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Compression coated tablets of Flurbiprofen: A chronotherapeutic approach

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Abstract

Aim of the present work was to formulate and evaluate an oral; time controlled drug delivery system of Flurbiprofen, based on chronotherapeutic approach for the treatment of Rheumatoid arthritis (RA). In this study, Compression coated time release tablets of Flurbiprofen were prepared by compression coating the core tablet with different polymers like HPMC K4M, HPMC K15M and HPC in various proportions. Different ratios of polymers were selected to achieve suitable lag time for the treatment of RA. The basic idea behind the dosage form development is to investigate effect of coating design on lag time and drug release from directly compressed time-controlled release tablet. The DSC and FTIR studies indicated that the drug is intact in the formulations and no possibility of interaction between the Flurbiprofen and other formulation excipients was observed. The compression coated tablets were evaluated for their hardness, thickness, friability, weight variation, drug content uniformity and core erosion ratio. The results obtained complied with the official standards. The *in-vitro* drug release profile of the formulations was performed in simulated gastric and intestinal pH conditions up to 8 h. The desired lag time of 6 h was obtained for selected formulations and burst release was obtained after the lag time, which was consistent with the demands of chronotherapeutic drug delivery. The compression coated tablets showed no change either in physical appearance, drug content or dissolution pattern after storage at 40°C/75% RH for 6 months. Thus, Compression coated tablets with a clear lag time before drug release is a potentially useful formulation for the treatment of RA which follows circadian rhythm.

Keywords: Chronotherapeutic approach, Circadian rhythm, Flurbiprofen, Compression coating, Time-controlled, Rheumatoid arthritis.

Introduction

Chronotherapeutic refers to a treatment method in which the in-vivo drug availability is timed to match the circadian rhythms of a disease in order to achieve desired therapeutic outcomes and minimize side effects.[1] The major objective of chronotherapy in the treatment of several diseases is to deliver the drug to the targeted sites in the body in higher concentrations when they are most needed. The chronotherapy of a medication may be achieved by the judicious timing of conventionally formulated tablets and capsules. However, in most cases, special drug delivery technology must be designed to harmonize drug concentrations with rhythms in disease activity.[2]

Some of the diseases with established circadian rhythms that can be successfully treated by chronotherapy include Arthritis, Hypertension, Cardiovascular diseases,

Bronchial asthma, Allergic rhinitis, Peptic ulcers, Sleep disorders, Cancer, Diabetes and Hypercholesterolemia.[3]

The approaches for chronotherapeutic drug delivery include Pulsatile delivery systems, Floating drug delivery systems, Membrane diffusion controlled systems, Osmotic system, Diffucaps /surecaps technology and Compression coated systems.

Advantages of such drug delivery systems include controlled onset and extended release of the drug. The delivery profile of the drug is designed to complement the circadian pattern of the disease and the rate of the drug release is independent of pH, posture and food.

Compression coating is the absolute dry coating without solvent and heat use. The compression coated tablet dosage form (i.e., the tablet-in-tablet design) is a time and rate-controlled drug delivery device, which consists of a core tablet and an outer layer that is considerably thicker than typical tablet coats and which completely, surrounds the core (inner) tablet. This method has no limitation for the cores and overcomes the adhesion problem found in spraying methods. Compression coating provides thick coatings within a short processing time.[4]

Compression-coating method can be been used to protect hygroscopic, light-sensitive, oxygen-labile or acid-labile drugs, to combine and separate different drugs and to modify a drug release pattern.

Rheumatoid arthritis is a form of chronic arthritis which chiefly affects young adults, mainly women. It also occurs in children (Still's Disease). It generally affects the joints and their synovial membranes, cartilages, capsules and the muscles supplying them.[5-7] The symptoms include joints pain, inflammation and stiffness and the joint is tender when touched. The fingers, arms, legs and wrists are mostly affected and symptoms are usually worst in the morning. The morning stiffness can last for 30 min. Hands may be red and puffy. Patients with rheumatoid arthritis have pain that usually peaks in the morning and decreases throughout day.[8] Chronotherapy for all forms of arthritis using NSAIDs should be timed to ensure that the highest blood levels of the drug coincide with peak pain. An NSAID such as Flurbiprofen would be effective for people with rheumatoid arthritis when taken after the evening meal.

In the present study an attempt was made to develop chronotherapeutic drug delivery system of Flurbiprofen using various polymers with a predetermined lag time of 6 h by compression coating technique. The compression coated tablets could be used to provide maximum drug plasma concentrations 6 to 8 hours after a night dose is taken at approximately 22:00. Flurbiprofen is chosen as the model drug as its physico-chemical properties and short half-life make it a suitable candidate for chronotherapeutic drug delivery system.

Materials and Methods

Materials

Flurbiprofen, Croscarmellose Sodium, HPMC K4M, HPMC K15M, Hydroxypropyl Cellulose, Povidone and Microcrystalline Cellulose were obtained from Yarrow Chemicals, Mumbai. All other reagents used were of analytical reagent grade.

Methods

FTIR studies

The IR spectra of pure Flurbiprofen, HPMC K4M, HPMC K15M and HPC along with physical mixture of polymers and drug were taken separately to check drug- polymer interaction by KBr disc method. A small amount of drug was mixed with the spectroscopic grade of KBr and triturated for uniform mixing. The prepared mixture was placed in the sample cell and was exposed to the IR beam and spectra were recorded in the range of 400-4000cm^{-1} by using FTIR spectrophotometer (FTIR 8400 Shimadzu, Japan).

DSC studies

DSC studies were carried out to investigate and predict any physiochemical interactions between the drug and the excipients. DSC was performed utilising Shimadzu, DSC-60 (Shimadzu, Japan).

2mg of sample was placed in a 50 µL perforated aluminium pan and sealed. Samples were allowed to equilibrate for 1 min and then heated in an atmosphere of nitrogen over a temperature range from 5ºC to 300ºC. Nitrogen was used as a purge gas, at the flow rate of 20 ml/min for all the studies.

Preparation of Flurbiprofen core tablets

The tablets formulations were prepared by wet granulation technique. The ingredients Flurbiprofen, croscarmellose sodium, PVP K-30 and lactose (previously passed through

sieve no. 85) were added, mixed and granulated using IPA solution as granulating agent. The wet mass was passed through sieve no. 12 and the granules obtained were dried at 45ºC for 30 min.

