International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.2, No.1, pp 361-367, Jan-Mar 2010

FORMULATION AND CHARACTERIZATION OF ALGINATE MICROBEADS OF FLURBIPROFEN BY IONOTROPIC GELATION TECHNIQUE

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Abstract: Flurbiprofen is a non-steroidal anti-inflammatory drug that can used for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis etc. its shorter biological half life (3 – 4.5 hrs) necessitates that it to be administered in frequent doses of 50 – 100mg. The main objective of this study was to develop suitable microparticulate system of Flurbiprofen for controlled release delivery system by varying the alginate, $CaCl_2$ and HPMC concentrations. In the present work Flubriprofen microbeads were formulated being sodium alginate by ionotropic gelation technique. Prepared beads were evaluated for granulometric studies, micromeretic, scanning electron microscopy, drug entrapment efficiency and in-vitro dissolution studies etc. The prepared beads were free flowing and white in colour. The drug loaded beads showed 83.6 – 98.2 % drug entrapment, which was found to increase with increase in sodium alginate concentration. Scanning electron microscopy revealed that the beads were spherical and rough in structure. The flow property of the all the batches of prepared microbeads were estimated by angle of repose in the range of $22^0 30 – 32^0 20$. *In vitro* drug release study of these microbeads indicated controlled release for Flurbiprofen 84.54 – 97.74 % release at the end of 10 h. Hence the observation of all results of the different batches fifth and sixth showed controlled release action and improved drug availability. The release of Flurbiprofen was found to be affected by both concentration of polymers such as sodium alginate and HPMC. By the observation of accelerated stability studies sixth batch formulation was found to be best formulation. From this study, it could be concluded that the spherical and free flowing microbeads of Flurbiprofen could be successfully prepared by ionotropic gelation technique with high entrapment efficiency and prolonged release characteristics.

Keywords: Flurbiprofen, Microparticulate system, Hydroxyl propyl methyl cellulose(HPMC), Oral sustained release systems, Angle of Repose.

Introduction

Oral sustained release dosage forms (SRDF's) have been developed for the part three decades due to their considerable therapeutic advantages[1, 2]. There are many methods to achieve controlled release of drug from the dosage form. Although gel forming ability by alginate salts is simple way of obtaining particulate drug carriers. Alginate salts are known to form a reticulated structure when in contact with calcium ions and their characteristic has been used to produce sustained release particulate systems for a variety of drugs. The preferential use for alginate gel beads in the delivery of low solubility or macromolecular drugs has been suggested. Successful attempts involving the cross linking of sodium alginate alone (or) with ovalbumin (or) gelatin alone, using aldehydes; have also been reported. However the technique utilized in these studies either may cause high degree of particle

aggregation (or) involve the use of methanol as a solvent.

Flurbiprofen is a non-steroidal anti-inflammatory drug that can used for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis etc. its short biological half life (3 – 4.5 hrs) necessitates that it to be administered in frequent doses of 50 – 100mg[3, 4]. The main objective of this study was to develop suitable microparticulate system of Flurbiprofen for controlled release delivery system by varying the alginate, $CaCl_2$ and HPMC concentrations.

Materials and methods

Flurbiprofen I.P was obtained as a gift sample from the Halmak pharmaceuticals Pvt. Ltd, Secunderabad. Hydroxy propyl methyl cellulose, Sodium alginate, Calcium chloride and petroleum ether obtained commercially from S.S.R Enterprises, Tirupati, Andhra Pradesh, India.

Preparation of Microbeads [5, 6,7]

Microbeads of Flurbiprofen were prepared by ionotropic gelation technique. Accurately Weighed quantity of flurbiprofen was added to 50 ml of sodium alginate solution and thoroughly mixed with a magnetic stirrer at 400rpm[8, 9]. For the formation of microbeads, 50 ml of this solution was extruded dropwise from a needle in to 100ml aqueous calcium chloride solution and stirred at 100 rpm for 10mits[10]. The obtained microbeads were washed with water and dried at 70^0C for 6 hrs in an oven. Total Two sets of microbeads were prepared in first set microbeads of flurbiprofen were prepared using only sodium alginate in different concentrations. In second set of microbeads are prepared in a combination of coating polymers like Hydroxy propyl methyl cellulose and sodium alginate combination[11, 12]. The detailed composition of the various formulations, were mentioned in the table No: - 01.

