EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 12
282-290
Year: 2018

FORMULATION AND *IN VITRO* CHARACTERISATION OF ETODOLAC FLOATING MICROSPHERES

Md. Reshma*[1], Dr. M. Dhanalakshmi[2] and D. Ramchakradhar[3]

[1,3]Department of Pharmaceutics, KLR Pharmacy College, Paloncha.
[2]Department of Pharmaceutical Analysis, KLR Pharmacy College, Paloncha Badradri Kothagudem District, Telangana.

***Corresponding Author: Md. Reshma**
Department of Pharmaceutics, KLR Pharmacy College, Paloncha.

Article Received on 03/10/2018 **Article Revised on 23/10/2018** **Article Accepted on 13/11/2018**

ABSTRACT
Gastroretentive dosage forms have potential for use as controlled- release drug delivery systems. The aim of the present study is formulation and characterization of floating microspheres using Etodolac as a model drug for the management of Etodolac is generally prescribed for arthritis-related inflammatory pains or severe toothaches that result in the inflammation of the gums. Floating microspheres were prepared by solvent evaporation technique using Sodium alginate, Guargum, and HPMC as release retarding polymers. The floating microspheres were evaluated for percentage yield (%), Mean particle size, drug content, drug entrapment efficiency, *In vitro* Buoyancy and *in vitro* drug release studies. Compatibility studies were performed by fourier transform infrared (FTIR) technique. The prepared microspheres showed prolonged drug release of 12 h. The optimized formulation (F4) showed better drug release 97.36% for 12 hours. It was concluded that developed floating microspheres of Etodolac offers a suitable and practical approach for prolonged release of drug over an extended period of time and thus oral bioavailability, efficacy and patient compliance is improved.

KEYWORDS: Etodolac, Floating Microspheres, Sodium alginate, Guargum and Hpmc.

INTRODUCTION
To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects.[1] One such approach is using microspheres as carriers for drugs. Microsphere can be used for the controlled release of drugs, vaccines, antibiotics, and hormones.[2] Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm).[5] Microspheres are sometimes referred to as micro particles.

The oral route is considered as the most promising route of drug delivery methods of formulation and provide a number of therapeutic benefits.

Floating microspheres (Hollow Microspheres) are gastroretentive drug delivery systems based on noneffervescent approach. The word Floating syst ems, first described by Davis in 1968.

Types of FDDS
Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS:
A. Effervescent System and Non- Effervescent System.

B Methods of Preparation of Floating Microspheres
- ✓ Spray Drying
- ✓ Solvent Evaporation
- ✓ Ionic gelation method
- ✓ Single emulsion technique
- ✓ Double emulsion technique
- ✓ Phase separation coacervation technique
- ✓ Spray drying and spray congealing
- ✓ Quasi emulsion solvent diffusion

Etodolac
Similar to other NSAIDs, the anti-inflammatory effects of etodolac result from inhibition of the enzyme cycooxygenase (COX). This decreases the synthesis of peripheral prostaglandins involved in mediating inflammation. Etodolac binds to the upper portion of the COX enzyme active site and prevents its substrate, arachidonic acid, from entering the active site. Etodolac was previously thought to be a non-selective COX inhibitor, but it is now known to be 5 – 50 times more selective for COX-2 than COX-1. Antipyresis may occur by central action on the hypothalamus, resulting in peripheral dilation, increased cutaneous blood flow, and subsequent heat loss.

METERIALS AND METHODS

Meterials: Etodalac was procured from IPCA Laboratories Ltd., Mumbai, India providedby SURALABS, Dilsukunagar, Hyderebad. sodium alginate from sd, fine chemicals. Mumbai. guargam from yarrow chemical products, india. Hpmc from ONTOP Pharmaceuticals, Bangalore, india. sodium bicarbonate from CDH (P)Ltd, New Delhi, India. calcium chloride and glitaraldihide purchase from merck specalities pvt Ltd, Mumbai. Acetic acid from Loba chemi Pvt Ltd. Mumbai.