The dried granules were subjected to dry screening by passing through sieve no. 16 and then the granules were blended with the mixture of talc and magnesium stearate. The granules were compressed into tablets using 6 mm round, concave shaped punch in a rotary tablet press (Rimek RSB-4 minipress, Cadmach). The composition of core tablets is shown in Table1.

Preparation of compression coated tablets of Flurbiprofen

Three different coating materials HPMC K4M (30%, 60% and 90%), HPMC K15M (30%, 60% and 90%) and HPC (30%, 60% and 90%) were selected for the compression coating of the core tablet. Preliminary studies were carried out in the lab to observe the minimum quantity of coating material required to completely coat the core tablet. Trials starting from 250 mg of coating material were taken and it was practically observed that an optimum quantity of 275 mg was required to coat the 6 mm core tablet equally on all sides. Since the coating material alone gave very soft coats, microcrystalline cellulose was included in the coat formulations to impart enough hardness.

Half the quantity of the coating polymers was placed in the die cavity to form a powder bed; the core was carefully positioned in the centre of the polymer bed. Then, the remaining half of the coating polymers was filled into the die and the contents were compressed using 8 mm round, concave shaped punch in a rotary tablet press (Rimek RSB-4 minipress, Cadmach). The coating compositions for all the batches of the tablets are reported in Table 2.

Table 1: Composition of Flurbiprofen core tablets

Sl.No	Ingredients	Quantity (mg)
1	Flurbiprofen	100
2	Croscarmellose Sodium (3%)	3.75
3	PVP K-30 (3%)	3.75
4	Magnesium stearate (2%)	2.5
5	Talc (2%)	2.5
6	Lactose (q.s)	12.5
Total weight		**125**

Table 2: Composition of compression coated tablets

S. No.	Ingredients	Formulation code (Quantity in mg)								
		F1	***F2***	***F3***	***F4***	***F5***	***F6***	***F7***	***F8***	***F9***
1	**Core tablet**	**125**	**125**	**125**	**125**	**125**	**125**	**125**	**125**	**125**
2	HPMC K4M	82.5	165	247.5	-	-	-	-	-	-
3	HPMC K15M	-	-	-	82.5	165	247.5	-	-	-
4	HPC	-	-	-	-	-	-	82.5	165	247.5
5	Microcrystalline Cellulose	192.5	110	27.5	192.5	110	27.5	192.5	110	27.5
Total Weight		**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**

Pre compression Studies

The prepared granular blend was evaluated for various parameters like bulk density, tapped density, angle of repose, compressibility index and Hausner ratio.

Post compression studies

The prepared core and compression coated tablets were evaluated for weight variation test, hardness, friability, thickness and core erosion test, whereas disintegration time and drug content were evaluated only for the core tablet.

Weight variation test:

Randomly selected 20 tablets of each formulation batch were weighed using an electronic digital balance and the test was performed according to the Indian Pharmacopeia.

Hardness test:

The tablet crushing strength, which is the force required to break the tablet by compression in the diametric direction was measured in triplicate using Monsanto tablet hardness tester. The tablet crushing strength was tested by using Monsanto tablet hardness tester. A tablet was placed between the anvils and the crushing strength which causes the tablet to break was recorded. Three tablets from each formulation batch were tested randomly and the average readings were expressed as mean values of triplicates.

Friability:

Randomly selected dedusted tablets of weight equivalent to 6.5g were placed in a Roche friability test apparatus and rotated 100 times at 25 ± 1 rpm. Then the tablets were removed, dedusted and re-weighed. The % friability were calculated by the given formula-

$$\% \text{ Friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

Thickness:

Three tablets were selected randomly from each batch and the thickness of the tablets was measured using Vernier caliper.

Drug content determination:

Ten core tablets were weighed, triturated and powdered. Powder triturated equivalent to average weight of tablet was weighed and transferred to a 100 ml volumetric flask. Initially about 50 ml of methanol was added and the flask was shaken thoroughly and the volume was made up to 100 ml with the methanol. The resulting solution was diluted suitably and the drug content was estimated spectrophotometically (Shimadzu, Japan, UV-v1701) at 248 nm using UV spectrophotometer against 7.4 pH phosphate buffer as blank. The drug content was calculated using calibration curve.

Core erosion test:

Compression coated tablets were separately immersed in the Petri plate containing 7.4 pH Phosphate buffer at 37ºC for 3 h.[9] After the tablets were removed from the medium, the gelated portion of the outer layer and the dissolved or gelated portion of each core tablets were carefully removed to obtain the non-eroded residual core. The dry mass of each non-eroded residual core (Wcore) was measured after drying for 20 h at 40ºC. The initial mass of each core tablet (Wini) and the mass of each non-eroded residual core were used to calculate the core erosion ratio as follows-

$$\text{Core erosion ratio (\%)} = \left[1 - \left(\frac{\text{Wcore}}{\text{Wini}}\right)\right] \times 100$$

***In-vitro* drug release studies:**

Drug release studies were carried out using USP XXIII dissolution test apparatus, rotating paddle method (Lab India, Mumbai, India). The study was conducted at 37±0.5ºC and 50 rpm using 900 ml of 1.2 pH buffers for 2 hr followed by 7.4 pH buffers until completion of the studies. Aliquots of sample (2 ml) were withdrawn at regular pre-determined time intervals, diluted suitably and the drug content was measured spectrophotometically at 248 nm, using 7.4 pH phosphate buffers as blank.

Drug release kinetics:

In-vitro drug release mechanism was determined by using PCP DISSO V2 software. Depending upon R and k values obtained from different models, the best-fit model was selected.[10, 11]

Stability studies:

The accelerated stability studies were carried out for the selected formulations. The tablet formulations were packed in aluminum foil and were placed in the stability test chamber and subjected to stability studies at accelerated testing conditions (40 ± 2°C/ 75 ± 5 % RH) for 6 months. At specified intervals of time, the samples were withdrawn and evaluated for their appearance, hardness, friability, drug content and *in-vitro* drug release.

Result and Discussion

FTIR studies

FT-IR was performed for the pure Flurbiprofen, HPMC K4M, HPMC K15M, HPC, physical mixture of pure drug + HPMC K4M, physical mixture of pure drug + HPMC K15M and physical mixture of pure drug + HPC to detect any sign of interaction which would be reflected by a change in the position or disappearance of any characteristic peaks of the compound. The IR spectra are shown in the Figure 1.

