74	10.10	-	14.88	9.32	-	14.82	10.23
5	-	16.59	14.50	-	16.70	14.38	-	16.64	14.25
6	-	18.31	16.81	-	18.50	16.97	-	18.62	16.90
7	-	-	18.61	-	-	18.13	-	-	18.91

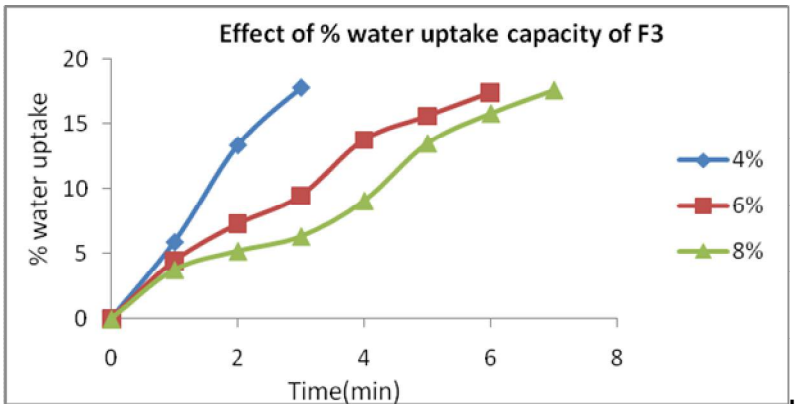

Fig. 7: Effect of% Water Uptake capacity of F3

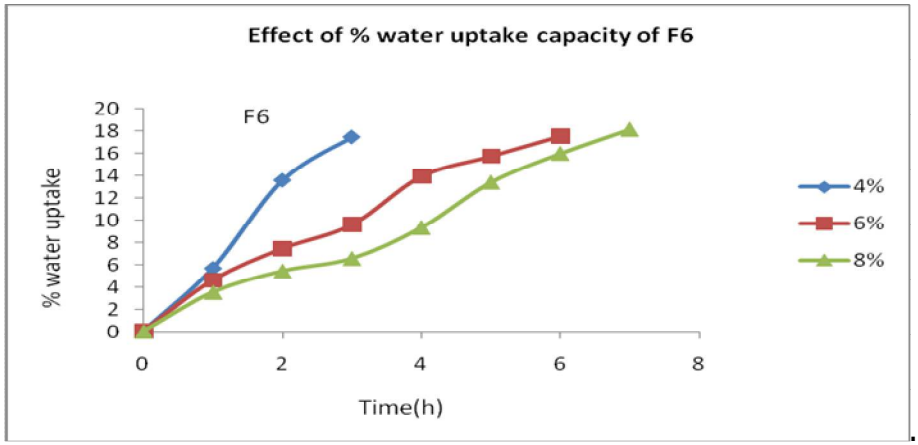

Fig. 8: Effect of% Water Uptake capacity of F6

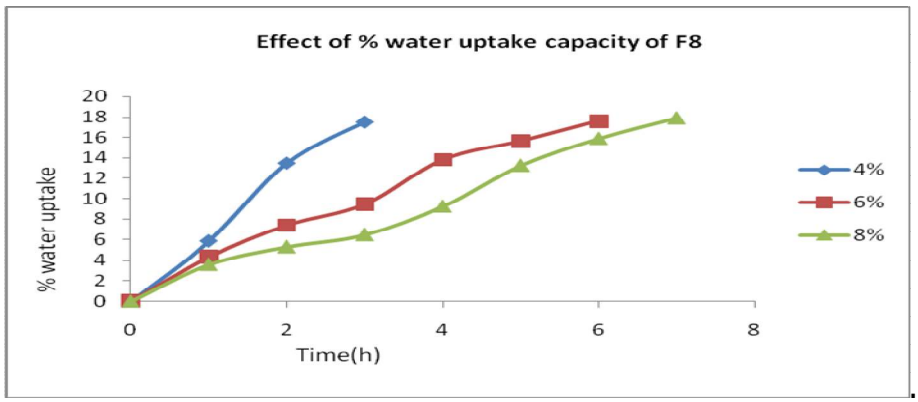

Fig. 9: Effect of % Water Uptake capacity of F8

Table 12:*in-vitro* drug release mechanism of different coated formula (F1toF8)