a) Methods: Determination of absorption maxima

100mg of Etodolac pure drug was dissolved in 15ml of Methanol and make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCL (stock solution-2 i.e 100µg/ml). From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). Scan the 10µg/ml using Double beam UV/VIS spectrophotometer in the range of 200 – 400 nm.

b) Preparation calibration curve

100mg of Etodolac pure drug was dissolved in 15ml of Methanol and volume make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCl (stock solution-2 i.e 100µg/ml). From this take 0.1, 0.2, 0.3, 0.4 and 0.5ml of solution and make up to 10ml with 0.1N HCl to obtain 2, 4, 6, 8, and 10 µg/ml of Etodolac solution. The absorbance of the above dilutions was measured at 225 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve.

c) Preparation of microspheres

The choice of methods for the preparation of microspheres depends on many factors such as the drug solubility, partition co efficient, Polymer composition, molecular weight etc.

The microsphere was prepared by solvent evaporation and ionic gelation technique. The 25 mg of Etodolac was dispersed uniformly in aqueous mucilage of Sodium alginate. To this dispersion desired polymer was mixed in suitable proportion. Then, gas-forming agent such as Calcium carbonate and sodium bicarbonate was separately added to the solution. The resulting solution was dropped through a 26G syringe needle into 5% (w/v) glutaraldehyde/$CaCl_2$ solution which is prepared in water containing 10% (v/v) acetic acid. The process done with constant stirring (600rpm) at 60-70^{o}C. The solvent is slowly evaporated. The solution containing suspend microsphere was kept for 1.5 hr. To improve the mechanical strength of the microsphere and allowed to complete the reaction to produce gas. The fully formed microsphere were collected, washed with distilled water and subsequently air dried. The composition of floating microsphere.

d) Composition of Floating Microspheres

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Etodolac	300	300	300	300	300	300	300	300	300	300	300	300
Sodium Alginate	150	300	450	600	-	-	-	-	-	-	-	-
Hydroxy propyl methyl cellulose	-	-	-	-	150	300	450	600	-	-	-	-
Guargum	-	-	-	-	-	-	-	-	150	300	450	600
Sodium bicarbonate (% w/w	50	50	50	50	50	50	50	50	50	50	50	50
Calcium chloride(% w/v	10	10	10	10	10	10	10	10	10	10	10	10
Acetic acid (%v/v)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Glutaralde hyde %	5	5	5	5	5	5	5	5	5	5	5	5

Fig. 1: Characterization of Etodolac Microspheres.

Determination of mean particle size

The particle size was measured using an optical microscope, and the mean particle size was calculated by measuring 200 particles with the help of a calibrated ocular micrometer6. A small amount of dry microspheres was suspended in purified water (10 ml). A small drop of suspension thus obtained was placed on a clean glass slide. The slide containing microspheres was mounted on the stage of the microscope and diameter of at least 100 particles was measured using a calibrated optical micrometer

Incorporation Efficiency (IE)

$$\% \text{ Incorporation efficiency} = \frac{\text{Actual drug content} \times 100}{\text{Theoretical content}}$$

Percentage Buoyancy

$$\% \text{ Buoyancy} = \frac{\text{Weight of floating microspheres} \times 100}{\text{Initial weight of microspheres}}$$

In vitro drug release study

The release rate of Etodolac from microspheres was determined using USP dissolution testing apparatus I (Basket type). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C and 100 rpm. Microspheres equivalent to 25 mg were used for the test. Aliquots (5 ml) were withdrawn at hourly intervals for 12 hours. Samples were replaced by its equivalent volume of dissolution medium. The samples were filtered through Whatman filter paper and solutions were

analyzed using UV spectrophotometer (Shimadzu 1700 UV/V is double beam Spectrophotometer Kyoto, Japan).

Micromeritic properties of microspheres

$$\text{Tapped density} = \frac{\text{Mass of microspheres}}{\text{Volume of microspheres after tapping}}$$

$$\%\text{Compressibility Index} = \left(1 - \frac{V}{V_0}\right) 100$$

Drug Release Kinetics

In order to investigate the mechanism of drug release from microspheres of different optimized batches, the release data were analyzed with the following mathematical models.