From the infrared spectral analysis, it was clear that the characteristic absorption peaks of Flurbiprofen were found in physical mixture of drug and polymers, so it indicates that there was no interaction between drug and polymers.

DSC studies

The DSC thermograms of the drug and polymers tested are shown in Figures 2-4. The thermograms of Flurbiprofen showed a sharp endothermic peak at 115.77ºC corresponding to the melting point of the drug in the crystalline form, indicating relative purity.

A similar endothermic peak was observed at 115.14ºC as in the case of physical mixture of Flurbiprofen with HPMC K15M and a sharp endothermic peak at 114.23ºC as in the case of physical mixture of Flurbiprofen with HPC. These studies further confirm that the drug has not undergone any type of interaction with the polymers HPMC K15M and HPC, thereby indicating the stability of drug and polymers.

The core tablets of Flurbiprofen were prepared by wet granulation technique using Croscarmellose Sodium as super disintegrant, PVP K-30 as binding agent, Lactose as diluent with talc and magnesium stearate as glidant and lubricant. The Flurbiprofen core tablets were compression coated using HPMC K4M, HPMC K15M and HPC as coating materials in different ratios. Microcrystalline cellulose was added to impart enough hardness to the coat formulations.

The cross section of a compression coated tablet is shown in Figure 5. The cores were coloured to clarify the boundary with the outer layer.

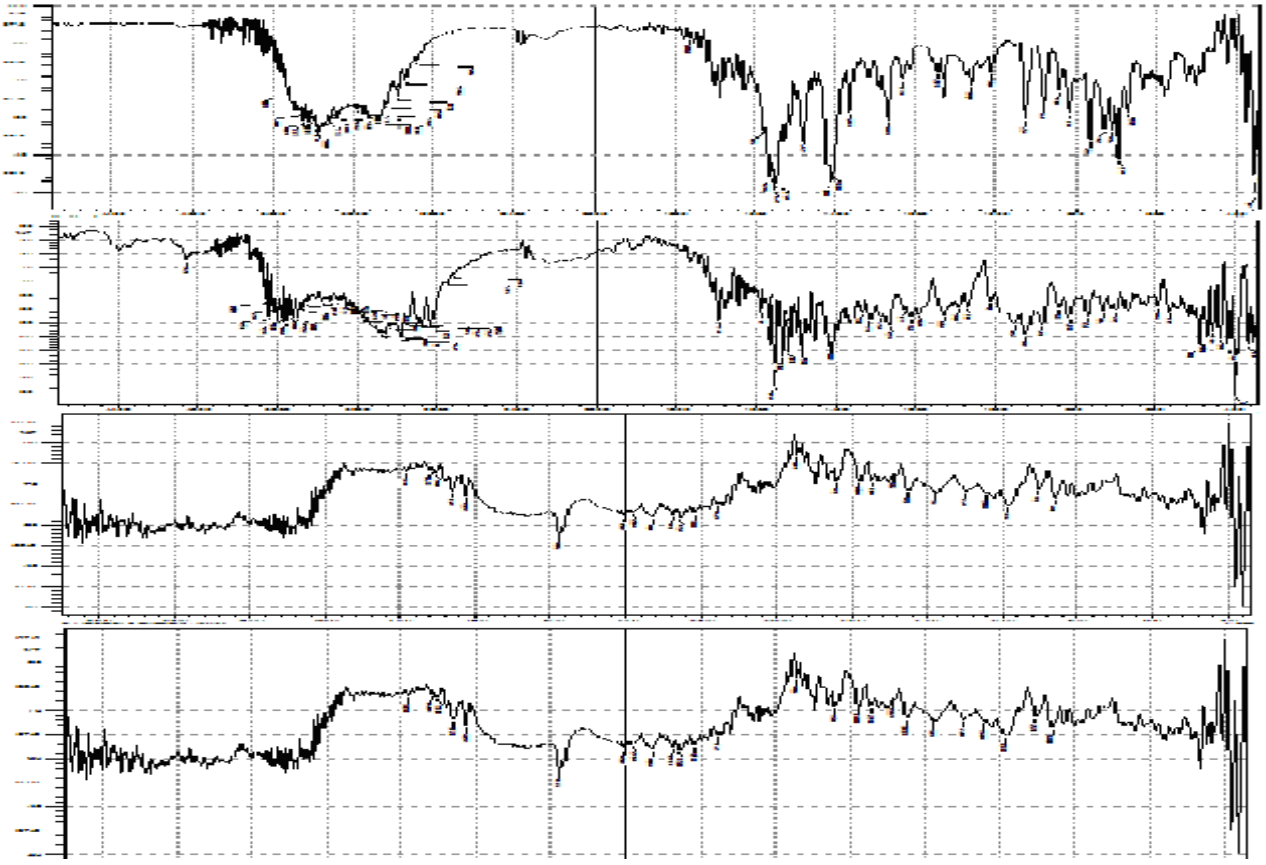

Figure 1: IR spectrum of (a) Flurbiprofen; (b) Flurbiprofen + HPMC K4M; (c) Flurbiprofen + HPMC K15M; (d) Flurbiprofen + HPC

