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Research Article

FORMULATION AND EVALUATION OF SOLID DISPERSION OF ANTI-ARTHRITIC DRUG AS FLOATING MICROSPHERES

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ABSTRACT

Arthritis is a form of joint disorder that causes inflammation in one or more joints. Ketoprofen is a NSAID commonly recommended for the relief of pain and inflammation in arthritis. One of the main side effects of Ketoprofen is gastric irritation. To avoid gastric irritation, Ketoprofen was formulated as solid dispersion by melt dispersion method using urea as carrier. For sustained release and for prolonging the pain relief, solid dispersion of Ketoprofen was finally formulated as floating microspheres by solvent evaporation method. HPMC K4M and EC were used as polymers in the formulation of floating microspheres. Seven formulations of floating microspheres were done by increasing the concentration of EC. Drug excipient compatibility studies were done by FTIR and DSC evaluations. Evaluation of solid dispersion was carried out by determining percentage yield, drug content, solubility determination and *in vitro* drug release studies. Characterization of floating microspheres was carried out by percentage yield, micromeritic properties, scanning electron microscopy, drug entrapment efficiency, *in vitro* buoyancy and *in vitro* drug release studies. F3 was found to be best formulation in terms of *in vitro* drug release studies. The kinetic study of the optimized formulation was carried out and found that the formulation undergo first order kinetics. The mechanism of drug release was found to be Higuchi model and Super case II transport. The stability studies were performed on optimized formulation F3 according to ICH guidelines.

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INTRODUCTION

Arthritis is a form of joint disorder which involves inflammation in one or more joints. The most common forms of arthritis are osteoarthritis and rheumatoid arthritis. There are different forms of arthritis.[1,2]

Prevalence of Arthritis:

According to a prevalence study carried out in adult Indian population, 89.5% of response rate was obtained and 3393 persons was listed as possible cases of arthritis. Preva-

lence of arthritis was found to be higher in urban areas than in rural areas so it can be concluded that both osteoarthritis and rheumatoid arthritis are common inflammatory and chronic arthritis which result in higher mobidity in the patients.[3,4] Non Steroidal Anti inflammatory Drugs are mainly used for the treatment of pain and inflammation in arthritis. Ketoprofen (2- aryl propionic acid derivative) is a NSAID which is used for the treatment of pain as well as inflammation in arthritis. Its plasma elimination half life is 2-2.5 hr. In order to maintain therapeutic plasma level drug must be administered at least thrice a day. The main side effect of NSAIDS is gastric irritation. To avoid gastric irritation NSAIDS can be formulated as solid dispersion. For prolonging the pain relief and for sustained release solid dispersion of NSAIDS finally can be formulated as floating microspheres. Sustained delivery of drug is mainly done by oral route. Fluctuation of therapeutic concentration of drug in the body is decreased by sustained drug delivery system.

ORAL SUSTAINED DRUG DELIVERY SYSTEM

For decades, oral drug delivery is known as the most widely utilized route of administration among all the routes that has been explored for systemic delivery of drugs. Due to convenience of self administration and compactness oral route of administration is considered as the most widely accepted route. [5] Drugs that have short half lives and which are easily absorbed from the GIT will be eliminated quickly from the systemic circulation. To achieve suitable therapeutic activity frequent dosing of these types of drugs is required. To avoid this limitation, an attempt is made to develop oral sustained release formulation to release the drug slowly into the GIT. It also maintains an effective drug concentration in systemic circulation for a long time. [5, 6, 7]

Solid Dispersion

Solid dispersion is a method available to improve dissolution rate, solubility characteristics, bioavailability of poorly water soluble drugs and to avoid gastric irritation. In solid dispersion drug is dispersed in inert water-soluble carrier at solid state. [8] Various methods are used for solid dispersion technique such as solvent evaporation, fusion, lyophilization, melt agglomeration, extruding and supercritical fluid technology.[9] The various carriers like mannitol, urea, citric acid, polyethylene glycols and polyvinyl pyrrolidone are used as water soluble carriers for solid dispersions.[9,10,11]