Characterization of microbeads

Granulometric studies[6]

Particle size distribution pattern was determined by sieve analysis on mechanical sieve shaker, using different meshes (12, 16, 20 and 30) of American society of testing materials . The size distribution of microparticles was reported in table No: - 02.

Scanning electron microscopy[10, 11]

Morphological details of the specimens were determined by using a scanning electron microscope (SEM), model ISM 35 CF, JEOL, japan.

Flow properties of Beads[20]

The flow properties of prepared microbeads were investigated by measuring the Angle of Repose by using fixed funnel method. Depend upon these values we can assume the flow properties of the microbeads. The Angle of Repose Values were mentioned in the table No:- 03.

Angle of repose $(\theta) = \tan^{-1} h/t$

Drug entrapment efficiency[13, 16]

Drug entrapment efficiency of Flurbiprofen microbeads was performed by accurately weighing 50mg of microbeads and suspended in 100 ml of simulated intestinal fluid of pH 7.2±0.2 and it was kept on a side for 24 hours. Then, it was stirred for 15 mins and filtered. After suitable dilution, Flurbiprofen content in the filtrate was analyzed Spectrophotometrically at 247 nm using U.V.Spectrophotometer. The drug entrapment efficiency values were mentioned in the table No: 03.

Estimation of Flurbiprofen[18]

About 25 mg of microbeads were weighed and added to 50 ml of phosphate buffer (pH 7.4). The resulting mixture was agitated on mechanical shaker for 24 hrs, then solution was filtered and the drug content was estimated at 247 nm spectrophotometrically after suitable dilution.

In-vitro release studies[14, 15, 18, 21]

In-vitro release studies of prepared microbeads were carried out using phosphate buffer (pH 7.4) using USP- XXII apparatus at 100 rpm, maintained at a temperature of 37 ± 1^0C for a period up to 10 hrs. Each time interval 5 ml of sample was withdrawn, at the same time 5 ml of fresh dissolution media was added to maintain sink condition. The withdrawn samples were suitably diluted and measure the absorbance at 247 nm Spectrophotometrically. Depend upon the absorbance values; we got the concentration values from the standard calibration curve. Then calculated the cumulative percentage drug release at regular time intervals. The *In-Vitro* drug release studies results were mentioned in the table No:- 04 and these values graphically represented in the graph No:- 1 and 2.

Stability studies for best formulation[22, 23]

The formulations were stored in oven at 37 ± 1^0C and 60 ± 1^0C for period of six weeks. The samples were analyzed for drug content every week by Spectrophotometrically at 247 nm. The accelerated stability studies of F-5 and F-6 formulations assay results were mentioned in the table No: 05.

Results and discussion

Microbeads of Flurbiprofen were prepared (six formulations) by ionotropic gelation technique and different evaluation parameters were assessed, with a view to obtain oral controlled release of flurbiprofen. In the granulometric study, it was observed from the Table No:- 02, that about 65 – 81 percent of microbeads were of 16 mesh size, which proves the flexibility of the method. In this prepared flurbiprofen

microbeads, with the increase in HPMC percentage the distribution of particle size shifts to the higher sieve size due to increase in the internal viscosity of the medium. The flow property of the microbeads was checked by using the angle of repose method. Acceptable range of angel of repose was found to be $20 - 35^0$. All the formulations angle of repose values were showed on the table no:- 03. The drug content of prepared formulations was found to be in the range of 87.25 – 97.87%. The drug entrapment efficiency of all the formulations were in the range between 83.6 – 98.2. The results of the each formulation drug entrapment efficiency values were shown in table No:- 03. Drug entrapment efficiency of microbeads values of the different formulations were observed and reported, as increases the concentration of sodium alginate and hydroxyl propyl methyl cellulose automativally drug entrapment efficiency also increases. The In-Vitro drug release studies of the different formulations cumulative percentage drug release was observed in the range of 84.54 – 97.74. The In-Vitro drug release profile was mentioned in the table No:- 04. The formulations F1, F2, F3 containing 1, 2, 3% sodium alginate respectively showed a release of 97.74, 94.35 and 92.55 % after 10 hours. This shows that more sustained release was observed with the increase in percentage of sodium alginate. The formulation F4, F5 and F6 containing 1, 2 and 3 % hydroxyl propyl methyl cellulose showed a release of 90.45, 87.65 and 84.54 % after 10 hours. This indicates that the release rate is further retarded due to addition of increasing concentration of HPMC. The Best formulation was observed as F-6, by the observation of all results of the six formulations of flurbiprofen microbeads. The prepared best formulation was observed the shape of the microbeads by using scanning electron microscopy, so the shape of the prepared microbeads was observed as spherical shape and it was shown on the figure No:-01. Accelerated stability studies of the fifth and sixth formulations were showed in the table No:-05, depend upon this results we concluded that sixth formulation was found to be best formulation.