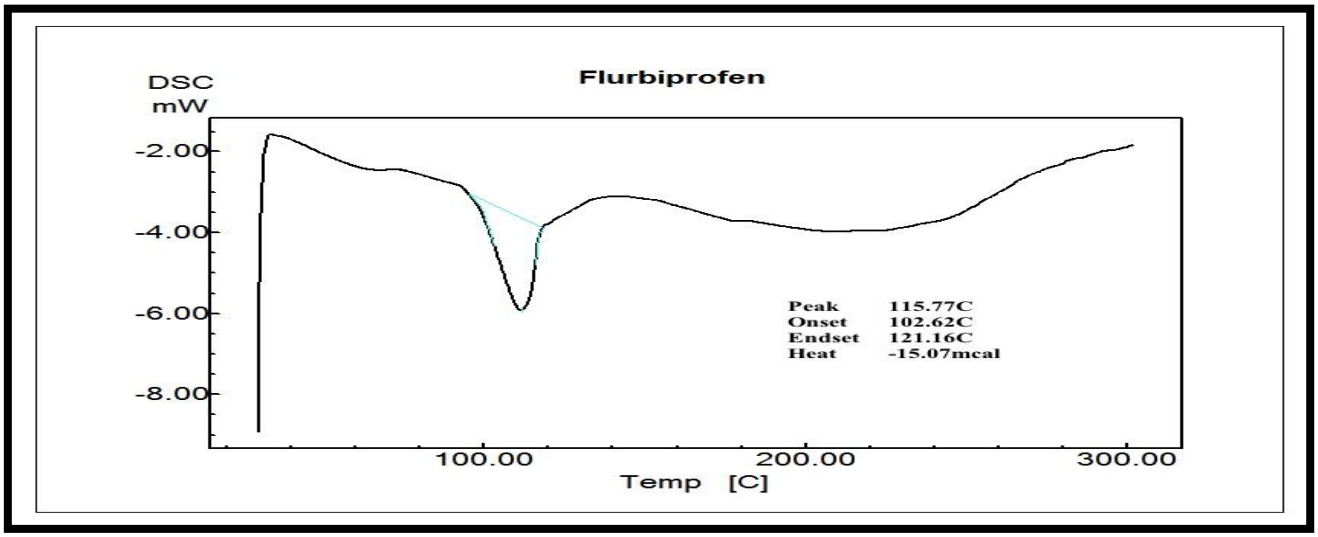

Figure 2: DSC thermogram of Flurbiprofen

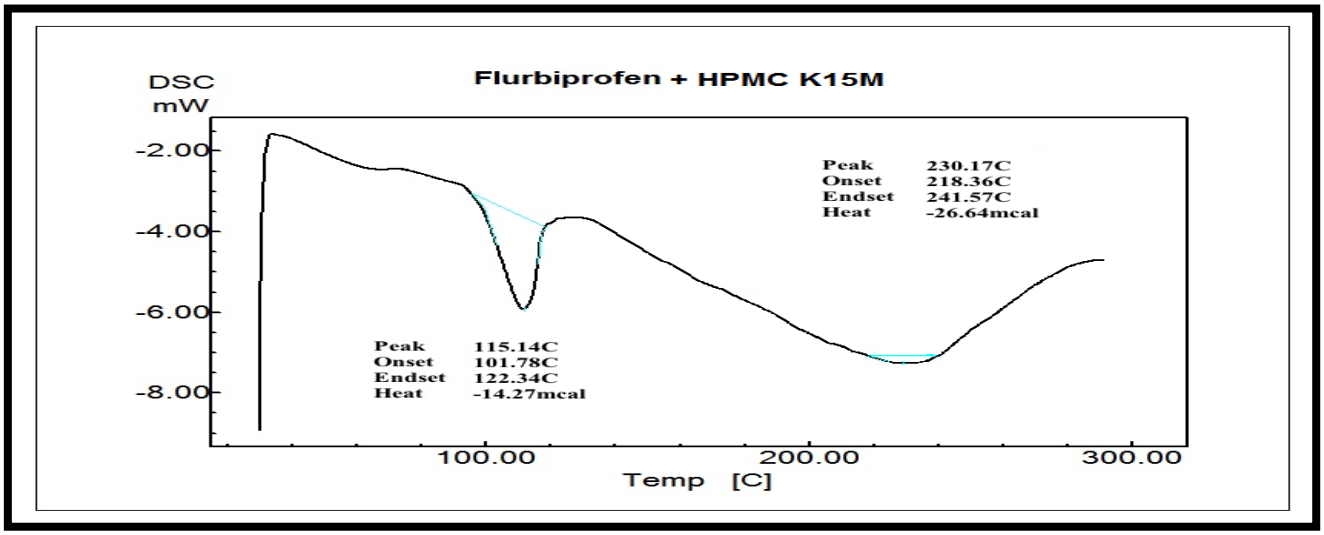

Figure 3: DSC thermogram of physical mixture of Flurbiprofen + HPMC K15M

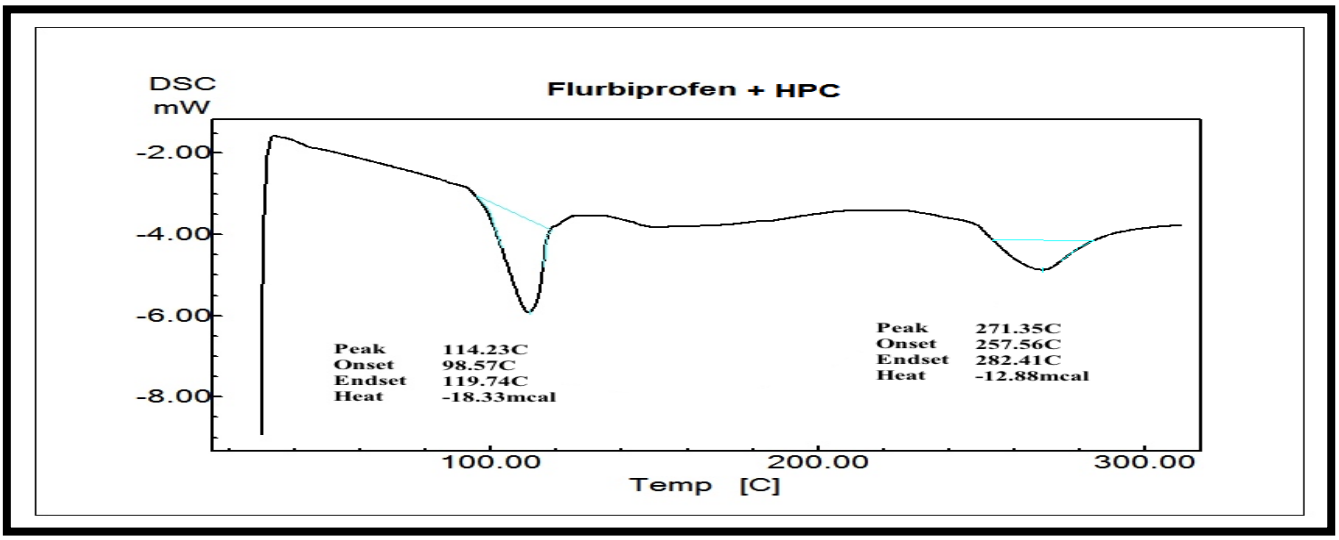

Figure 4: DSC thermogram of physical mixture of Flurbiprofen + HPC

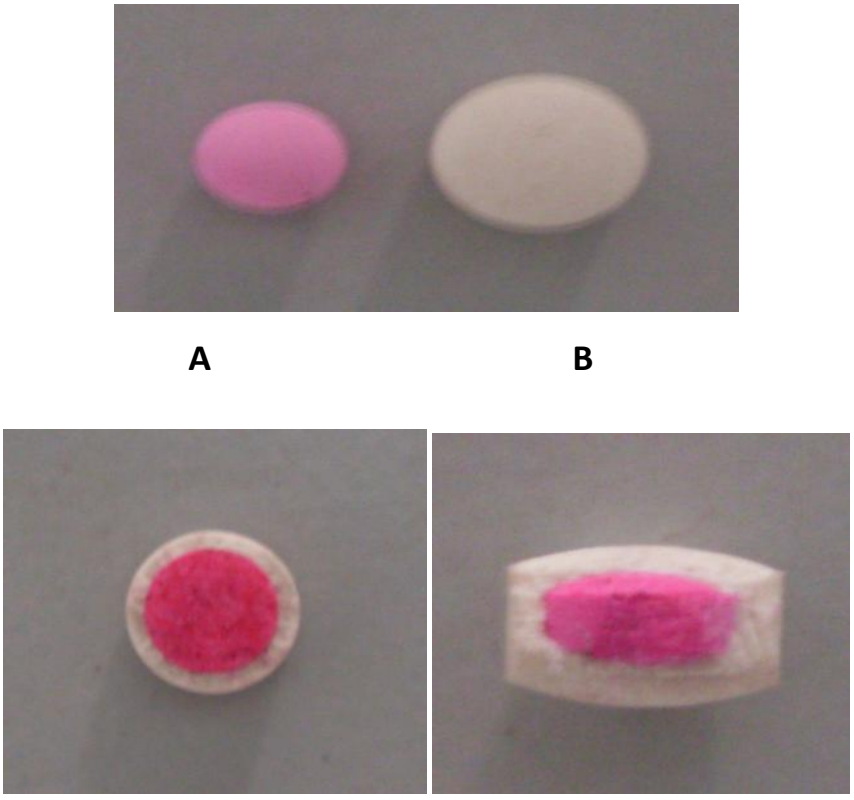

Figure 5: Photographs of compression coated tablet of Flurbiprofen

(A) Core tablet (B) compression coated tablet

Pre compression studies of Flurbiprofen core granules

The results of the preformulation studies of Flurbiprofen core granules are represented in Table 3. The bulk density and tapped bulk density for core granules were found to be 0.333±0.045 g/cc and 0.374±0.048 g/cc respectively. Hausner's ratio with values less than 1.13±0.057 indicates good flow property. The Carr's index value was 9.42±0.487 %, which confirmed that core granules showing excellent flow properties and good compressibility. The angle of repose was found to be 27.91±1.174 thereby confirming the excellent flow property of the granules.

Pre compression parameters of coating material

The pre-compression parameters for the all 9 formulations were carried out and the results are shown in Table 4. The bulk density of all 9 formulations ranged between 0.238±0.015 g/cc to 0.441±0.015 g/cc and tapped density ranged from 0.283±0.015 to 0.512±0.016 g/cc. Hausner's ratio with values less than 1.25 indicates good flow property. The Carr's index value was between the range 9.41±0.201 to 18.01±0.421% which confirmed that all 9 formulations showed excellent flow properties and good compressibility. The angle of repose was found to be between 23.17±0.357 to 28.72±0.450 thereby confirming the excellent flow property of the granules.

Table 3: Data for Pre compression and Post compression studies of the core tablet

Pre compression parameters	
Parameters	**Core tablet**
Bulk density* (g/cc)	0.333±0.045
Tap density* (g/cc)	0.374±0.048
Angle of repose* (θ)	27.91±1.174
