Basavaraja et al /J. Pharm. Sci. & Res. Vol. 7(6), 2015, 274-281

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Formulation and Evaluation of Sustained Release Matrix Tablets of Flurbiprofen by Using Natural and Synthetic Polymers

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Abstract

The objective of the present work is to design of novel sustained release matrix tablets of Flurbiprofen influence of natural, synthetic polymers, on the release rate and *in vitro* evaluation.Flurbiprofen is NSAID drug used extensively in the treatment of rheumatoid arthritis, degenerative joint disease, osteoarthritis, Ankylosing Spondylitis, acute musculoskeletal disorders, low back pain and allied conditions.

The natural polymers are Xanthan gum, Karaya gum, and synthetic polymers like HPMC K- 100, Ethyl cellulose were utilized in the formulation of matrix tablets containing Flurbiprofen by wet granulation technique and evaluated for its *in-vitro* drug release. Natural polymer is hydrophilic in nature and rate controlling polymers. Granules were prepared and evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. Formulation was optimized on the basis of acceptable tablet properties (hardness, friability, drug content and weight variations), *in vitro* drug release and stability studies. All the formulations showed compliance with Pharmacopeial standards. The *in vitro* release study of matrix tablets were carried out in pH 1.2 HCl for 2 hours and pH 7.4 phosphate buffer for the remaining 10 hours as dissolution medium.

Among all the formulation, F12 shows 97.23% of drug which was better controlled release at the end of 12 hrs. It has been found that the optimized formulation F-12 containing 500 mg of ethyl cellulose better sustained effect for 12 hr, The results indicated that a decrease in release kinetics of the drug was observed by increasing the polymer concentration. The release data was fitted to various mathematical models such as, Higuchi, Korsmeyer-Peppas, First-order and Zero order to evaluate the kinetics and mechanism of the drug release. The stability studies were carried out according to ICH guideline which indicates that the selected formulations were stable.

Keywords: Sustained release tablets, Flurbiprofen, Xanthan gum, Karaya gum, HPMC K - 100, Ethyl cellulose.

INTRODUCTION

Oral drug delivery is the most preferred and convenient choice as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs. Normally conventional dosage form produces wide range of fluctuation in drug concentration in the bloodstream and tissues with resultant undesirable toxicity and poor efficiency. The maintenance of concentration of drug in plasma within therapeutic index is very critical for effective treatment. These factors as well as factors such as repetitive dosing and unpredictable absorption lead to the concept of oral Sustained release drug delivery systems. Developing oral sustained release matrix tablets for drug with constant release rate has always been a challenge to the pharmaceutical technologist. Drug release through matrix system is determined by Water penetration, Polymer swelling, Drug dissolution, Drug diffusion, Matrix erosion have been utilized as formulation approaches. [1]

Sustained release systems consist of any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled-release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered as a prolonged release system. [2]

Matrix systems are widely used for the purpose of sustained release. The first sustained release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida. [3]

NSAIDs exert their anti-inflammatory effect through inhibition of prostaglandin G/H synthase, or cyclooxygenase, which is the enzyme catalyzing the transformation of arachidonic acid to prostaglandins and thromboxanes. This enzyme has two recognized forms: cox-1 and cox-2. Selective inhibition of cox-2 leads to decreased GI side effects. Recent work suggests that activation of endothelial cells and expression of cell adhesion molecules play a role in targeting circulating cells to inflammatory sites.

NSAIDs may inhibit expression of these cell adhesion molecules and may directly inhibit activation and function of neutrophils. Rheumatoid arthritis (RA) is a chronic (long-term) disease that causes pain, stiffness, swelling and limited motion and function of many joints. While RA can affect any joint, the small joints in the hands and feet tend to be involved most often. Inflammation sometimes can affect organs as well, for instance, the eyes or lungs. For instance, Osteoarthritis most often does not cause prolonged morning stiffness.

RA is an autoimmune disease. This means that certain cells of the immune system do not work properly and start attacking healthy tissues the joints in RA. The cause of RA is not known. Yet, new research is giving us a better idea of what makes the immune system attack the body and create inflammation. In RA, the focus of the inflammation is in the synovium, the tissue that lines the joint. Immune cells release inflammation causing chemicals. These chemicals can damage cartilage (the tissue that cushions between joints) and bone. [4]

Flurbiprofen is newer derivative of Ibuprofen and having less GIT complications with short biological half-life of 4 hrs and dosing frequency more than one time, makes an ideal candidate for modified release multiple unit preparation. To reduce the frequency of administration and to improve patient compliance.Flurbiprofen is suitable for making sustain release dosage form. Flurbiprofen is given orally as 150–200 mg daily in 3 or 4 divided doses. Flurbiprofen is 99% bound to plasma proteins. Consequently no drug accumulation with once daily dosing is observed. Excretion of Flurbiprofen is by renal route [5].