Conclusion

Oral controlled release of flurbiprofen can be successfully achieved by ionotropic gelation technique using a combination of sodium alginate and HPMC as polymers. Prepared microbeads shown higher drug entrapment efficiency and prolonged release characteristics. Flurbiprofen release from microbeads was influenced by alginate and HPMC concentration. Among the dfferent formulations of Microbeads, F-5 and F-6 were estimated as best formulations because these formulations drug release was observed that drug was released in controlled manner. The comparison of these two formulations F-6 was found to be as a best formulation.

Table No: 01, Composition of alginate Microbeads of Flurbiprofen.

Formulation Code No	Sodium alginate (W/V)	Calcium Chloride	HPMC (w/v)	Drug (Flurbiprofen) In mg
F – 1	1%	6%	--	200
F – 2	2%	6%	--	200
F – 3	3%	6%	--	200
F – 4	4%	6%	1	200
F – 5	4%	6%	2	200
F – 6	4%	6%	3	200

Table No:- 02, Percentage weight remained on various sieve size.

Batch No	#12 (1.68 mm) 1190 – 1680 µm	#16 (1.19 mm) 840 –1190 µm	#20 (0.84 mm) 590 – 840 µm	#30(0.59 mm) 297 – 590 µm
F-1	17.6	6.56	8.23	4.65
F-2	14.8	8.2	9.56	3.76
F-3	13.8	8.56	7.65	2.84
F-4	17.65	8.9	5.87	1.85
F-5	23.67	9.4	5.12	1.56
F-6	27.52	9.85	4.95	0.85

Table No: 03, Drug entrapment efficiency of Microbeads and angle of repose

S.No	Formulation Code	% Drug Entrapment Efficiency	Angle of Repose
1	F – 1	83.6	$32^0 20$
2	F – 2	89.5	$29^0 30$
3	F – 3	91.4	$24^0 50$
4	F – 4	93.4	$22^0 30$
5	F – 5	94.6	$23^0 60$
6	F – 6	98.2	$24^0 75$

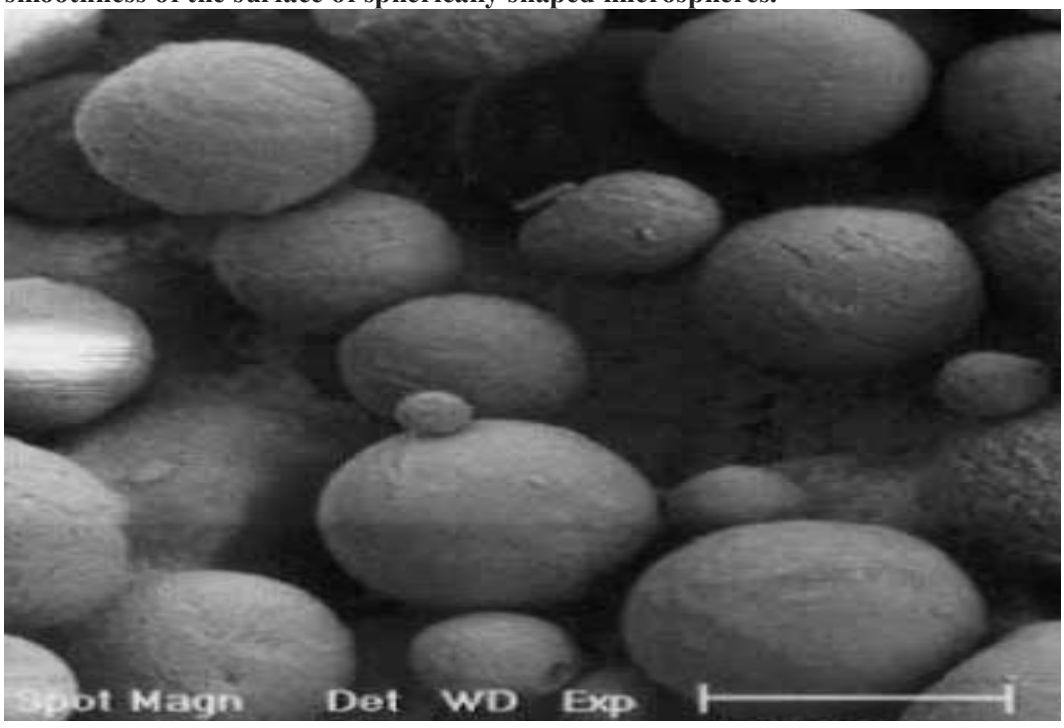
Table No: 04, *In-vitro* drug release studies for prepared Flurbiprofen Microbeads