Batch	Zero Order	First Order	Higuchi release	Peppas release		Best fit release mechanism
Code	r^2	r^2	r^2	r^2	N	
F1	0.978	0.862	0.955	0.974	2.183	Zero order
F2	0.934	0.807	0.877	0.972	2.697	Peppas release
F3	0.903	0.723	0.844	0.960	2.875	Peppas release
F4	0.928	0.735	0.898	0.955	2.661	Peppas release
F5	0.923	0.742	0.870	0.944	2.921	Peppas release
F6	0.903	0.812	0.850	0.970	2.866	Peppas release
F7	0.898	0.715	1	0.950	2.511	Higuchi release
F8	0.901	0.770	0.813	0.952	2.638	Peppas release

Rupture Test

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

Table 13: RuptureTime

Formulation No.	F1	F2	F3	F4	F5	F6	F7	F8
Rupturetime (hrs)	9:11	4:36	5:46	4:43	5:06	5:44	4:57	5:56

Stability Studies

Stability Studies were carried out at 40^{O}c temp and 75% RH for 30days. The core tablet and coated tablet of selected formulation were packed in amber-colored bottles tightly plugged with cotton and capped. And %drug content was checked at regular time intervals.

Table 14: Stability Studies

Time in Days	%Drug Content in CoreTablets	%Drug Content in CoatedTablets
0	99.86	99.95
10	97.32	99.80
20	94.70	99.49
30	92.77	99.12

DISCUSSION

Pulsatile drug delivery system is a useful approach for the drugs for local as well as systemic action. This is used with prevent and control neuropathic pain. Can be treated by Pulsatile drug delivery system which promises the predetermined Lag-time followed by the immediate release of drug.

In the present study, an attempt was made to develop and evaluate pulsatile drug delivery system containing Flurbiprofen as active ingredient for better treatment of Antipyretic and analgesic. Pulsatile drug delivery of Flurbiprofen could prevent unwanted systemic side effects and subsequently a lower dose of the drug may be sufficient to prevent the pain.

PREFORMULATION STUDIES

Melting Point Determination

Melting point of Flurbiprofen was determined by capillary method. The melting point of Flurbiprofen was found to be in the range114-117°C,whichcomplied with BP standards thus indicating purity of the drug sample.

Solubility

Soluble in water (10 mg/mL), and methanol. Sparingly soluble in ethanol, DMSO, and DMF and soluble in 0.1N NaOH.

Calibration curve

In preformulation studies, it was found that, the estimation of Flurbiprofen by spectrophotometric method at 245n min pH1.2 and pH 6.8 buffers had good reproducibility, at the concentration between 2-10 µg/ml. Correlation between concentration coefficient was found 0.999 for both pH1.2 and pH6.8 and

slope for pH 1.2 and pH 6.8 was found0.045 and 0.029 respectively.

Drug-Excipient compatibility study
From the I.R. Spectrum no.1, 2and3 it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers.
The peaks obtained in the spectra of drug and polymers mixtures correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

Carr's Index
Carr'sindex was carried out and the results were shown in Table-16. It was found to be between 10.90±0.15% and 13.43±0.16% indicating the granules have the required flow property for compression.

Angle of Repose (θ)
The angle of repose for the formulated blend was carried out and the results were shown in Table-16. It can be concluded that all the formulation blends angle of repose was found to be in the range26.54±0.36 to29.43±0.22. Hence the entire formulation blends was found to possess good flow property.

EVALUATION OFCORE TABLETS
Weight Variation Test
The percentage weight variations for all formulations were tabulated in Table-17. All the formulated (F1 to F8) tablets passed weight variation test as the %weight variation was within the pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values.

Hardness test
The measured hardness of tablets of all the formulations ranged between 5.12±0.5to5.23±0.18kg/cm^2 (Table-17). This ensures good handling characteristics of all batches.

Disintegration test for core tablets
The values of Disintegration test were tabulated in Table-20. It was found between 3 min 6seconds to 9min 46seconds ensuring that all the cores of different formulations were rapid disintegrating type.

Friability Test
The values of friability test were tabulated in Table-17. The % friability was less than 0.6% in all the formulations ensuring that the tablets were mechanically stable.

Drug Content Uniformity
The percentage of drug content for F1 to F8 was found to be between 99.09±1.33% and 100.43± 2.15 %. It complies with official specifications. The results were shown in Table-19.

