IJPSR (2013), Vol. 4, Issue 2 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 03 November, 2012; received in revised form, 14 December, 2012; accepted, 25 January, 2013

DEVELOPMENT OF A NOVEL ENTERIC COATED EXTENDED RELEASE PELLETS USING MODEL NSAID FLURBIPROFEN

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Keywords:

Enteric coated, Extended release, Pellets, Flurbiprofen, Spheronization method

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ABSTRACT

The aim of this study was to develop a pH responsive enteric coated extended release pellets containing a model drug flurbiprofen, a non-steroidal anti-inflammatory drug used for rheumatoid arthritis. The drug loaded pellets were prepared by using extrusion/ spheronization method. Core pellets were coated with polymer Eudragit RS30D in a coating pan to achieve a sustainable release for 12 hours. A ph responsive barrier coat of Eudragit L 100-55 was employed in a coating pan for abstaining release in acidic media. The drug excipient mixtures were subjected to pre-formulation studies. The pellets were subjected to physicochemical studies, *in-vitro* drug release, Kinetic studies and stability studies. FTIR studies shown there was no interaction between drug and polymers. The physicochemical properties of pellets were found within the limits. The drug release from the optimized formulations was extended for a period of 12 hrs i.e. first 2 hrs no drug release was observed and gradually drug release was increased up to 12 hrs. From the above results, achievement of site specific release to lower part of gastrointestinal tract might be due to Eudragit L 100-55 stability in acidic pH. The prepared pellets apart from fulfilling all official and other specifications, exhibited good extended release of Flurbiprofen. The optimized formulations were subjected to stability studies and shown there were no significant changes in drug content, physicochemical parameters and release pattern. In conclusion, development of Eudragit RS30D-Eudragit L 100-55 was novel and good approach to achieve the site specific release of drug to colon.

INTRODUCTION: The term arthrities is used to describe changes in the joints which may be either inflammatory or degenerative in character [1, 2].

Circadian variation in pain, stiffenss and manual dexterity in patients with osteo and rheumatoid arthritis have been studied and has implication for timing anti-rheumatoid drug treatment [2]. Morning stiffness associated with pain at the time of awakening is a diagnostic criterion of the rheumatoid arthritis and these clinical circadian symptoms are supposed to be outcome of altered functioning of hypothalamic–pituitary adrenocortical axis. Chronopharmacotherapy for rheumatoid arthritis has been recommended to ensure that the highest blood levels of the drug coincide with peak pain and stiffness [3]**.** A sustained drug delivery system that can be administered at night (before sleep) but that release drug in early morning would be a promising chronopharmaceutic system [4, 5].

Drug targeting to colon would prove useful where intentional delayed drug absorption is desired from therapeutic point of view in the treatment of disease that have peak symptoms in the early morning such as nocturnal asthma, angina, arthritis [6, 7, 8, 9].

Some orally administered drugs (e.g. Diclofenac, Theophyllin) may exhibit poor uptake in the upper regions of GIT or degrade in the presence of GIT enzymes. Better bioavailability can be achieved through colonspecific drug delivery. Colonic targeting is also advantageous where delay in systemic absorption is therapeutically desirable [6, 9].

Flurbiprofen **(see Figure 1)** is an important analgesic and non-steroidal anti-inflammatory drug (NSAID) also with anti-pyretic properties whose mechanism of action is the inhibition of prostaglandin synthesis. It is used in the therapy of rheumatoid disorders.

Flurbiprofen is rapidly eliminated from the blood, its plasma elimination half-life is 3-6 hours and in order to maintain therapeutic plasma levels. The drug must be administered approximately 150-200mg daily by oral in divided doses [10]. Therefore, to improve the biological half-life and to improve patient compliance, an Enteric coated sustained release formulation of Flurbiprofen is desirable.

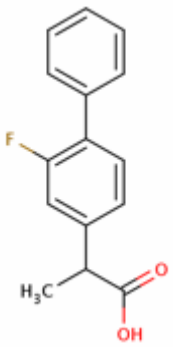

FIGURE 1: CHEMICAL STRUCTURE OF FLURBIPROFEN

MATERIALS AND METHODS:

Materials: Flurbiprofen was obtained as a gift sample by FDC Pharmaceutical Pvt. Ltd., Mumbai. Eudragit RS30D and Eudragit L 100-55 were obtained from Degussa India Pvt. Ltd. Mumbai. Pharmatose, Crospovidone, Polyvinyl pyrollidone (PVPK-30), Avicel were purchased from Rajesh chemicals, Mumbai. All other chemicals were of A.R grade purchased from S.D Fine chemicals Limited, Mumbai, India.