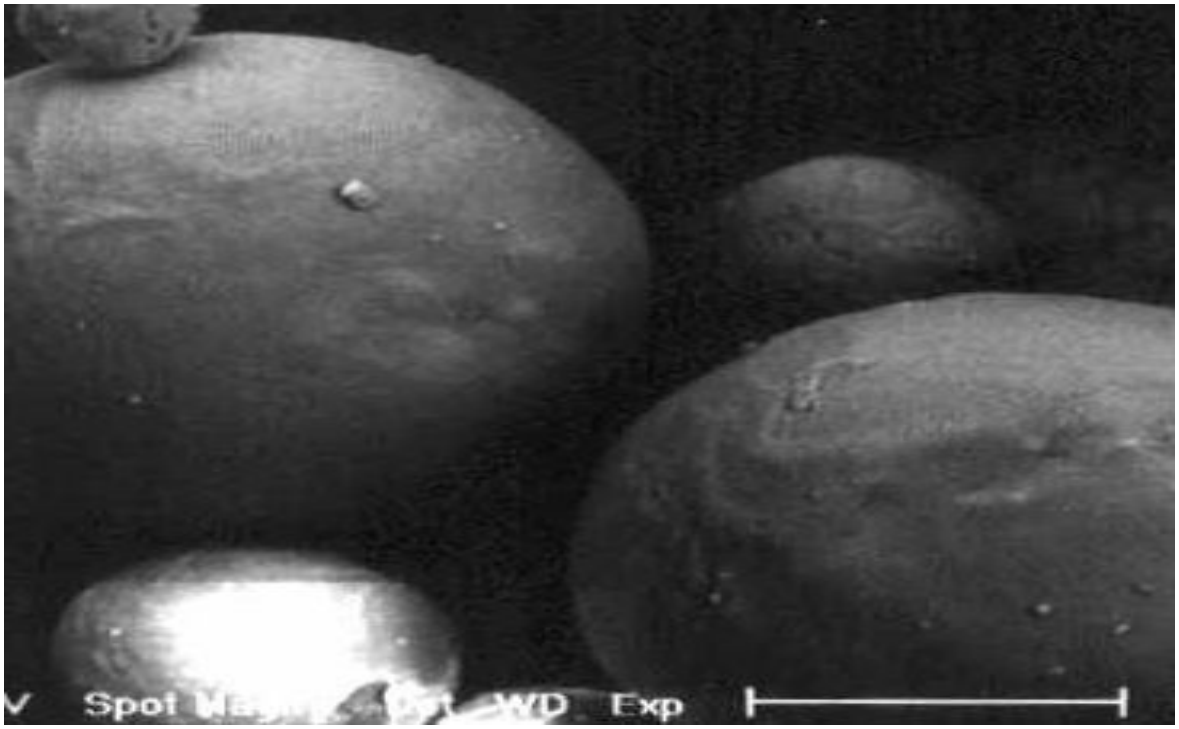
Time in hours	Cumulative Percentage Drug Release					
	F - 1	F – 2	F - 3	F - 4	F - 5	F – 6
0	0	0	0	0	0	0
2	14.74	13.56	13.21	12.85	12.25	11.56
4	32.55	31.51	29.85	28.45	27.56	26.54
6	54.73	52.45	51.75	50.65	49.65	47.56
8	72.45	71.32	70.34	69.95	65.75	64.85
10	97.74	94.35	92.55	90.45	87.65	84.54

Table No: 05, Results of assay for formulations F-5 and F-6 after accelerated stability studies.