MATERIALS AND METHODS

Raw materials

Flurbiprofen was obtained from Yarrow chem. Products, Mumbai. Xanthan gum and Karayagum was obtained from Research- Lab Fine Chem. Industries. Mumbai, polymers like HPMC K100 M, Ethyl cellulose and microcrystalline cellulose obtained from Research- Lab Fine Chem Industries. Mumbai and PVP K 30, Talc, Magnesium Stearate was obtained from SD Fine Chem. Limited, Mumbai.

Preparation of matrix tablets:

Tablet formulations were prepared by wet granulation method. Aqueous granulation process was used to prepare Flurbiprofen SR matrix tablets Proportion of excipients with drug was as given in Table no 1 and 2. All ingredients were sifted through sieve no.40. The sifted ingredients were mixed thoroughly in a polybag for 15min. PVP K30 was dissolved in distilled water and used for wet granulation of the final blend. To get the desired wet mass. This wet mass was passed through sieve # 16. The prepared granules were dried at 60 ^{O}C for 1 hour in hot air oven, dried granules were sized by passing it through sieve No.20 and lubricated with magnesium stearate and Talc for 1 minute. Finally tablets were compressed at 500 mg weight on a 16 station mini rotary tableting machine with 11 mm standard concave punches.

Polymers used - HPMC K100M, Xanthan gum, Karayagum, Ethylcellulose,
Diluent used - MCC
Lubricant used- Magnesium Stearate
Glidant used- Talc

Evaluation of Granules [6, 7, 8]

Angle of Repose

The angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

Tan θ= h/r

Where,
h and r are the height and radius of the powder cone.

Bulk Density

Both loose bulk density and tapped bulk density were determined and calculated by using the following formulas.

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

Carr's index (%) = [TBD-LBD] X 100 / TBD

Where, TBD is Tapped bulk density
LBD is loose bulk density
The physical properties of granules were shown in Table 3.

Evaluation of Tablets [6, 7, 8]

Post Compression Parameters

A. Thickness and Diameter

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm.

B. Hardness

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero, load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm^2.

C. Friability (F)

Tablet strength was tested by Roche friabilator. Pre weighed tablets were allowed for 100 revolutions (4min), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets.

$$F = \frac{(W\ initial) - (W\ final)}{(W\ initial)} \times 100$$

D. Weight Variation

Randomly selected 20 tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods shown in Table 5 and 6.

E. Uniformity of Drug Content

Weigh and powder 20 tablets. Weigh accurately a Quantity of the powder equivalent to 100 mg of Flurbiprofen, transfer to a 250 ml volumetric flask. Add about 150 ml of 7.4 Phosphate buffer. Shake well and sonicate it for 25-30

min. Make up the volume up to 250 ml with 7.4 Phosphate buffer Filter the solution, take 10 ml of filtrate in 100 ml volumetric flask and make up the volume with 7.4 Phosphate buffer Measure the absorbance, of the resulting solution at the maxima at about 246 nm spectrophotometrically. Measure the concentration of drug in tablet powder using following equation:

Cu/Cs = Au/As * dilution factor

Cu = Concentration of unknown sample,
Cs = Concentration of Standard sample
Au = Absorbance of unknown sample
As = Absorbance of standard sample. [9]

F. *In-Vitro* Dissolution Study

Dissolution tests were performed in a USP Dissolution Test Apparatus II (Paddle method) at 37 ± 0.5°C. The Paddles were rotated at a speed of 100 rpm. The prepared tablets of Flurbiprofen tablets were placed in the dissolution vessel containing 0.1 N HCl solutions (pH 1.2) for 2 hrs. These were then transferred to phosphate buffer (pH 7.4) and continue dissolution. 5 ml of solution were withdrawn at different time intervals, filtered through 0.45 µm filter paper and the content of Flurbiprofen was determined spectrophotometrically at a wavelength of 246nm. At each (hour) time of Withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask. On the basis of release studies the formulation which gave desired twice a day release of Flurbiprofen was chosen as the optimized formulation. The dissolution profiles of different formulations are shown in figure 11 and 12. Among different formulations F12, F11, F10 were found to be better formulations, they followed the sustained release for long period of time in the following order **F12 > F11> F10.**

Drug Release Kinetics

To determine the mechanism of drug release from this formulation, the drug release data of *in-vitro* dissolution study was analyzed with various kinetic equations.