EXPERIMENTAL METHODS:

Drug-excipient compatibility studies [11]: Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the pre-formulation stage during the development of solid dosage form. Therefore, the pure drug and the formulations mixed with polymers were subjected to infra-red (IR) studies.

The pure drug and formulations mixed with polymers were separately mixed with IR grade potassium bromide in a ratio (1:100) and pellets were prepared by applying 10 metric ton of pressure in hydraulic press. The pellets were then scanned over range of 4000-400cm^{-1} in FTIR instrument.

Preparation of Flurbiprofen core pellets[12]: Drug containing core pellets were prepared by extruder-spheronizer (NAOMI, Mumbai, India). The flurbiprofen, spheronizing agents Avicel pH 101, lactose (filler), superdisintigrant croscarmellose sodium were mixed to form a uniform blend. The binder solution PVPK-30 (2.5% in 50:50 alcohol/ water) was slowly added in the powder mixture to achieve a consistency of the damp mass suitable for further extrusion-spheronization process. The composition of core pellets is given in Table 1. the prepared mass was immediately passed through a screw type extruder using 1mm diameter screen with the speed set at 15 rpm. The extrudes were then transferred to spheronizer for 15-20 min at a rotation speed of 700 rpm. The resultant pellets were dried at 50^{0}C in oven for 30 min.

TABLE 1: COMPOSITION OF CORE PELLETS

Ingredients	Quantity (mg)
Flurbiprofen	100
Pharmatose	60
Crospovidone	10
Polyvinyl pyrollidone (PVPK-30)	2.5
Avicel q.s to make	250

Preparation of Flurbiprofen extended release pellets [12]: The 200gm core pellets containing 100mg drug per 250mg of pellets were coated with sustained release polymethacrylate polymer Eudragit RS30D aqueous dispersion to achieve a weight gain of 6-15% using a 6 inches coating pan (United technologies, Mumbai). The coating composition for Eudragit RS30D aqueous dispersion coating by coating pan are shown in **Table 2.**

TABLE 2: COATING SOLUTION COMPOSITION

Ingredients	% Polymer	Quantity taken (gms)
Eudragit RS30D	-	80.04
Glyceryl Monostearate	5	1.22
Triethyl citrate	20	4.82
Tween 80	40% of GMS	0.5
Water q.s.	-	100

Preparation of Flurbiprofen enteric coated extended release pellets [12]: The Eudragit RS30D coated extended release pellets prepared in the above step was evaluated for shape, size, uniformity and friability before proceeding to coating step. Further, the sustained release pellets were coated with pH-sensitive water insoluble layer of Eudragit L100-55 to achieve a weight gain of 5%. The composition of coating solution is given in **Table 3**.

TABLE 3: EUDRAGIT L100-55 COATING SOLUTION COMPOSITION

Ingredients	Quantity taken (gms)
Eudragit L100-55	5g
Dibutyl phthalate	1gm
Talc	1.3827gm
Water	5gm
Isopropyl alcohol q.s to make	100gm

Coating [12, 13]: The coating solution was sprayed on to the core pellets using a spray gun in a coating pan, United technologies, Mumbai **(see Figure 3)**. The conditions for coating were shown as follows: Pellets charged-25 g, Preheating temperature 50^0C, Preheating time-10min, Outer blower temperature-75^oC. The final coating batches with various levels of polymers are shown in **Table 4.**

Percentage weight gain was calculated by following equation:

$$\text{Percentage weight gain} = [(Wt - Wo)/Wo]*100$$

Where Wt = Weight of tablet after coating, Wo= Initial weight of tablet

TABLE 4: FORMULATION BATCHES

Formulation Batch	Eudragit RS30D	Eudragit L100-55
	Percentage increase in weight of pellets	
F1	6	5
F2	9	5
F3	12	5
F4	15	5

Pellets characterization [12]: The pellets were characterized for the size, shape using vernier caliper. The diameter of the core pellets, Eudragit coated pellets were measured to assess the parameters like size and shape uniformity.