GASTRORETENTIVE DOSAGE FORM

For long periods gastroretentive dosage form can remain in the gastric region and thus it prolong the GRT of drugs.[12]

For the development of gastro retentive dosage forms FDDS is considerably an easy approach. Thus in the present study, formulation of gastro retentive dosage form is done by floating drug delivery system

FLOATING MICROSPHERES IN ARTHRITIS

Floating microspheres are gastro retentive drug delivery systems based on non effervescent approach. The drug is slowly released at desired rate as the system floats over gastric contents, resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. Prolonged gastric retention of floating microspheres improves bioavailability, improves solubility of drugs and reduces drug waste. Thus floating microspheres are used in arthritis to improve therapeutic effect. The quantity of polymers and the solvent used for formulation modulates buoyancy and drug release from the dosage form.[12]

MATERIALS AND METHODS

MATERIALS

Ketoprofen was procured from Infinity Rampur, Sainia. HPMC K4M and Ethyl Cellulose were purchased from Chemdyes Corporation, Vadodara. Urea, Dichloromethane and Tween 80 were purchased from Spectrum Reagents and Chemicals Pvt. Ltd. Cochin. Methanol was procured from Sara Fine Chemicals, Baroda.

PREFORMULATION STUDY

Preformulation studies was carried out by identification of drug, organoleptic evaluation, melting point determination and by solubility determination [13, 14, 15, 16, 17]

Analytical Method

a. Determination of λ_{max} of Ketoprofen

A sample of 100 µg/ml was prepared and scanned for maximum absorbance using UV Visible spectrophotometer in the range from 200 - 400 nm. [18]

b. Calibration Curve of Ketoprofen

Stock solution (100 µg/ml) of Ketoprofen was prepared. [19] From the above stock solution 10 µg/ml, 20 µg/ml, 30 µg/ml, 40µg/ml and 50 µg/ml was prepared in a 100 ml volumetric flasks

C. Compatibility Studies

The compatibility studies were carried out by FTIR and DSC studies. [20]

FORMULATION OF SOLID DISPERSION OF KETOPROFEN

The solid dispersion of Ketoprofen was prepared by melt dispersion method. The ratio of drug and urea was kept constant in 7 formulations. 0.2 g of Ketoprofen and 0.2 g of urea (1:1) was melted together in a china dish. To accomplish a homogenous dispersion the mixture was heated at or above the melting point of the components. Then both the ingredients were mixed thoroughly. After mixing the china dish was put on ice bath to cool the mixture to acquire a congealed mass. [21]

EVALUATION OF SOLID DISPERSION

Determination of Yield

The % yield was calculated by using following equation. All the results were taken in a triplicate manner.[22]

% Yield =

$$\frac{\text{Weight of prepared solid dispersion}}{\text{Theoretical Yield}} \times 100$$

Determination of Solubility

For the solubility determination of solid dispersion, 100 mg of solid dispersion was taken in a test tube containing 10 ml phosphate buffer pH7.2. For few hr the tube was shaken occasionally and maintained at 25ºC. The saturated solution was centrifuged. The supernatant was filtered and diluted with buffer. Then the solution was analyzed by UV Spectrophotometer at 254 nm. All the results were taken in a triplicate manner.[23]

Drug Content

Solid dispersion equivalent to 80 mg of Ketoprofen was weighed and dissolved in phosphate buffer pH 7.4 in a 100 ml volumetric flask. Then the volume was made up to 100 ml with the buffer. The solution was analyzed by UV Spectrophotometer at 254 nm. All the results were taken in a triplicate manner.[22]