1) Zero-order equation,

$Q=Q0+k0t$

Where, Qtis the amount of drug release in time t, Q0 is the initial amount of drug in the solution (most times, Q0= 0) and k0 is the zero-order release rate.

1) First-order equation

$\ln Qt=\ln Q0+k1t$

Where, Qt is the amount of drug released in time t, Q0 is the initial amount of drug in the solution and k1 is the first-order release rate constant.

3) Higuchi s equation

$Q= kH\ t½$

Where, Q is the amount of drug release at time t, and kH is the Higuchi diffusion rate constant.

4) Koresmeyer's peppas equation

Further, to confirm the mechanism of drug release, the first 60% of drug release was fitted in Korsmeyer-Peppas model following equation,

$Mt= M\infty\ Kt$

Where, Mt is the amount of drug released at time t, M∞ is the amount of drug released after infinite time, Kt is a kinetic constant and n is the diffusional exponent indicative of the drug release mechanism. and is calculated from the slope of the plot of log of fraction of drug released.

(Mt / Mα) vs. log of time (t)

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

Drug excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of physicochemical compatibility and interactions, which helps in the prediction of interaction between drug and other excipients. In the current study 1:1 ratio was used for preparation of physical mixtures used for analyzing of compatibility studies. FT-IR studies were carried out with a Bruker, ATR FTIR facility using direct sample technique.

SEM (Scanning Electron Microscope) studies

The surface morphology of the layered sample was examined by using SEM(JEOL Ltd., Japan). The small amount of powder was manually dispersed onto a carbon tab (double adhesive carbon coated tape) adhered to an aluminum stubs were coated with a thin layer (30^0A) of gold by employing POLARON - E 3000 sputter coater. The samples were examined by SEM with direct data capture of the images onto a computer.

RESULTS AND DISCUSSION

The present work was designed to developing Floating Microspheres of Etodolac using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method

Standard graph of Etodolac in 0.1N HCL

The scanning of the 10µg/ml solution of Etodolac in the ultraviolet range (200-400 nm) against 0.1 N HCL the maximum peak observed at λ_{max} as 225 nm. The standard concentrations of Etodolac (2-10 µg/ml) was prepared in 0.1N HCL showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

Table 1: Standard curve of Etodolac in 0.1N HCL.

S.No	Concentration mcg/ml	Absorbance
1.	0	0
2.	2	0.121
3.	4	0.217
4.	6	0.334
5.	8	0.428
6.	10	0.536

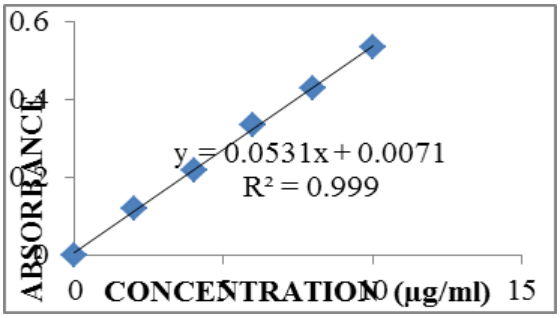


Fig. 2: Calibration curve of Etodolac in 0.1 N HCL at 225 nm.

Evaluation Parameters

Table 2: Valuation of Floating Microspheres.