The data were treated according to:

1. Zero order kinetic model – Cumulative % drug released versus time.
2. First order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model – Log cumulative percent drug released versus log time.

Stability Study

The optimized formulation was subjected to stability at 25^0 C ± 2^0 C / 60% ± 5% RH, 30^0 C ± 2^0 C / 65% ±5% RH and 40^0 C ± 2^0 C / 75% ± 5% RH for period of 90 days. After each month tablet sample was analyzed for physical characteristics and drug release profile. The optimized formulation was subjected to stability at 25^0 C ± 2^0 C / 60% ± 5% RH, 30^0 C ± 2^0 C / 65% ±5% RH and 40^0 C ± 2^0 C / 75% ± 5% RH for period of 90 days. After each month tablet sample was analyzed for physical characteristics and drug release profile. [10]

RESULTS AND DISCUSSION

Preformulation studies

a) Melting point determination

Melting point of Flurbiprofen was found to be in the range 133^0 C, which complied with standards limits range131-133^0 C, indicating purity of the drug sample.

b) Solubility

Flurbiprofen is low soluble in water. It is soluble in DMSO (50 mg/ml), methanol (50 mg/ml), ethanol (~100 mg/ml), DMF (~100 mg/ml).

c) Compatibility study

Compatibility studies were performed using FTIR spectrophotometer.

Table 1. Composition of matrix tablet of Flurbiprofen with different polymer Concentrations

Formulation Code	F1	F2	F3	F4	F5	F6
Flurbiprofen	200	200	200	200	200	200
Xanthan gum	50	75	100	-	-	-
Karayagum	-	-	-	50	75	100
HPMC K 100	-	-	-	-	-	-
Ethyl cellulose	-	-	-	-	-	-
PVP K 30 (5%)	25	25	25	25	25	25
MCC	220	195	170	220	195	170
Magnesium sterate	3	3	3	3	3	3
Talc	2	2	2	2	2	2

Table 2. Composition of matrix tablet of Flurbiprofen with different polymer concentrations.

Formulation Code	F7	F8	F9	F10	F11	F12
Flurbiprofen	200	200	200	200	200	200
Xanthan gum	-	-	-	-	-	-
Karayagum	-	-	-	-	-	-
HPMC K 100	50	75	100	-	-	-
Ethyl cellulose	-	-	-	50	75	100
PVP K 30 (5%)	25	25	25	25	25	25
MCC	220	195	170	220	195	170
Magnesium sterate	3	3	3	3	3	3
Talc	2	2	2	2	2	2