I*n-vitro* Dissolution of Core Tablet
All the eight formulations of prepared core tablets of Flurbiprofen were subjected to *in vitro* release studies. The values of Dissolution test were tabulatedinTable-21.It was found to be between97.79% and101.56%. All the formulations gave maximum release within 90 minutes.

EVALUATION OFCOATED TABLETS
Shape of the tablet
Microscopic examitions Flurbiprofen of tablets from F1 to F8 were found to be oval in shape with smooth shining surface and free from cracks.

Disintegration test for coated tablets of Flurbiprofen
The values of Disintegration test for coated tablets were tabulated inTable-20. It was found to be between 171.5±4.91to 225.5±4.91 minutes. It ensures that all the formulations remained intact for 2hours in pH1.2 buffer and later in 6.8 pH buffer. Formulations F2 to F8 disintegrated within 196.5 ± 3.51 minutes and F1disintegrated in 225.5±4.91 minutes, because F1 does not contain any effervescent agent oranosmogen.

Hardness test

The measured hardness of coated tablets of each formulation ranged between 5.12±0.5to 5.23 ± 0.18kg/cm^2. This ensures good handling characteristics of all formulations.

Thickness of Coated Tablets

Thickness of the coated formulation was measured with Digital verniar caliper. The measured thickness of coated tablets of each formulation ranged between 5.54±0.022 mm to 5.71±0.016mm (Table18). This ensures uniform coating to all batches.

***In-vitro* Dissolution of Coated Tablet**

All the eight formulations of prepared coated tablets of Flurbiprofen were subjected to *in-vitro* release studies. These studies were carried out using USP dissolution apparatus type-II, and pH 1.2 buffer and pH 6.8 phosphate buffer as dissolution media. (Table-22)

In-vitro release profiles of pulsatile device during 8hrs studies were found to have very good sustaining efficacy. During dissolution studies, it was observed that, the enteric coat of the cellulose acetate phthalate was intact for 2hours inv pH1.2buffer, but dissolved in intestine pH, leaving the insoluble coat of EC:HPMC(9:1) ,in which HPMC swells and form pores. Through these pores water penetrates inside the membrane and came in contact with 3%HPMC coated ayer and HPMC layer swells.

Then water penetrated inside the core tablet which contained sodium bicarbonate Flurbiprofenin their core which generated carbondioxide, which resulted in building up of pressure inside the core and helped in early rupturing of the outer polymeric layer. The presence of an osmotic agent helped in drawing water towards the tablet which resulted in rupturing of outer coating layer in pH6.8buffers.

With all the formulations, there was no drug release in pH 1.2, thus indicating the efficiency of 3%CAP for enteric coating. In case of formulation F1, at the end of 6th hour the cumulative drug release was found to be 36.32%, because it does not contain Sodium bicarbonate and Sodium chloride. Therefore enough pressure was not created inside to rupture the tablet. It contains chitosan which is rate controlling polymer. So F1is having lowest cumulative percentage drug release.

In case of formulation F2 & F3, Formulation F2 contains 2.5% Sodium bicarbonate and 2.5% Sodium chloride and formulation F3 contains 3.5% Sodium bicarbonate Flurbiprofen and 3.5% Sodium chloride. At the end of 6th hour the cumulative drug release was found to be 70.73% and 79.95%. So as the content of sodium bicarbonate Flurbiprofen and sodium chloride increase, drug release is going to be increase which might be due to increase in pressure inside coated layer. Formulation F4, F6 and F8 contain 5% sodium bicarbonate Flurbiprofen, 5% tartaric acid and 5% citric acid respectively. Formulation F6 and F8 also contain 2.5% sodium bicarbonate. Here in F4,F6 and F8 cumulative drug release was found to be79.45%, 82.09% and 84.01 % respectively after 6thhour.

So as the content of tartaric acid and citric acid increased with sodium bicarbonate pressure inside the coated layer increased which rupture the layer which leads to increase the cumulative percent drugr elease. Tartaric acid is retarding drug release as compared to citricacid.