Batch No	Mean Particle size(µm)	Bulk Density (gm/ml)	Tapped density (gm/ml)	Carr's Index	Hausner's ratio	Angle of repose (θ)
F1	410.32	0.525±0.11	0.619±0.02	15.32±0.09	1.197±0.07	35.24±0.07
F2	256.29	0.522±0.34	0.621±0.04	14.87±0.35	1.185±0.06	36.27±0.06
F3	453.81	0.526±0.65	0.614±0.01	15.62±0.72	1.187±0.13	34.65±0.08
F4	290.53	0.522±0.25	0.615±0.04	15.64±0.26	1.175±0.02	33.54±0.04
F5	338.56	0.516±0.24	0.622±0.05	14.96±0.15	1.186±0.03	32.21±0.01
F6	462.12	0.527±0.45	0.618±0.01	16.53±1.6	1.198±0.21	39.23±0.01
F7	459.87	0.522±0.36	0.623±0.02	14.56±0.20	1.170±0.01	31.10±0.02
F8	329.68	0.525±0.99	0.611±0.01	14.91±0.33	1.175±0.03	32.19±0.02
F9	337.61	0.517±1.05	0.617±0.03	15.66±0.10	1.185±0.15	33.28±0.01
F10	498.36	0.518±0.25	0.613±0.02	15.35±0.3	1.18±0.01	30.86±0.03
F11	381.24	0.523±0.45	0.612±0.01	14.95±0.66	1.17±0.02	31.24±0.04
F12	489.49	0.515±1.47	0.610±0.01	15.57±1.4	1.18±0.01	30.48±0.02

Micromeritic properties of Microspheres

The Micromeritic properties of different batch are shown in above table. The mean diameter of the Sodium alginate microspheres, the mean diameter of batch 1 to 12 ranges between 256.29 and 498.36 µm. The average size of the microspheres increased slightly as the amount of polymer concentration increased. The hardening agent caused a decrease in bead size as it promoted the formation of cross-links between the alginate molecules.

The tapped density of beads of different batch 1-12 ranges between 0.610±0.01 - 0.623±0.02 gm/ml respectively. The Compressibility Index ranges between 14.56±0.20 -16.53±1.6 gm/ml, shows that all the formulation preparations were good flowability. The Hausner's ratio of different batch ranges between 1.17±0.02 - 1.198±0.21. The Hausner's ratio result shows that all the preparations were good flowability.

Table 3: Result of mean Particle Size, *In vitro* Buoyancy and Encapsulation efficiency%.

Batch No:	*In vitro* Buoyancy (in sec)	Encapsulation efficiency%
F1	58.01	98.36
F2	42.36	95.22
F3	39.12	99.35
F4	61.90	97.61
F5	48.64	98.20
F6	69.45	99.48
F7	56.39	97.69
F8	68.99	99.34
F9	36.24	96.75
F10	26.87	97.58
F11	56.99	99.61
F12	45.21	97.43

Drug Entrapment Efficiency (EE) and Floating Property

The floating property of the microspheres was calculated from the fractional amount of drug and polymer density of the microspheres. As shown in above table the Floating efficiency of the sodium alginate microspheres. The floating agent sodium bicarbonate containing (batch 1-12) ranges from 26.87 and 69.45% and floating agent Calcium chloride containing formulations (batch 1-12) shows from 97.43 – 99.61.

Table 4: In vitro drug release of containing Etodolac F1 to F4 formulations.

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED			
	F1	F2	F3	F4
0	0	0	0	0
0.5	5.77	3.86	05.39	08.75
1	18.25	13.79	17.94	26.1
2	21.72	21.15	21.37	29.7
3	23.68	27.86	24.52	41.4
4	27.71	30.70	30.42	47.7
5	45.93	39.50	46.34	57.6
6	54.76	45.40	55.08	67.5
7	57.92	53.33	59.13	81
8	60.26	57.17	64.94	82.8
9	62.57	63.21	69.81	84.6
10	67.62	67.98	75.49	87.3
11	69.49	73.59	80.67	90.15
12	73.68	78.64	87.97	97.36

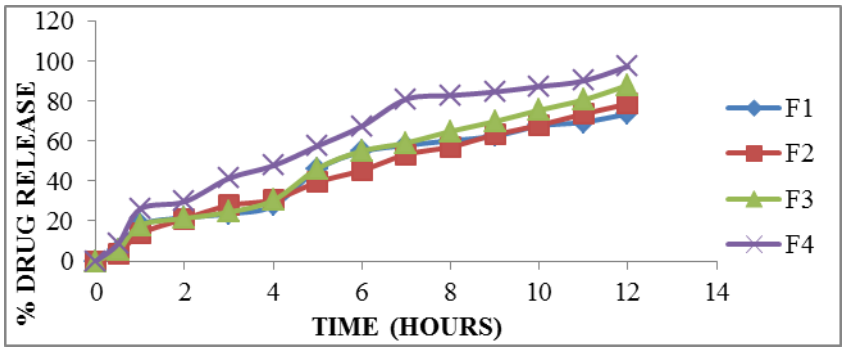


Fig. 3: Dissolution study of Etodolac Floating Microspheres (F1 to F4).