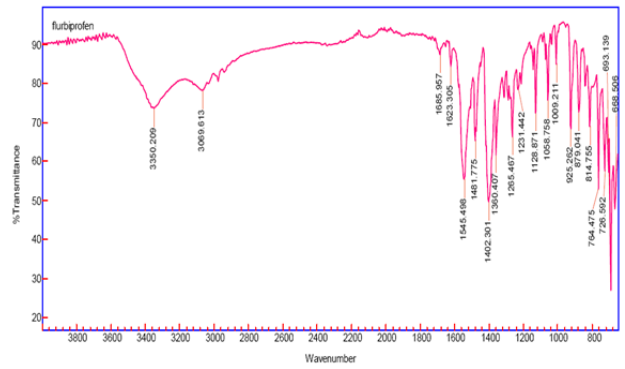

Figure: 1; FTIR of pure drug Flurbiprofen

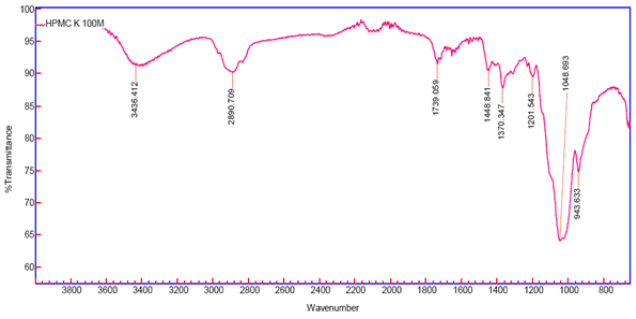

Figure 2; FTIR of HPMC K100 M

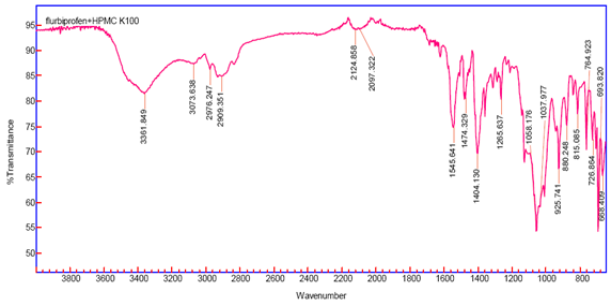

Figure 3; FTIR of HPMC K 1OOM + Drug (1:1)

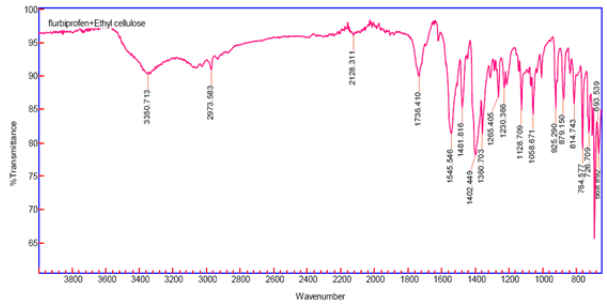

Figure 4: FTIR of Ethylcellulose + Drug (1:1)

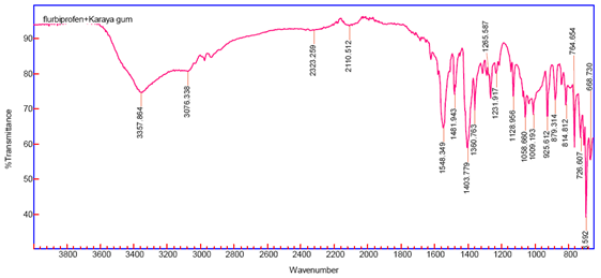

Figure 5: FTIR of Karaya gum + Drug (1:1)

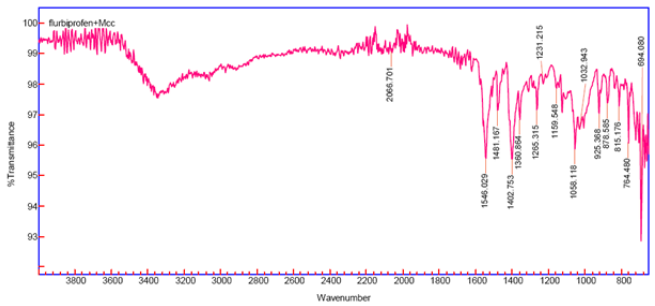

Figure 6: FTIR of MCC+ Drug (1:1)

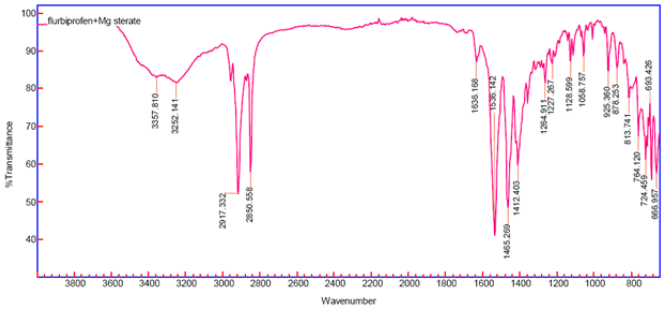

Figure 7: FTIR of Magnesium sterate+ Drug(1:1)

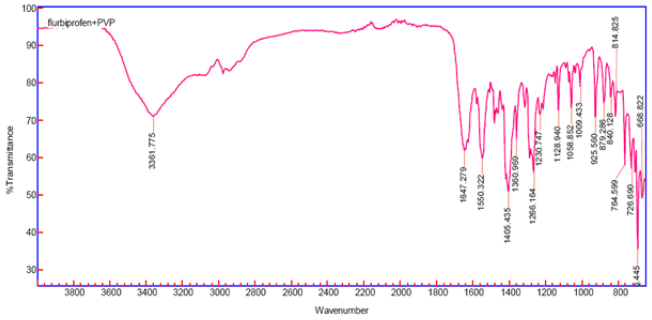

Figure 8: FTIR of PVP + Drug (1:1)