Micromeritic properties [14]: The bulk density and tapped density of drug powder and pellets were evaluated to assess the packing ability due to tapping. The carr's compressibility index and hausner's index was computed.

Friability [12]: Friability studies on core pellets were performed by placing 5g in a friabilator (Veego, Mumbai) and tumbled for 200 revolutions at 25rpm. Twelve steel balls (Diameter 6.3 mm, weighing 1 g each) were used as attrition agents. After friability testing the pellets were sieved through a sieve of 16# size. The weight loss (% F) after friability testing was calculated.

pH solubility study [12]: The pH solubility was performed by adding excess amount of flurbiprofen to various buffer solutions. The buffer solutions of pH 1.2, 2.4, 6.8, 7, 7.4, 10 were prepared. The vials containing drug in buffer solutions were kept for continous stirring for 24hr under controlled temperature 25^oC. The solubility was determined spectrophotometrically by suitably diluting the aliquot and determining absorbance at 247 nm.

Drug content estimation [14]: The Eudragit RS30D and L30D-55 coated pellets equivalent to 100mg of Flurbiprofen were weighed accurately, grinded in motor and dissolved in phosphate buffer, pH 6.8, and was analyzed spectrophotometrically at 247 nm after sufficient dilution with the respective solvent of phosphate buffer solution pH 6.8. All the experiments were performed in triplicate.

***In-vitro* drug release studies for Enteric Coated Extended Release Pellets** [14]: Dissolution studies were performed using USP standard dissolution apparatus at 37±0.5^{o}C. The basket was immersed in 900ml of dissolution medium and rotated at 50 rpm. The dissolution Media used was initially 0.1N HCl up to 2hrs, then continuation with fasted buffer having pH 6.8. During the test 5 ml of the sample was withdrawn at specific time intervals 1, 2, 4, 6, 8, 10, 12 hrs after each withdrawal, same volume of fresh dissolution

medium was added to maintained sink conditions. Different aliquots were suitably diluted. The absorbance was measured in the UV Spectrophotometer at 247 nm.

Release kinetics studies [11, 14]: To study the release kinetics in-vitro release data was applied to kinetic models such as zero-order, First-order, Higuchi and Korsemeyer peppas.

Stability studies [16, 17]: For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated.

The design of the formal stability studies for the drug product should be based on the knowledge of the behaviour and properties of the drug substance and formal stability studies on the drug substance.

The stability studies were carried out of the most satisfactory formulation as per ICH guidelines to assess the drug and formulation stability. The most satisfactory formulation sealed in aluminum packaging and kept in humidity chamber maintained at 30±2^{o}C, 65±5% RH and at 40±2^{o}C, 75±5% for two months. At the end of studies, samples were analyzed for the post-compression parameters and in-vitro drug release profile.

RESULTS AND DISCUSSION:

Drug-excipient compatibility studies: Compatibility study Spectra of the pure drug, excipient and physical mixture of drug and excipient were recorded in between 400-4000 wave number (cm^{-1}) **(see Figure 2)**.

The FTIR spectral analysis showed that there is no appearance or disappearance of any characteristic peaks of pure drug flurbiprofen and in the physical mixture which confirms the absence of chemical interaction between drug and polymers.