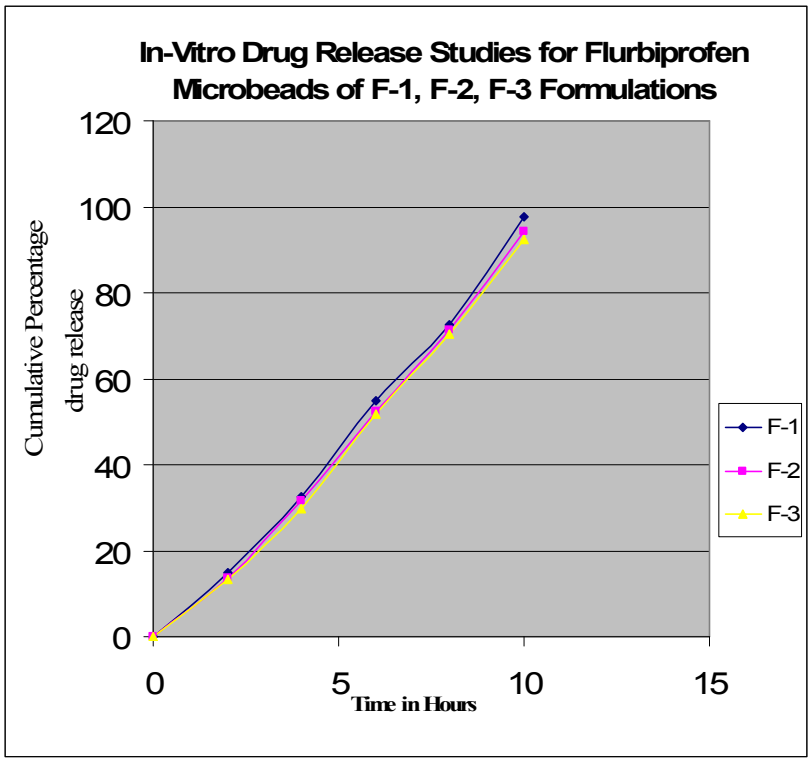
Days	F – 5		F – 6	
	37^0	60^0	37^0	60^0
1	96.46	93.54	97.54	96.76
7	94.50	93.23	97.16	96.14
14	93.50	92.65	96.85	95.85
21	93.23	92.25	96.25	95.54
38	92.89	91.73	95.75	94.57
45	92.54	91.25	95.21	94.15

Figure No:- 01, Scanning electron microphotographs of prepared Flurbiprofen Microbeads (batch F-6): smoothness of the surface of spherically shaped microspheres.

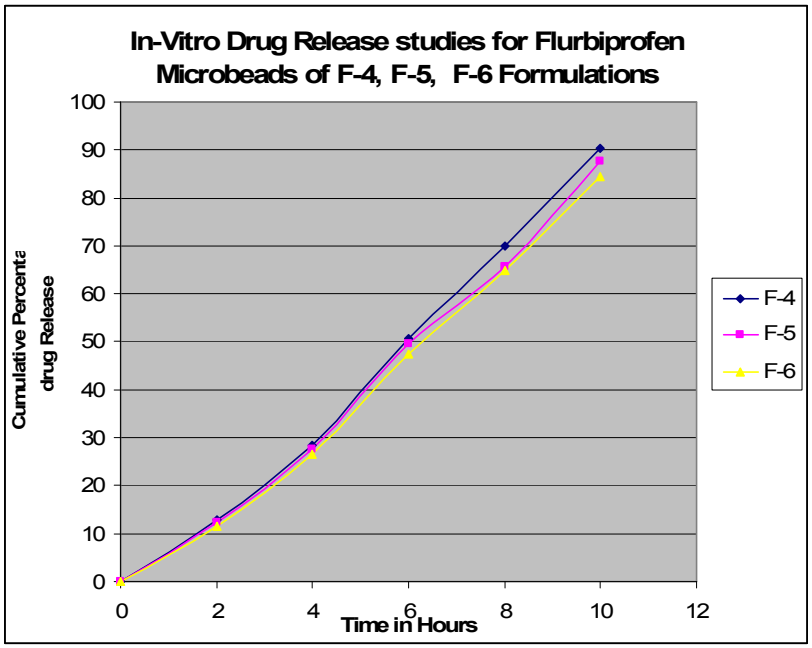




Graph No: - 01, In-Vitro drug release studies for F-1, F-2 and F-3 Formulations of flurbiprofen microbeads



Graph No: 02, In-Vitro drug release studies for F-4, F-5 and F-6 formulations of flurbiprofen microbeads



Acknowledgement

The authors are thankful to Hallmak pharmaceuticals Pvt. Ltd, Secunderabad for providing the gift sample of Flurbiprofen. The authors also thankful to S.S.R Enterprises, Tirupati, for providing the polymers and solvent systems and also thankful to management of Annamacharya College of Pharmacy for providing the all facilities for carried out this research work.

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