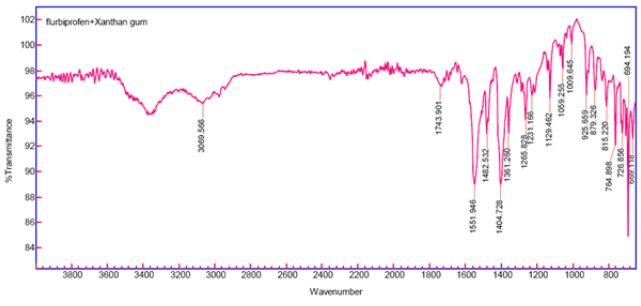

Figure 9: FTIR of Xanthan gum + Drug (1:1)

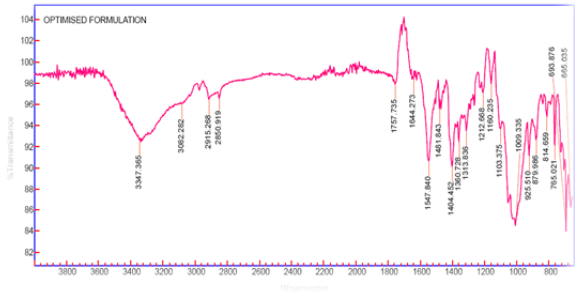

Figure 10:Optimised formula containing Drug (F-12)

Evaluation of Pre-Compression Parameters

Pre-compressional parameters of Flurbiprofen blends were evaluated for bulk density, tapped density, angle of repose, compressibility index shown in Table 3 & 4. The Bulk densities were found to be in the range of 0.43 to 0.48 gm/cc, Tapped densities were in the range of 0.50 to 0.54 gm/cc, Compressibility index were in the range of 7.07 to 12.42 % and Angle of repose were found to be between 24.30 to 27.53 (Table 3& 4).

Evaluation of Post Compression parameters

The punches used to compress the tablets were 11mm, standard cancave shaped. The shape and size of the tablets were found to be within the limit. Thicknesses of the tablets were found to be in the range of 3.78 to 3.93mm. The results are given in the Table No.5and 6.The hardness of the tablets was found to be in the range of 5.5 to 6.6 Kg/cm^2. It was within the range of monograph specification. . The friability of the tablets was found to be less than 1% and it was within the range of standard specification. The drug content of the tablets was found to be in the region of 97.23% to 99.62% it was within the range of monograph of specification. Weight variation is pass the limit and it found to be within the range of monograph of specification. (Table 5 & 6).

Drug release studies:

In vitro release studies were carried out for all the formulations as per USP XXII tablet dissolution tester employing paddle at 50rpm using 900ml 0.1N HCL for 2 hours an continue the dissolution with 7.4 phosphate buffer as a dissolution medium up to remaining hours. The results were evaluated for 12 hours, as per the results of dissolution study formulations F-1, F-2, F-3, F-4, F-5, F-6, F-7 ,F-8, F-9 ,F-10 F-11 ,F-112 however showed 85.62%, 97.54%, 91.25%, 97.35%, 98.43%, 94.43%, 97.83%, 98.96%, 94.78%, 95.3%, 98.41%, 97.23% release over a period of 12 hours.

Formulation F-5, F-11 failed to sustain release beyond 11 hours, among all the formulations, F-1, F-2, F-3, F-4, F-6, F-7, F-8, F-9, F-10 shows 85.62%, 97.54%, 91.25%, 97.35%, 94.43%,9 7.83%, 98.96%, 94.78% and 95.30% but does not showed sustained release till the end of 12 hours. Hence they were not suitable formulations for sustaining the drug release. However the percentage of drug release was maximum. It was found that the cumulative percentage of drug release decreases with increase in the polymer concentration. The dissolution studies were carried out for 12 hours. As per the result of dissolution study formulation F-5 and F-11 showed reasonable release 98.43% and 98.41% respectively. F-12 showed good drug release profile 97.23% they showed excellent matrix integrity during the period of study, when compare to other formulations. Based on all these results, formulation F-12 is selected as the optimized formulation with 97.23% drug release. (Figure 11 and 12).

Kinetics studies.