The % drug release of formulations (F1 to F4) containing Sodium Alginate depends on the concentration of polymer. The concentration of Sodium Alginate 1:0.5, 1:1, 1:1.5 and 1:2 was able to retard the drug release up to desired time. When the concentration of polymer increased to 1:1.5, 1:2 was able to retard the drug up to 12 hours. In F4 formulation 1:2 ratio (drug: polymer) ratio was maximum drug release was showed at 12 hours.

Table 5: In vitro drug release of Etodolac F5 to F8 formulations.

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED			
	F5	F6	F7	F8
0	0	0	0	0
0.5	10.6	4.46	2.68	3.58
1	20.65	16.91	14.72	11.07
2	22.63	21.50	27.77	14.16
3	26.35	23.46	31.05	27.39
4	33.21	27.89	35.85	30.54
5	39.76	46.03	41.87	30.83
6	54.76	54.70	48.02	38.40
7	60.3	58.76	55.57	41.63
8	74.23	60.98	57.76	49.48
9	78.93	64.12	62.07	56.78
10	87.0	71.95	64.59	67.15
11	89.8	78.34	66.93	71.84
12	93.10	81.28	69.31	78.69

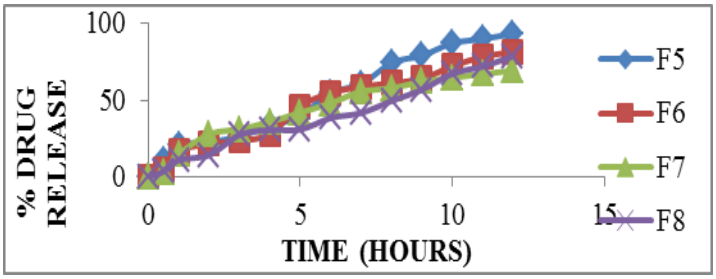


Fig. 4: Dissolution study of Floating Microspheres (F5 to F8).

The % drug release of F5 to F8 formulations depends on polymer ratio Guargum. The concentration of Hydroxy propyl methyl cellulose 1:0.5, 1:1, 1:1.5 and 1:2 ratios was excess retard the drug release up to desired time. In F5 formulations, Hydroxy propyl methyl cellulose contain 1:0.5 ratio showed maximum % drug release i.e 93.10% at 12 hours.

Table 6: *In vitro* drug release of Etodolac F9 to F12 formulations.

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED			
	F9	F10	F11	F12
0	0	0	0	0
0.5	3.86	2.85	7.98	2.9
1	13.79	16.81	19.91	20.93
2	21.15	26.80	21.66	24.31
3	27.86	27.52	31.55	27.74
4	30.70	30.58	39.68	29.74
5	39.50	38.85	46.82	38.47
6	45.40	45.12	54.75	46.18
7	53.33	49.05	71.19	49.46
8	57.17	55.73	75.62	55.42
9	60.60	56.92	79.26	57.82
10	61.75	60.60	82.89	62.07
11	75.16	67.84	85.58	65.49
12	82.64	70.18	88.25	73.49

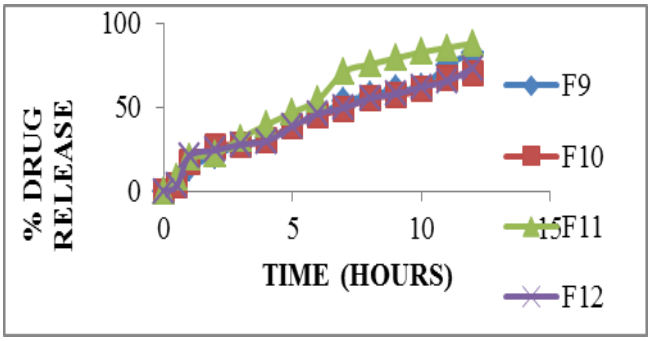


Fig. 5: Dissolution study of Etodolac Floating Microspheres (F9 to F12).