Carr's index* (%)	9.42±0.487
Hausner's ratio*	1.13±0.057
Post compression parameters	
Hardness* (kg/cm^2)	5±0.24
Friability* (%)	0.8±0.06
Weight variation*(mg)	125±4.24
Thickness* (mm)	3.14±0.041
Drug content* (%)	99.25±1.7
Disintegration time*	1 min 24 sec

Table 4: Data for pre compression studies of the prepared coating materials

Formulation code	Bulk density* (g/cc)	Tap density* (g/cc)	Angle of repose* (θ)	Carr's index* (%)	Hausner's ratio*
F1	0.242±0.012	0.304±0.006	27.23±0.681	18.01±0.421	1.21±0.125
F2	0.261±0.004	0.307±0.0025	25.33±0.486	14.42±0.45	1.14±0.047
F3	0.257±0.009	0.291±0.012	24.46±0.271	9.41±0.201	1.11±0.055
F4	0.238±0.015	0.283±0.015	28.72±0.450	16.19±0.371	1.2±0.037
F5	0.261±0.006	0.305±0.019	27.20±0.362	14.42±0.249	1.16±0.11
F6	0.25±0.012	0.289±0.023	23.94±0.187	13.49±0.307	1.15±0.063
F7	0.305±0.007	0.366±0.009	28.05±0.281	16.66±0.415	1.2±0.081
F8	0.323±0.014	0.366±0.011	24.41±0.427	11.74±0.386	1.13±0.063
F9	0.323±0.008	0.379±0.017	23.17±0.548	14.77±0.331	1.17±0.13

*Values are represented as mean ± SD (n=3)

Post compression studies of Flurbiprofen core tablets

The data obtained from post compression parameters of core tablets are shown in Table 3. The hardness of the core tablets of flurbiprofen was found to be 5±0.24 kg/cm^2. The core tablets of Flurbiprofen were also found to comply with the friability test since the weight loss was found to be 0.8±0.06%. The average weight of Flurbiprofen core tablets were in the range of 115.6 to 134.3 mg, in contrast to theoretical weight of 125mg. All the tablets passed the weight variation test as the average percentage weight variation was within the Pharmacopoeial limits. The thickness of the tablets was found to be 3.14±0.041mm. The mean drug content of the Flurbiprofen core tablets was found to be 99.25±1.7 indicating uniformity of drug content in the formulation. The core tablets were found to disintegrate within 1 min 24 sec showing the required fast disintegration characteristics.