Formulation F5 and F7 commonly contain 2.5% sodium bicarbonate and 2.5% tartaric acid and 2.5% citric acid respectively, and formulation F4 contain 5% sodium bicarbonate, Here in F4, F5, and F7 cumulative drug release was found to be 79.45%, 67.86% and 74.51% respectively after 6thhour. So it can be concluded that tartaric acid is most pressure controlling gas producing excipient while citric acid and sodium bicarbonate are followed by tartaric acid.

Effect of outer polymer concentration and water uptake performance

Formulations F3, F6 and F8 were coated with different outer polymeric coating (4%, 6% and8%). Tablet coated with 4% EC: HPMC (9:1) showed 18.72% water uptake after 3hour. Tablet coated with 6% EC: HPMC (9:1) showed 18.31% water uptake after 6 hour. Tablet coated with 8% EC: HPMC (9:1) showed 18.61% water uptake after 7hours. So increasing outer coating decreased % water uptake capacity and increased Lag-time.

SUMMARY AND CONCLUSION

The usual dose of Flurbiprofen is maintenance dose: 300mg orally once a day as anti epileptic agent. So Flurbiprofen was chosen as a model drug with an aim to develop a pulsatile drug delivery system for treatment of Anti epilepsy. In this research work preparation of pulsatile drug delivery system was prepared by wet granulation method using polymers Chitosan, PVPK30, CAP, EC and HPMC50CPSwereselectedinthe system. Sodium bicarbonate, sodium chloride, citric acid and tartaric acid were used as gas producing agent in system.

Prepared pulsatile drug delivery system were evaluated for hardness, friability, weight variation, drug

content uniformity, drug-polymer interaction, invitro drug release and short-term stability studies.
Further core tablets were coated with different levels of Ethylcellulose /HPMC (9:1)i.e. 4%,6%and8%w/w coating (inner swelling layer remained the same). The % water uptake capacity of tablets was determined.
Among the various formulations prepared, formulation F3, F6 andF8 were selected as optimized formulations.

REFERENCES

1. SharagilL and Pony S. appliedBio-pharmaceutics and Pharmacokinetics. 5th ed.Singapur;2005:p.481-2.
2. Robert W and Thomas P. Drug therapy for hypercholestemia and Dyslipidemia. In: Goodmen and Gilmans. The pharmacological basis of therapeutics.10th ed.2003: McGraw-hill. Medical publishing division p. 971-972.
3. Filippatos TD, Derdemezis CS and Elisaf MS. Department of Internal Medicine, School of Medicine, University of Loannina Greece. Available from:articles\Dietfor hyperlipidemia.mht.
4. Scott MG. Atherogenicdyslipidemiaassociatedwithmetabolicsyndromeand Insulin resistance. 8:1.
5. Bi-Botti CY.Chronopharmaceutics:Gimmickorclinicallyrelevantapproachtodrug delivery-A Review. J Control Rel. 2004;98(3):337-353
6. Jain NK. Controlled and novel drug delivery. 1st Ed. New Delhi: CBS Publishers;2002.
7. Bussemer T, Ottol and Bodmeier R. Pulsatile drug delivery systems. Crit Rev Ther Drug Carrier Syst. 2001;18(5):433-58.
8. Gothaskar AV, Joshi AM and Joshi NH. Pulsatile drug delivery system-A review. Drug Del Tech.2004 June;4(5).
9. Anal AK. Time-Controlled Pulsatile Delivery Systems for Bioactive Compounds. Recent Patentson Drug Delivery & Formulation. 2006;1:73-79.
10. Bjorn Lemmer. The clinical relevance of chronopharmacologyin therapeutics. Pharmacological Research.1996;33(2):107-115.
11. Sarasija S and Stutie P. Chronotherapeutics: Emerging roleofbiorhythmsin optimizing drug therapy. Indian J Phrm Sci. 2005;67(2):135-140.
12. Peep Veski. ChronopharmaceuticalDrug Delivery. Institute of pharmacy. UniversityofTartu, Estonia.
13. LiboYang, James SC and Joseph AF.Colonspecificdrugdelivery:newapproachesand in vitro/in vivo evaluation-Review. IJPharm. 2002;253:1-15.
14. Shivakumar HG, Pramod KTM and Kashappa GD. Pulsatiledrugdeliverysystems. Indian J Pharm Educ. 2003July-Sept;37(3):125-128.
15. Sangita V. Timing is everything. (Cited 17 november2009)http://www.pharmaquality.com/Feature.7ahtm.