Correlation coefficients of different mathematical models for formulations F- 1 to F-12

The release data fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetics data of all formulations F1-F12 could be best expressed by zero order equations as the plots shows highest linearity(0.968 to 0.995)than first order(0.636 to 0.983) The n values obtained from korsmeyer peppas plots range from (0.946 to 0.997) indicates that mechanism of release formulations F1 to F12 was anomalous (non Fickian) diffusion.(Table No.7)

Table 3: Evaluation of Pre Compression parameters

Formulations	Bulk Density* (g/ml)	Tapped bulk* density (g/ml)	Carr's index (%)	Angle of repose*
F1	0.48+0.00	0.53+0.00	9.66+1.33	26.21+1.40
F2	0.48+0.00	0.53+0.01	10.26+0.78	26.03+1.25
F3	0.46+0.00	0.51+0.01	10.27+1.35	25.62+1.43
F4	0.45+0.00	0.50+0.01	9.32+1.63	27.53+1.16
F5	0.45+0.01	0.50+0.01	11.84+0.75	26.77+1.39
F6	0.45+0.00	0.50+0.01	9.78+1.48	24.32+1.14

Table 4: Evaluation of Pre Compression parameters

Formulations	Bulk Density* (g/ml)	Tapped bulk* density (g/ml)	Carr's index (%)	Angle of repose*
F7	0.43 ± 0.001	0.54 ± 0.016	7.07±1.39	27.33±1.74
F8	0.46 ± 0.006	0.53 ±0.011	10.20±1.44	26.71±1.14
F9	0.47 ± 0.003	0.54 ± 0.013	10.42±1.36	27.33±1.15
F10	0.46±0.004	0.51±0.016	9.74±1.40	27.20±1.18
F11	0.44 ± 0.005	0.53 ± 0.010	9.38±1.32	26.12±1.42
F12	0.48 ±0.004	0.54± 0.017	12.42±1.43	24.30±1.44

Table 5: Evaluation of Post Compression parameters

Parameters	Formulation code					
	F1	F2	F3	F4	F5	F6
Thickness* (mm)	3.91±0.16	3.88±0.13	3.93±0.15	3.90±0.01	3.89±0.09	3.92±0.14
Hardness* (kg/cm^2)	5.6±0.09	6.1±0.1	6.2±0.06	6.1±0.18	5.9±0.20	5.8±0.06
Friability*(%)	0.23±0.09	0.17±0.22	0.36±0.10	0.31±0.16	0.30±0.13	0.18±0.116
Weight variation	Pass	pass	pass	Pass	pass	pass

Table 6: Evaluation of Post Compression parameters

Parameters	Formulation code					
	F7	F8	F9	F10	F11	F12
Thickness* (mm)	3.78±0.06	3.85±0.02	3.89±0.07	3.93±0.05	3.99±0.06	3.92±0.02
Hardness* (kg/cm^2)	5.5±0.11	6.3±0.08	6.6±0.06	6.1±0.15	6.2±0.20	5.9±0.08
Friability* (%)	0.33±0.19	0.32±24	0.31±0.10	0.35±0.31	0.29±0.12	0.28±0.31
Weight variation	Pass	pass	pass	Pass	pass	pass

Table 7: Correlation coefficients of different mathematical models for formulations F- 1 to F-6

Formulation Code	Zero Order R^2	First Order R^2	Higuchi R^2	Peppas- model	
				R	Slope n
F1	0.995	0.660	0.984	0.997	0.850
F2	0.987	0.954	0.983	0.969	0.773
F3	0.983	0.975	0.992	0.995	0.674
F4	0.969	0.934	0.979	0.977	0.845
F5	0.990	0.636	0.962	0.989	0.847
F6	0.986	0.706	0.932	0.946	0.734

Table 8: Correlation coefficients of different mathematical models for formulations F- 7 to F-12

Formulation Code	Zero Order R^2	First Order R^2	Higuchi R^2	Peppas- model	
				R^2	Slope n
F7	0.991	0.692	0.943	0.987	0.874
F8	0.968	0.971	0.990	0.961	0.782
F9	0.995	0.982	0.975	0.988	0.920
F10	0.995	0.935	0.965	0.983	0.823
F11	0.994	0.947	0.962	0.981	0.807
F12	0.991	0.983	0.980	0.992	0.841

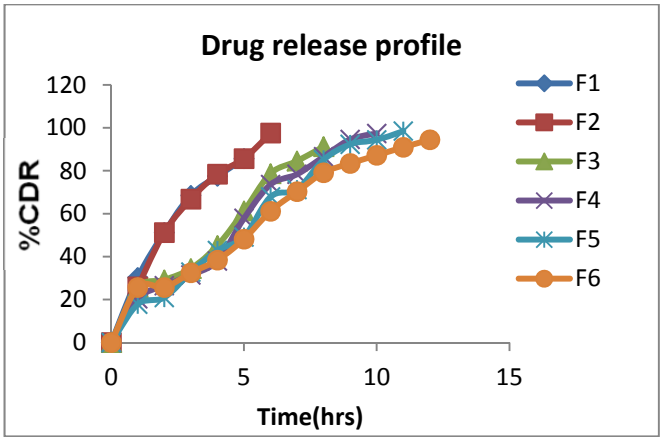

Fig: 11 Drug release profile for formulations F1-F6.