The % drug release of F9 to F12 formulations depends on polymer ratio Guar gum. The concentration of Guar gum was retard the drug released. In F11 formulations, Hydroxy propyl methyl cellulose showed maximum % drug release i.e 88.25% at 12 hours.

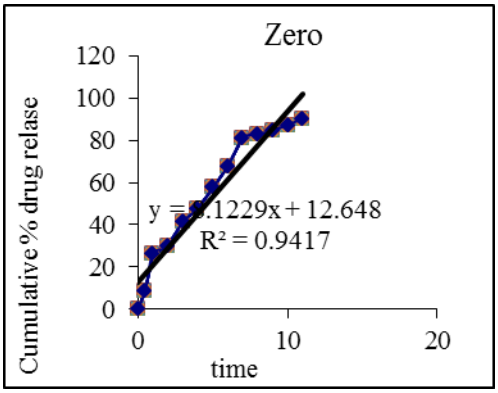
Hence based on dissolution data of 12 formulations, F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12 formulations showed better release up to 12 hours. Among these formulations F4 formulation showed the drug release (97.36%) within the specified limits. So F4 formulation is optimised formulation.

Application of Release Rate Kinetics to Dissolution Data

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Etodolac release. The data was fitted into various kinetic models such as zero, first order kinetics; higuchi and korsmeyer peppas mechanisms and the results were shown in below table.

Table 7: Release kinetics data for optimized formulation.

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	**0**	0			2.000				100	4.642	4.642	0.000
8.75	**0.5**	0.707	0.942	-0.301	1.960	17.500	0.1143	-1.058	91.25	4.642	4.502	0.140
26.1	**1**	1.000	1.417	0.000	1.869	26.100	0.0383	-0.583	73.9	4.642	4.196	0.445
29.7	**2**	1.414	1.473	0.301	1.847	14.850	0.0337	-0.527	70.3	4.642	4.127	0.514
41.4	**3**	1.732	1.617	0.477	1.768	13.800	0.0242	-0.383	58.6	4.642	3.884	0.757
47.7	**4**	2.000	1.679	0.602	1.719	11.925	0.0210	-0.321	52.3	4.642	3.740	0.902
57.6	**5**	2.236	1.760	0.699	1.627	11.520	0.0174	-0.240	42.4	4.642	3.487	1.155
67.5	**6**	2.449	1.829	0.778	1.512	11.250	0.0148	-0.171	32.5	4.642	3.191	1.450
81	**7**	2.646	1.908	0.845	1.279	11.571	0.0123	-0.092	19	4.642	2.668	1.973
82.8	**8**	2.828	1.918	0.903	1.236	10.350	0.0121	-0.082	17.2	4.642	2.581	2.060
84.6	**9**	3.000	1.927	0.954	1.188	9.400	0.0118	-0.073	15.4	4.642	2.488	2.154
87.3	**10**	3.162	1.941	1.000	1.104	8.730	0.0115	-0.059	12.7	4.642	2.333	2.308
90.15	**11**	3.317	1.955	1.041	0.993	8.195	0.0111	-0.045	9.85	4.642	2.144	2.498
97.36	**12**	3.464	1.988	1.079	0.422	8.113	0.0103	-0.012	2.64	4.642	1.382	3.260