Post compression characteristics of compression coated Flurbiprofen tablets

The tablets of all the formulations were subjected to post compression tests and the results obtained are represented in Table 5. The compression coated tablets were prepared by applying maximum compression force and the hardness of the tablets were found to be in the range of 5-6 kg/cm^2. The Friability values which were in the range of 0.24 to 0.76 showed that the formulations are physically stable to mechanical shocks during handling and transportation. Weight variation was carried out for all the designed formulations and was found to be within the average weight variation limits. The tablet thickness of all formulations was found to be in the range of 5-6 mm.

Table 5: Data for post compression studies of the prepared formulations

Formulation code	Hardness* (kg/cm^2)	Friability* (%)	Weight variation* (mg)	Core erosion* (%)	Thickness* (mm)
F1	5±0.24	0.51±0.07	398±5.32	36±2.7	5±0.08
F2	5±0.16	0.75±0.03	399.3±4.76	18±4.2	5±0.12
F3	6±0.36	0.5±0.06	400±6.11	5.2±1.1	6±0.10
F4	5±0.40	0.76±0.05	398±3.76	7±1.8	5±0.06
F5	6±0.28	0.51±0.09	399±5.92	2.4±0.14	6±0.08
F6	6±0.12	0.25±0.04	398.6±4.38	0	6±0.17
F7	5±0.42	0.52±0.02	400.66±2.57	3.4±0.11	5±0.14
F8	6±0.33	0.24±0.03	400±3.85	1.7±0.06	5±0.08
F9	5±0.38	0.52±0.06	399.3±5.12	0	5±0.11

*Values are represented as mean ± SD (n=3)

A new method called core erosion test was performed to evaluate the extent of water penetration into the core of compression coated tablets. The core erosion values of all the formulation were in the range of 1.1±0.2 % to 36±2.7 % except F6 and F9 which showed 0% core erosion. The highest percentage of core erosion was observed with 30% HPMC K4M coating. The core erosion was found to be more with low concentration of the polymers.

In-vitro drug release studies

In-vitro drug release of core tablets

The core tablets showed complete drug release within 30 minutes upon contact with dissolution medium (Figure 6).

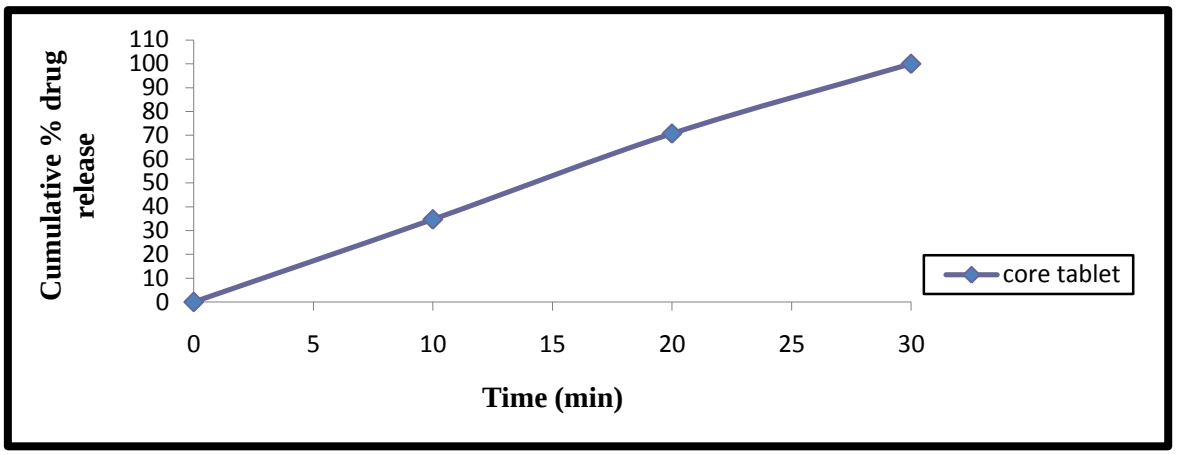

Figure 6: In-vitro drug release profile of Core Tablet

In-vitro drug release of compression coated Flurbiprofen tablets

The main aim of the drug delivery system was to release the drug in an immediate release pattern after a non delivery period (Lag Time) of 6 h. The lag time before the immediate release of the drug from all the batches is summarized in Table 6 and Figure 7.

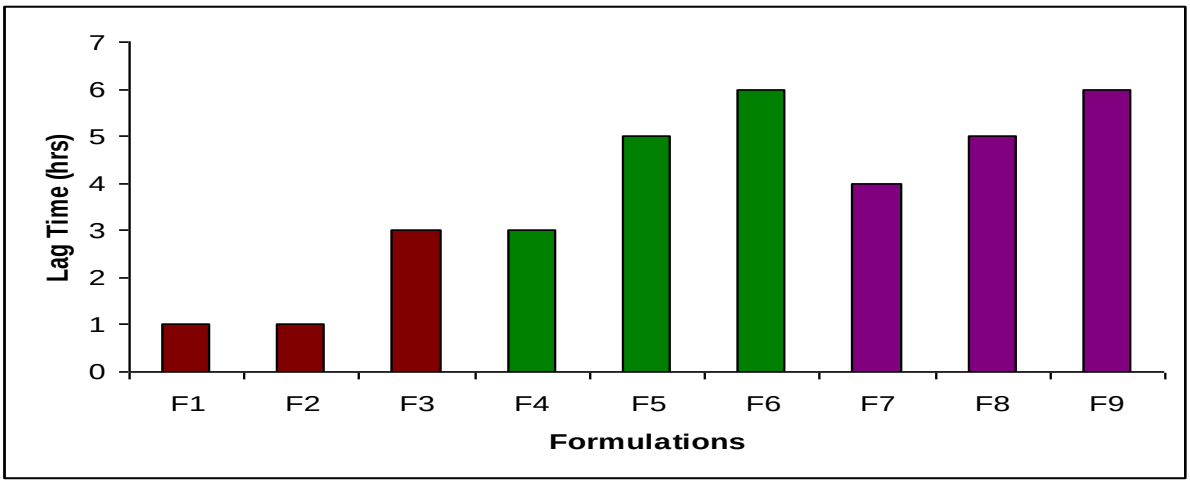

Figure 7: Lag time of compression coated tablets

Table 6: Lag time of compression coated tablets

S. No	Formulation code	Lag time (hrs)
1	F1	1
2	F2	1
3	F3	3
4	F4	3
5	F5	5
6	**F6**	**6**
7	F7	4
8	F8	5
9	**F9**	**6**

In-vitro drug release studies were performed for all the batches of tablets using USP XXIII tablet dissolution apparatus employing rotating paddle method at 50 rpm using 900 ml of pH 1.2 buffers for first two hours and pH 7.4 phosphate buffers for next six hours and the temperature of dissolution medium was maintained at 37±0.5°C. The drug release profiles are shown in Figures 8-10.