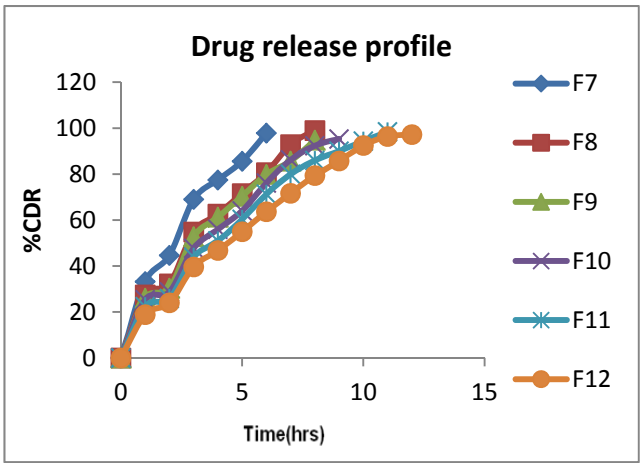

Fig: 12 Drug release profile for formulations F7- F12.

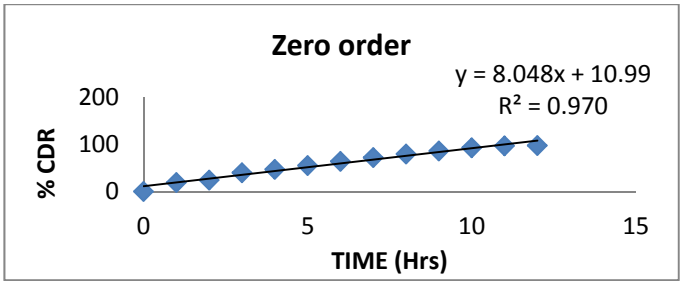

Fig: 13.Zero order equation for optimised F-12 formulation

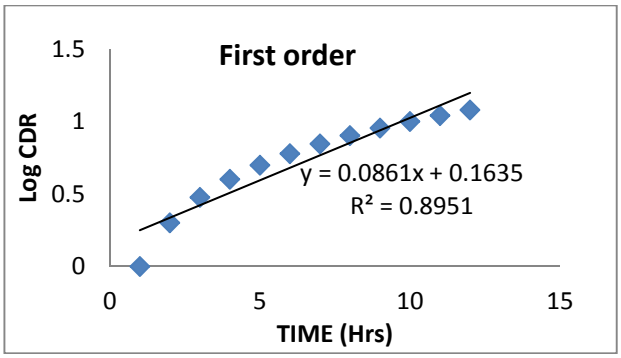

Fig: 14 first order equation for optimised F-12 Formulation.