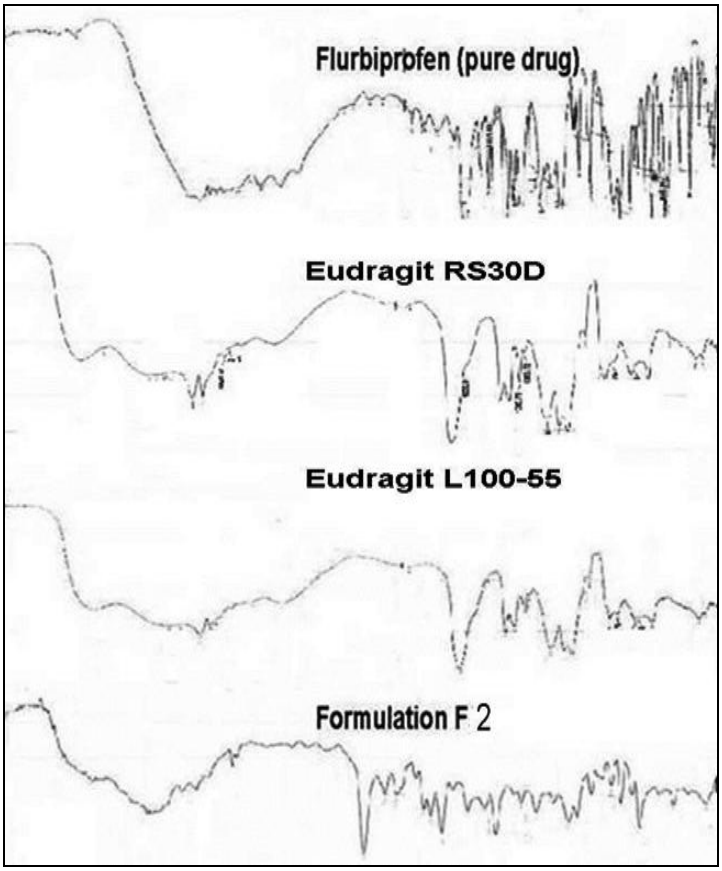

FIGURE 2: IR SPECTRAS OF 1) FLURBIPROFEN (PURE DRUG) 2) EUDRAGIT RS30D 3) EUDRAGIT L100-55 4) FORMULATION F4

Pellet characterization: It was observed that pellets were of uniform in size and shape. The average size of drug containing core pellets was 1.3-1.7 mm (n=100). The uniform size of pellets indicates good content uniformity, good flow and ease of capsule filling.

Micromeritic properties: The micromeritic properties of pure flurbiprofen, Eudragit RS30D and Eudragit L100-55 is shown in **Table 5**. The carr's compressibility of Eudragit coated pellets was significantly improved compared with plain drug.

TABLE 5: MICROMERITIC PROPERTIES OF DRUG AND COATED PELLETS

Parameters	Flurbiprofen	Eudragit RS30 coated pellets	Eudragit L100-55 coated pellets
Angle of repose (degree) ± SD, n=3	37°.67"±0.58	14.27±0.38	13.92±0.40
Bulk density (gm/cc) ± SD, n=3	0.229±0.042	0.576±0.048	0.697±0.032
Tapped density (gm/cc) ± SD, n=3	0.343±0.034	0.605±0.053	0.756±0.018
Carr's index (%) ± SD, n=3	33.23±1.63	4.793±0.036	7.80±0.066
Hausner's ratio ± SD, n=3	1.49±0.028	1.05±0.041	1.08±0.012

Friability: Friability of pellets is an important parameter to withstand handling, shipping, storage and other processing parameters such as coating. The weight loss after friability testing was calculated as 0.637±0.14 showing good friability.

pH solubility study: The Flurbiprofen had least solubility in lower pH, and has good solubility in basic pH. The official dissolution media of Flurbiprofen pellets is pH 6.8. The drug was found to be having best solubility above this range **(as shown in Figure 3)**.

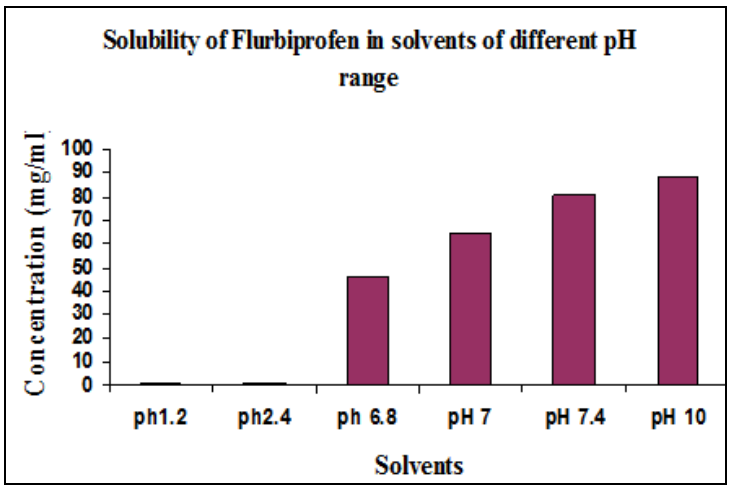

FIGURE 3: pH SOLUBILITY PROFILE OF FLURBIPROFEN

Drug content estimation: The drug content uniformity was performed for both all the batches of formulations. Three trials from each batch were analyzed spectrophotometrically. The average value and standard deviations of all the batches of formulations were calculated. The percentage drug content in the Flurbiprofen core pellets was found to be 99.07±0.14 indicating good content uniformity in all the batches. That indicates drug was uniformly distributed through out the core pellets.