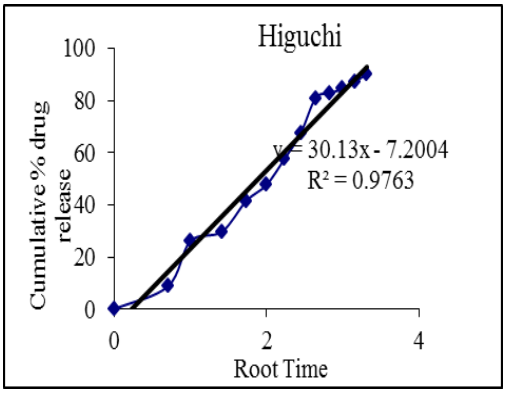
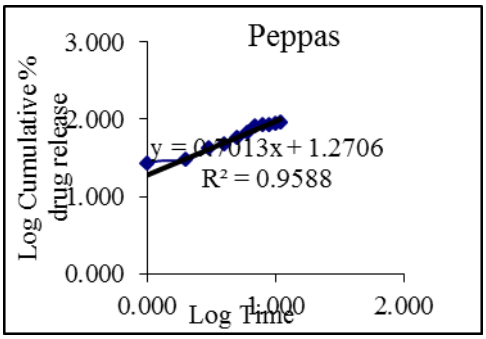


Fig. 6: Graph of Zero Order kinetics. Fig. 7: Graph of Higuchi Release kinetics.



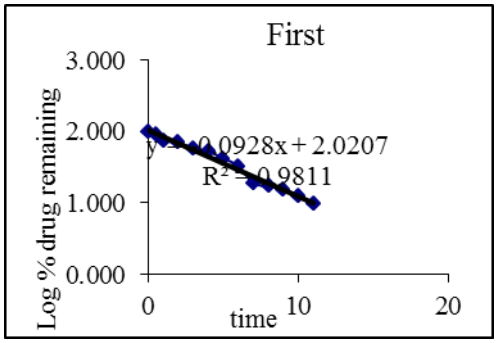


Fig. 8: Graph of Peppas Release kinetics. Fig. 9: Graph of First Order Release Kinetics.

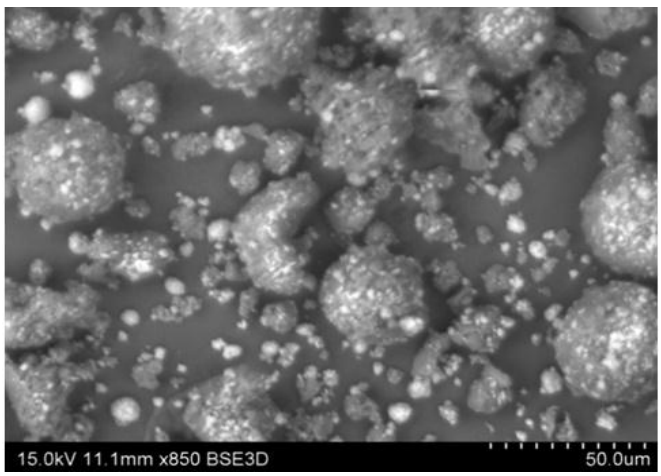


Fig. 10: SEM of Etodolac Floating Microspheres optimised formulation.

CONCLUSION

Etodolac floating microspheres were successfully developed using solvent evaporation technique. The microspheres had good yield and showed high, drug entrapment efficiency. The flow properties of microspheres were within the acceptable range and therefore would be easily filled into capsules. Release properties were satisfactory and the formulations hold promise for further development into drug delivery systems for oral administration of Etodolac.

ACKNOWLEDGEMENT

With deep gratitude I would like to thank Mr.Praveen kumar M.Pharm. My sincere thanks & gratitude to our principal Dr.M.Dhanalakshmi, M.Pharm, Phd, KLR Pharmacy College Paloncha, for this constant encouragement, throughout the course of work. I would like to thank and express muy sincere gratitude, to Mr.D.Ramchakarthar, M.pharm, KLR Pharmacy college paloncha. I Sincerely thank them all. Finally Iare indebted to my parents for their understanding and encouragement when it was most required.

REFERENCES

1. N. K. Jain, Controlled and Novel drug delivery, 04 Edition, CBS Publishers New Delhi, India, 21: 236-237.
2. Chein YW. Oral Drug Delivery Systems: In Novel drug delivery systems. Vol.50, Marcel Dekker, Inc., New York., 1992; 139- 177.