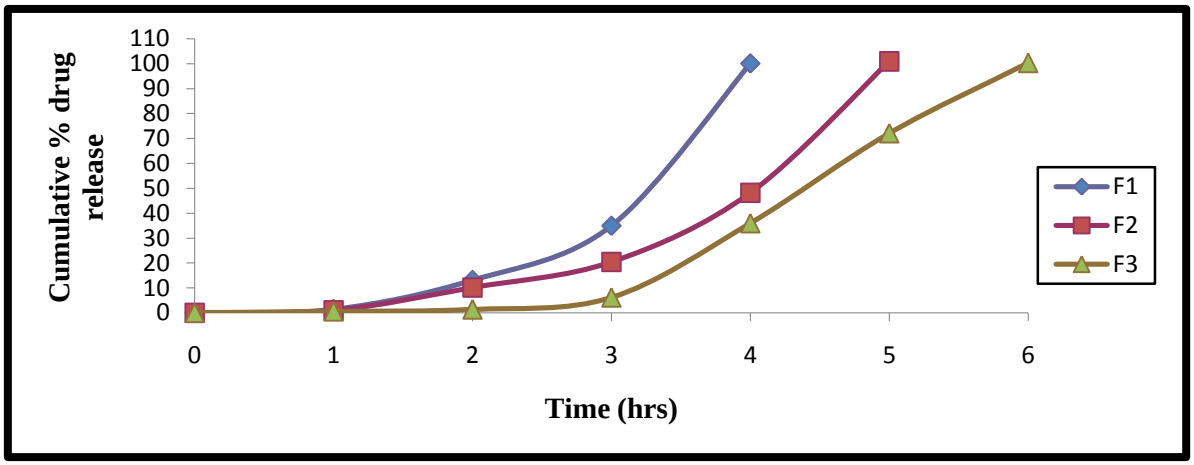

Figure 8: Comparative in-vitro drug release profiles of the formulations F1-F3

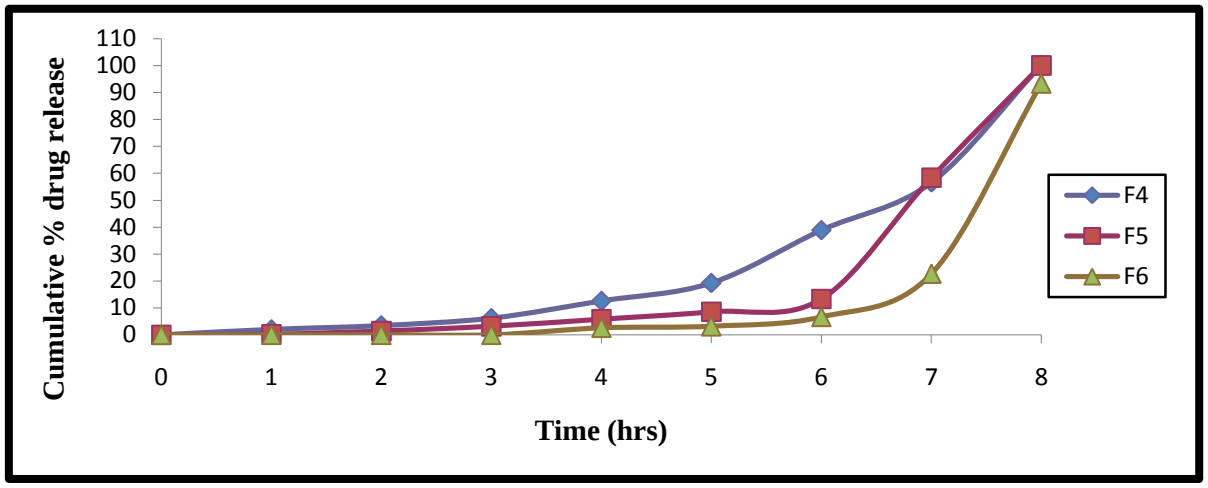

Figure 9: Comparative *in-vitro* drug release profiles of the formulations F4-F6

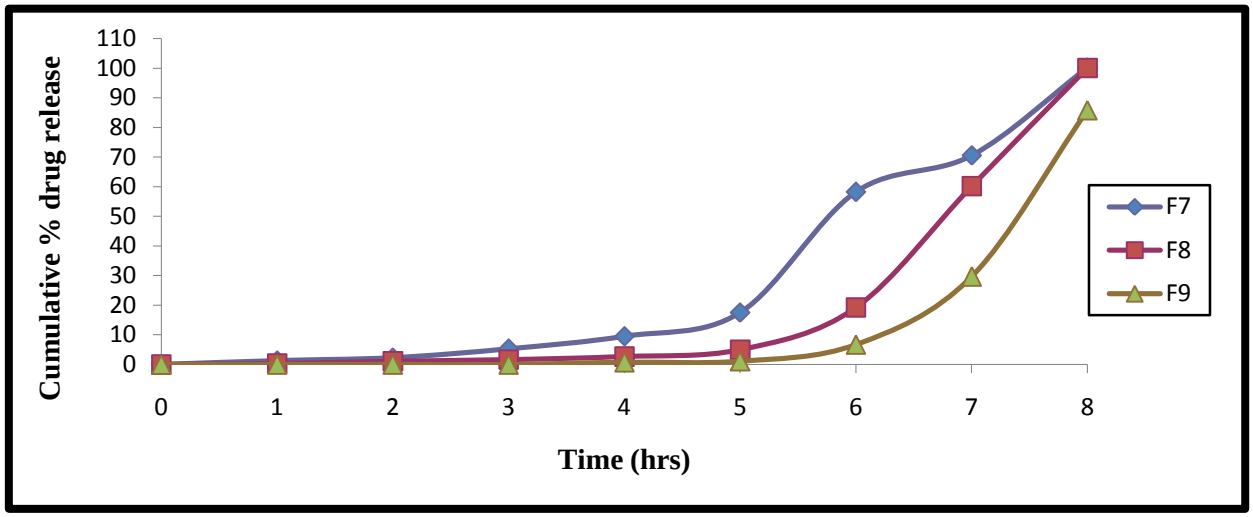

Figure 10: Comparative in-vitro drug release profiles of the formulations F7-F9

During dissolution study, it was observed that, only formulations F6 and F9 showed no drug release for 2 hours in 1.2 pH buffer.