***In-vitro* release profile of extended release pellets of Flurbiprofen:** From the results of *in vitro*-dissolution study **(as shown in Table 6, figure 4),** it was found for all the formulations polymer Eudragit L100-55 was able to inhibit the drug release in the gastric medium for first 2 hours followed by sustained release effect for 12 hours. The drug release was found to be 82.76±0.64, 95.88±0.55, 86.81±0.27 and 31.48±0.75 % for F1, F2, F3 and F4 formulations respectively. Formulation F1 was extended only for a period of 8 hrs, whereas F2, F3 and F4 were extended for a period of 12 hrs.

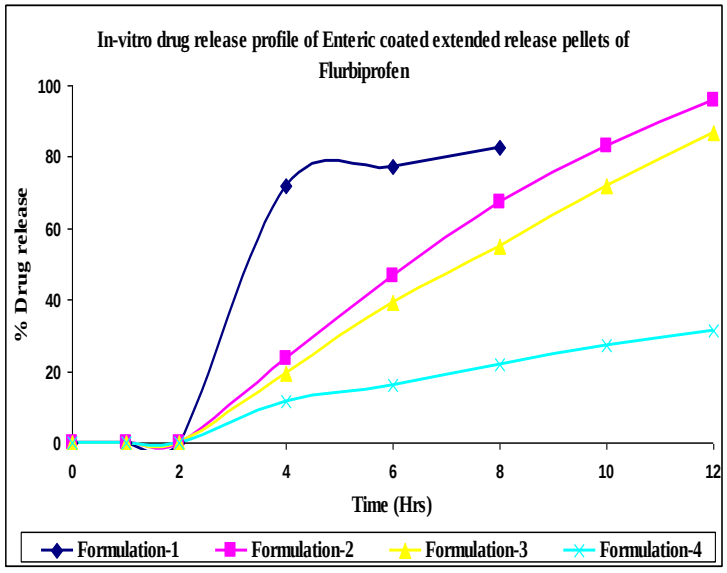

FIGURE 4: *IN-VITRO* DRUG RELEASE PROFILE OF ENTERIC COATED EXTENDED RELEASE PELLETS OF FLURBIPROFEN

From this, we conclude that as the weight gain of sustained release polymethacrylate polymer Eudragit RS30D increased from 6-15% the release profile of formulations decreased. As our aim was to achieve extended release for 12 hrs, Formulation F2 with 9% Eudragit RS30D and 5% Eudragit L100-55 was considered to be most suitable as it released maximum drug for a period of 12 hrs with a 2 hr lag time in acidic medium. This 2hr lag time might be due to Eudragit L 100-55 stability in acidic pH. Hence, it was considered as the best formulation.

TABLE 6: COMPARATIVE DISSOLUTION STUDY OF FORMULATIONS 1-4

Dissolution medium	Time (Hrs)	% Cumulative drug release			
		F 1	F 2	F 3	F 4
0.1N HCl	0	0±0.44	0±0.60	0±0.20	0±0.95
	2	0±0.73	0±0.49	0±0.76	0±0.10
6.8 pH buffer	4	71.79±0.35	23.37±0.33	19.31±0.11	11.68±0.25
	6	77.27±0.81	46.74±0.92	39.11±0.18	16.21±0.13
	8	82.76±0.64	67.26±0.59	54.85±0.86	21.94±0.10
	10		83.24±0.16	71.79±0.41	27.42±0.74
	12		95.88±0.55	86.81±0.27	31.48±0.75

Release Kinetics studies: The kinetic data of the optimized formulation F2 is represented in **Figures 5-8**. The results revealed that Formulation F2 release the drug by zero-order kinetics. To ascertain the drug release mechanism, the *in-vitro* release data was also subjected to Higuchis diffusion plots and Peppas plots and the correlation coefficient values was found to be 0.8607 and 0.9340 respectively. So it confirms that, the calculated R^2 values for Higuchi plot and Peppas plots were nearer to one (1) suggesting that drug released by diffusion mechanism.