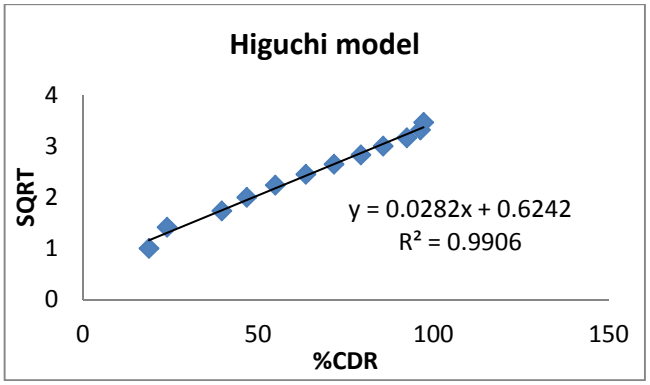

Fig: 15: Higuchi Equation for optimised F-12 formulation

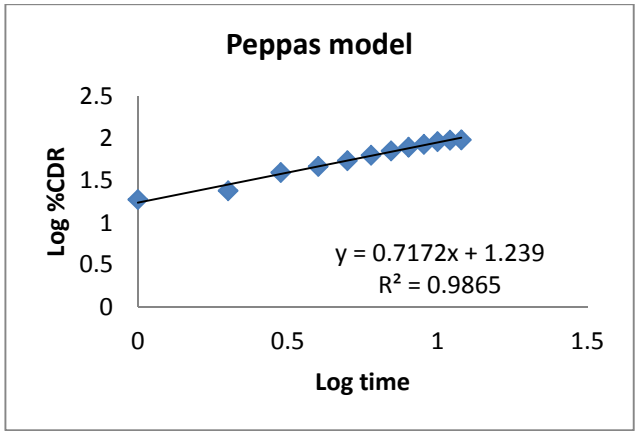

Fig: 16: Korsmeyer's Peppas Equation for optimised F-12 Formulation

Table 9: Physical appearance of optimized formulation after stability studies.

TEMPERATURE AND RELATIVE HUMIDITY	FORMULATION F-12								PARAMETERS
	Days								
	0	15	30	45	60	75	90	105	
25^0C± 2^0 C / 60% ± 5% RH	No change								Physical appearance
35^0C± 2^0 C / 60% ± 5% RH									
40^0C± 2^0 C / 60% ± 5% RH									

Table: 10 Hardness and friability of optimised formulations after stability studies.

No. of Days	Formulation F-12					
	Friability (%)			Hardness (Kg/cm^2)		
	25^0 C /60% RH	30^0 C /65% RH	40^0 C /75% RH	25^0 C / 60% RH	30^0 C /65% RH	40^0 C /75% RH
0	0.28	0.38	0.41	6.7	6.6	6.4
15	0.31	0.44	0.48	6.7	6.5	6.4
30	0.37	0.50	0.56	6.6	6.4	6.3
45	0.42	0.57	0.62	6.4	6.3	6.2
60	0.49	0.60	0.66	6.3	6.1	6.0
75	0.53	0.69	0.71	6.2	6.2	6.0
90	0.61	0.72	0.74	6.0	5.8	5.7

Table11: % Drug release and Drug content of optimized formulation after stability studies.

No. of Days	Formulation F-12					
	% Drug release			Drug content (%)		
	25^0C /60% RH	30^0C /65% RH	40^0C /75% RH	25^0C / 60% RH	30^0C /65% RH	40^0C /75% RH
0	99.54	97.34	97.28	99.26	99.26	99.26
15	98.19	97.10	97.04	99.16	99.10	99.04
30	98.10	97.0	98.0	99.06	98.96	98.86
45	98.0	97.98	97.94	98.86	98.88	98.74
60	97.0	97.89	98.87	98.80	98.66	98.63
75	97.81	97.78	98.72	98.69	98.52	98.48
90	97.80	97.76	97.69	97.50	97.34	97.28

Stability studies

The stability studies for optimized formulation F12 was carried out by accelerated stability conditions & study of various parameters carried out at 0, 30, 60, 90 days of intervals and the results found satisfactorily, revealed that the optimized formulation was stable under accelerated condition.

CONCLUSION:

In this study matrix tablet of Flurbiprofen was prepared by wet granulation technique, using xanthan gum, karaya gum, HPMCK100M, ethyl cellulose polymers as retardant. Low permeable nature of ethyl cellulose played a major role in retarding the drug release. The drug and other excipients and also the optimized formulation was evaluated by FTIR.

It showed there is no much interaction between drug and polymers also with optimised formula F-12. The formulations F-12 showed good drug release with good matrix integrity. Different parameters like hardness, friability, weight variation, drug content uniformity, *in-vitro* drug release etc, were evaluated for all the formulations. Based on these results formulation F-12 was found to be the most promising formulation. The optimized formulation F-12 follows zero order, its regression coefficient values were ranges from (0.968 to 0.995).The optimised formulation follows anomalous (non Fickian) diffusion (Table No.7 & 8), this confirms that the drug release through the matrix was diffusion. Stability studies were conducted for the optimized formulations as per ICH guidelines for a period of 90 days which revealed the stability of the formulations. The results suggest that the developed sustained-release tablets of Flurbiprofen could perform better than conventional dosage forms, leading to improve efficacy and better patient compliance. Thus the aim of this study was achieved. Further preclinical and clinical studies are required to evaluate the efficacy of these formulations of Flurbiprofen in the treatment of inflammation and pain caused by rheumatoid arthritis.

ACKNOWLEDGEMENT

The authors are thankful to the Management, Sree Siddaganga College of Pharmacy, Tumkur for providing necessary facilities to carry out this work.

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