3. Mathew Sam T., Devi Gayathri S., PrasanthV.V., Vinod B; NSAIDs as microspheres, The Internet Journal of Pharmacology, 2008; 6(1): 67-73.
4. Li, S.P., Kowalski C.R., Feld K.M., Grim W.M. Recent Advances in Microencapsulation Technology and Equipment, Drug Dev Ind. Pharm., 1988; 14: 353-376.
5. Praveen Nasa, Sheefali Mahant, Deepika Sharma, "Floating Systems: A Novel Approach Towards Gastroretentive Drug Delivery Systems", Int J Pharmacy and Pharm Sci, 2010; 2(3): 27.
6. Gayathridevi M, J. Adlin Jino Nesalin and T. Tamizh Mani. Floating Microsphere: A Review. IJRPC, 2016; 6(3): 501-510.
7. Audumbar DM, Rithesh S and Manoj\ KP. Floating Microspheres: A Novel Approach in Drug delivery system. GCC Journal of Science and Technology, 2015; 1(5): 134-153.
8. Griffith, g.h.; owen, g.m.; kirkman, s.; shields, R. Measurement of rate of gastric emptying using Chromium-51. Lancet, l966; 1: 1244-1245.
9. Wilding, i.r.; coupe, a.j.; davis, S. S. The role of g-scintigraphy in oral drug delivery. Adv. Drug Del. Rev., 2001; 46: 103-124.
10. Abdul Hafeez, Arun Maurya, Jagpal Singh, Ankit Mittal, Lakhan Rana. An overview on floating microsphere: Gastro Retention Floating drug delivery system (FDDS). The Journal of Phytopharmacology, 2013; 2(3): 1-12.
11. Kavitha K, Sudhir K Yadav, Tamizh Mani T, "The Need of Floating Drug Delivery System", Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2010; 1(2): 396.
12. S. H. Shaha, J.K. Patel, K. Pundarikakshudu, "An overview of a gastro-retentive floating drug delivery system", Asian Journal of Pharmaceutical Sciences, 2009; 4(1): 65-80.
13. S. U. Zate, P.L. Kothawade, G.H.Mahale, "Gastro Retentive Bioadhesive Drug Delivery System: A Review", Int. J. Pharm Tech Res., 2010; 2(2): 12-19.
14. Chawla C, Gupta P, Koradia V, Bansal AK, Gastroretention: A Means to Address Regional Variability in intestinal drug Absorption. Pharmaceutical technology, 2003; 27(2): 50-68.
15. Sangekar S. Evaluation of effect of food and specific gravity of the tablets on gastric retention time. Int J Pharm, 1987; 35(3): 34-53.
16. Jain NK. Progress in Controlled and Novel Drug Delivery Systems, 1st Ed. CBS Publishers and Distributors, New Delhi, Bangalore, 2004; 84-85.
17. Chawla G, Gupta P, Koradia V, Bansal AK. Pharm Tech., 2001; 27(7): 50-51.
18. Debjit B, Chiranjib B, Margret C, B Jayakar. Floating Drug Delivery System: A Review. Der Pharmacia Lettre, 2009; 1(2): 199-218.
19. Chawla G, Gupta P, Koradia V, Bansal AK. Floating Drug Delivery Systems: An approach to Gastro retention, Pharm. Tech, 2003; 27(2): 50-68.
20. Garg R, Gupta GD. Progress in Controlled Gastro retentive Delivery Systems, Trop. J. Pharma. Res, 2008; 7(3): 1055-1066.
21. Hoffman A. Adv. Drug Deliv. Rev, Expandable gastro retentive dosage forms, 1998; 33: 185-199.
22. Hoffman A, Stepensky D. Floating multiparticulate oral sustained release drug delivery system, Crit. Rev. Ther. Drug Carrier Syst, 1999; 16: 571-639.
23. Sangekar S. Int. J. Pharm, Review on Stomach Specific Drug Delivery Systems: Development and Evaluation, 1987; 35(3): 34-53.
24. Mojaverian P, Vlasses PH, Kellner PE, Rocci ML. Floating drug delivery system: An innovative acceptable approach in gastroretentive drug delivery, Pharm. Res, 1988; 10: 639-64.