The value of n indicates the drug release mechanism related to the geometrical shape of the delivery system, if the exponent n = 0.5, then the drug release mechanism is Fickanian diffusion. If n < 0.5 the mechanism is quasi-Fickanian diffusion, and 0.5 < n < 1.0, then it is non-Fickanian or anamolous diffusion and when n = 1.0 mechanism is non-Fickanian case II diffusion, n > 1.0 mechanism is non-Fickanian super case II. In the present study the mean diffusional exponent values (n) for the optimized formulation was found to be 2.06 indicating that it presented a dissolution behaviour controlled by non-Fickanian super case II. (When n > 1.0).

Stability studies: The optimized Formulation 4 was subjected to stability studies and shown there were no significant changes in drug content, physicochemical parameters and release pattern **(as shown in Table 7).**

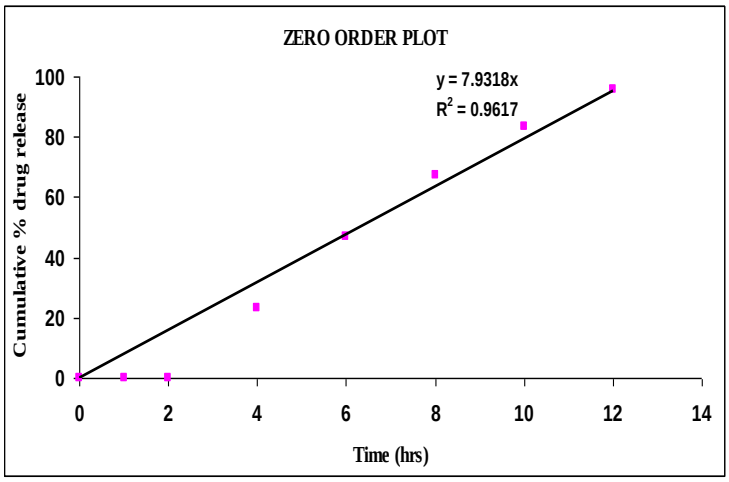

FIGURE 5: ZERO ORDER RELEASE PLOT OF OPTIMIZED FORMULATION 2

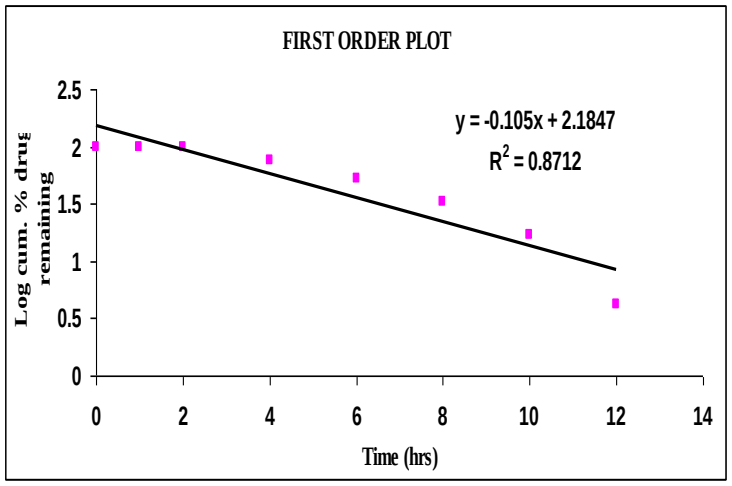

FIGURE 6: FIRST ORDER RELEASE PLOT OF OPTIMIZED FORMULATION 2

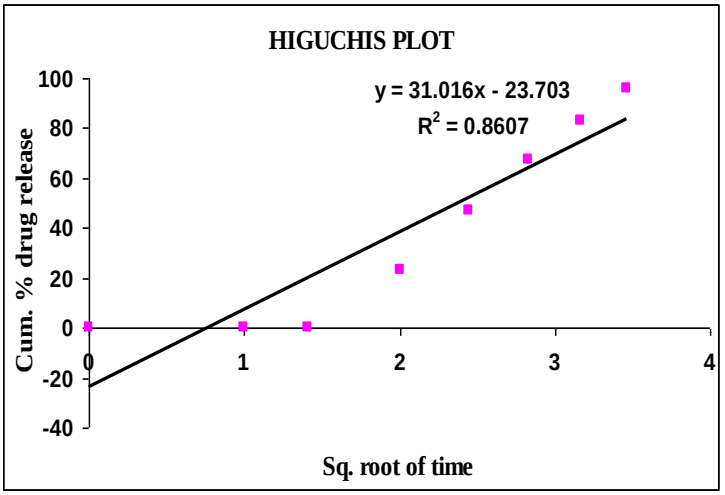

FIGURE 7: HIGUCHI PLOT OF OPTIMIZED FORMULATION 2

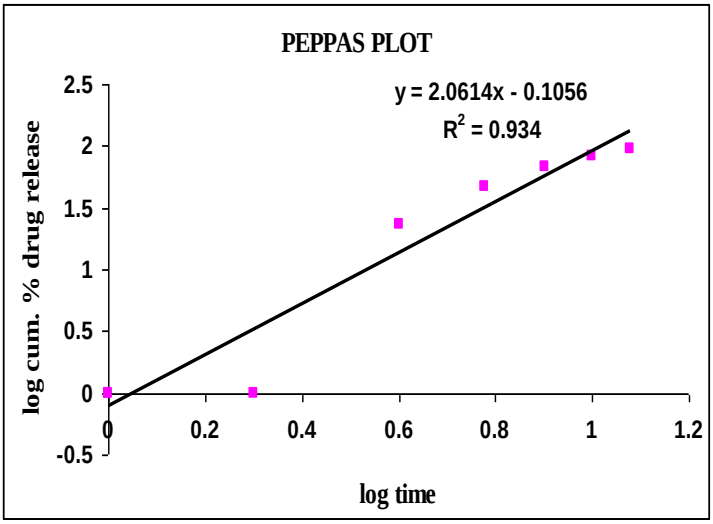

FIGURE 8: PEPPAS PLOT OF OPTIMIZED FORMULATION 2

TABLE 7: EVALUATION PARAMETERS OF MOST SATISFACTORY FORMULATION F2 DURING STABILITY STUDIES

Time (Days)		% Drug content (±SD), n=3	*In-vitro* drug release study	
			0.1N HCl	6.8 pH buffer
0		99.07±0.14	0.000	95.88±0.55
30	At 30 ± 2°C, 65 ± 5% RH	98.75±0.05	0.000	95.12±0.94
	At 40 ± 2°C, 75 ± 5% RH	98.64±0.09	0.000	94.78±0.51
60	At 30 ± 2°C, 65 ± 5% RH	98.18±0.18	0.000	94.60±0.11