The *in-vitro* release of the drug from tablets coated with coat formulation containing HPMC K4M in different ratios (F1, F2, and F3) exhibited the fastest release. F1 released 100.06% of the drug at the end of 4 h. F2 showed 100.9% drug release after 5 h and F3 showed complete drug release at the end of 6 h. The desired lag times were not obtained with HPMC 4K coatings because this low viscosity of the polymer underwent rapid hydration and swelling.

On the other hand, at the end of 8 h, the cumulative percentage of drug release from the formulations F4, F5 and F6 coated with HPMC K15M were found to be 100.2%, 100.02% and 93.31% respectively. F6 coated with HPMC K15M (90%) showed no drug release during first 3 h of the study. The total percentage of the drug released in the case of F7 and F8 coated with HPC were 100.16% and 100.03%, respectively, after 8 h. F9 (coated with HPC 90%) prevented drug release for 3 h but could release only 85.79% of drug at the end of the release experiment

During the study, it was observed that on exposure to the dissolution medium the coating polymers got hydrated to form a viscous gel layer that slowed the entry of dissolution fluid towards the core tablet. As the concentration of the coating polymer increase the lag time also increased.

Formulations F6 and F9 showed a drug release of 6.64% and 6.75% respectively at the end of 6 h and released about 93.31% and 85.79% of the drug respectively at the end of 8 h. This indicated that the formulations could satisfy the criteria for lag time (i.e., considered to be less than 10% drug release within 6 h). F6 and F9 gave the desired predetermined lag time of 6 h and hence these three formulations were considered for stability studies.

Drug release kinetics

The dissolution data of all the formulations obtained were processed with the software PCP Disso V3 to predict the best fit model. Models with the highest correlation coefficient were judged to be the most appropriate model for the dissolution data. The best fit model for all the formulations was Korsmeyer-Peppas model as their r^2 values are between 0.7838 and 0.9818. The mechanism of drug release are non-fickian diffusion (Super case II), since the 'n' values for the Korsmeyer-Peppas equations were found to be >1.0. This indicates the drug delivery depends on swelling and diffusion process. The data is summarized in Table 7.

Table 7: Curve fit data for the prepared formulations

	Zero order		First order		Higuchi		Hixson-Crowell		Korsmeyer-peppas equation		
	R	**k**	**R**	**k**	**R**	**k**	**R**	**k**	**R**	**k**	**n**
F1	0.8248	12.4231	0.7601	-0.2024	0.6820	19.6674	0.7808	-0.0564	**0.9818**	2.0451	2.3848
F2	0.8315	10.0459	0.7553	-0.1629	0.6830	17.5729	0.7813	-0.0454	**0.9661**	1.6773	2.1516
F3	0.8598	10.2131	0.7954	-0.1821	0.7019	19.3514	0.8211	-0.0489	**0.9369**	0.7566	2.4733
F4	0.8216	6.1845	0.7170	-0.1013	0.6634	13.3825	0.7548	-0.0280	**0.9044**	1.3272	1.6599
F5	0.7273	5.5083	0.6526	-0.0965	0.5700	11.6369	0.6793	-0.0260	**0.8938**	0.5729	1.9208
F6	0.6387	4.1989	0.5749	-0.0715	0.4911	8.7294	0.5953	-0.0195	**0.8319**	0.3388	1.9101
F7	0.8428	7.0804	0.7732	-0.1193	0.6826	15.3307	0.8011	-0.0327	**0.9099**	0.9936	1.8806
F8	0.7305	5.6083	0.6582	-0.0991	0.5701	11.8013	0.6847	-0.0266	**0.8241**	0.4903	1.9255
F9	0.6497	3.9818	0.5955	-0.0625	0.4987	8.2646	0.6135	-0.0176	**0.7838**	0.3159	1.8532

Stability studies

The accelerated stability studies of Flurbiprofen tablets were performed as per the ICH guidelines to investigate whether the tablets are affected during storage conditions. The sample batch tablets from selected formulations F6 andF9 were kept at 400C±20C/75%±5% RH for a period of 6 months.

The physical appearance, hardness, friability, drug content and dissolution rate were measured for selected formulations (Table 8) at the end of 2, 4 and 6 months. The results showed that there was no significant difference between the initial and aged Flurbiprofen tablets.

Table 8: Stability studies of selected formulations F6 and F9 at accelerated storage conditions

Selected formulations	Time (months)	Physical appearance	Hardness* (kg/cm^2)	Friability* (%)	Percentage drug content* (%)	Percentage drug release (%) (at 8 h)
F6	**0**	++	6±1.2	0.25±0.04	99.25±1.7	93.31
	2	++	6±0.09	0.27±0.03	99.05±2.1	92.97
	4	++	5.5±0.22	0.27±0.06	97.60±4.4	91.65
	6	++	5.5±0.14	0.29±0.05	96.69±3.5	89.76
F9	**0**	++	5±0.38	0.52±0.06	99.25±1.7	85.79
	2	++	5±0.17	0.53±0.07	98.37±3.6	85.16
	4	++	5±0.04	0.54±0.05	97.83±4.2	84.53
	6	++	4.5±0.32	0.57±0.04	97.14±2.8	83.78

*Average of three determinations

+: Slight change in appearance **++:** Same as on '0' day

Conclusion

The main objective of the studies described was to develop a time-controlled release formulation of Flurbiprofen based on compression coating technique. The intention is that the formulation should be administered in the night at 22:00 for treating Rheumatoid Arthritis in which symptoms are worse in the early morning hours (from 04:00 to 06:00).

The compression coated tablets of Flurbiprofen, a non-steroidal anti-inflammatory drug had been successfully developed with various coating polymers to achieve maximum release drug after a predetermined lag time of 6 h. The *in-vitro* drug release studies showed that amongst all the formulations F6 and F9 could release the drug completely after a distinct lag time of 6 h. The high viscosity of polymers such as HPMC 15K and HPC were found to be responsible for delaying drug release, thus making these formulations useful as chronotherapeutic drug delivery systems for the treatment of Rheumatoid arthritis which follow circadian rhythms.

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