	At 40 ±2°C, 75 ± 5% RH	98.10±0.20	0.000	94.92±0.49

CONCLUSION: An Enteric coated extended release pellets was successfully developed by coating the Flurbiprofen core pellets with Eudragit L100-55 and Eudragit RS30D which produces a 2 hr lag time in acidic medium followed by sustained release phase for 12hrs. The produced coated pellets were stable for a period of 2 months when stored as per ICH guidelines. Therefore, these findings suggest the suitability of these polymers for preparing the above mentioned formulation. Hence, it can be concluded that the enteric coated extended release pellets would be a promising drug delivery system for systemic administration of Flurbiprofen for rheumatoid arthritis.

ACKNOWLEDGEMENTS: Author's are thankful to FDC Pharmaceutical Pvt. Ltd., Mumbai for providing gift sample of Flurbiprofen and United technologies, Mumbai for supplying the coating pan at the same time. The authors are also thankful to Mr.Vishal Patel ex-student of Luqman college of Pharmacy, Gulbarga and Mr.Devilal, Associate Professor Bhaskar Pharmacy College for their valuable suggestion in carrying out this research work. The authors are also thankful to Sri. J. Bhaskar Rao Garu, chairman, and Dr. A Srinivasa Rao, Principal, Bhaskar Pharmacy College, Moinabad, R.R.District, Hyderabad (India), for providing suitable research laboratory to carry out this project work

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How to cite this article:
Abhinetri V, Hadi MA, A. Rao S and Sravani V: Development of a Novel Enteric Coated Extended Release Pellets using Model NSAID Flurbiprofen. *Int J Pharm Sci Res*. 2013; 4(2); 758-764.