***In Vitro* Dissolution Studies**

Dissolution studies of Ketoprofen drug and Solid Dispersion was performed using USP dissolution test apparatus II with the paddle rotating at 50 rpm in 900 ml phosphate buffer (pH7.4) at 37 ± 0.5ºC. The solid dispersion equivalent to 80 mg of Ketoprofen was taken for the dissolution test. 5 ml samples were withdrawn and the same volume was replaced with fresh dissolution medium. The samples were then analyzed by UV spectrophotometer at 254 nm.[22]

FORMULATION OF SOLID DISPERSION OF KETOPROFEN AS FLOATING MICROSPHERES

Floating microspheres were prepared by solvent evaporation method. Distilled water used as continuous phase. The solid dispersion of drug and polymers were weighed in different proportions. Seven formulations were prepared. Each formulation varied in EC concentration. The EC concentration was increased by 0.1 gm in each formulation. The solid dispersion of drug and HPMC K4M concentration was kept constant. The mixture of solid dispersion of drug and polymer was co dissolved into previously cooled mixture of methanol: dichloromethane at room temperature. The uniform solid dispersion of drug and polymer dispersion was obtained by stirring the mixture vigorously. The above organic phase was added to 100 ml distilled water which contains 0.01 % Tween 80. The temperature was maintained at 15 – 20ºC. Then it was emulsified by stirring for 20 min. The microspheres formed was filtered and washed with water. Finally dried under vacuum. The formulation is given in Table No. 1[22,23]

EVALUATION OF FLOATING MICROSPHERES

Micromeritic Properties

a. Particle Size

The particle size of floating microspheres was analyzed using optical microscopy method.[22]

b. Bulk Density,Tapped Density, Compressibility Index, Hausner's Ratio and Angle of Repose

Bulk Density, Tapped Density, Compressibility Index, Hausner's Ratio and Angle of Repose were determined to check the flow properties. [24]

Yield of Floating Microspheres

The prepared floating microspheres were collected and weighed. All the results were taken in a triplicate manner [22]

% yield =

$$\frac{\text{Actual weight of product}}{\text{Total weight of excipient and drug}} \times 100$$

***In Vitro* Buoyancy**

300 mg of floating microspheres was placed in 50 ml beakers and 20 ml of 0.1 M HCl containing 0.02 % Tween 80 was added. The beakers were shaken horizontally in a water bath at 37 ± 0.1 ºC. Floated particles was collected after 10 hr and dried in a desiccator to constant weight. All the results were taken in a triplicate manner. The % of floating microspheres was calculated as [22]

Buoyancy (%) =

Weight of floating microspheres/Initial weight of floating microspheres x 100

Drug Entrapment Efficiency

The prepared floating microsphere was dissolved in a minimum amount of methanol. The drug was extracted into suitable aqueous media (0.1 N HCl) by evaporating methanol. The solution was then filtered through filter paper. The solution was diluted suitably and analyzed for drug content spectrophotometrically at 254 nm. The blank was 0.1 N HCl. All the results were taken in a triplicate manner [22]

Scanning Electron Microscopy

SEM analysis was carried out to study the surface morphology.[22]

***In Vitro* Drug Release Studies**

The floating microspheres equivalent to 100 mg of drug was determined using paddle method at 100 rpm for 8 hr in 900 ml 0.1 N HCl. 5 ml of samples was withdrawn at different time intervals. The solution was replaced with 0.1 N HCl. The amount of drug release was analyzed at 254 nm by using UV Visible Spectrophotometer.[22]

KINECTIC MODELLING OF DISSOLUTION PROFILES

The various kinetic models such as Korsmeyer Peppas plot, Higuchi plot, Hixson Crowell plot, First order plot and Zero order plot was used to study the drug release kinetics of F3.The data obtained from *in vitro* drug release was plotted in various kinetic models. The best fit model was confirmed by the value of R^2 which is near to 1. [25]

STABILITY STUDIES

Accelerated stability was performed on optimized formulation F3 according to ICH guidelines. The optimized formulation was stored in stability chamber in glass vials. Stability studies on the optimized formulation were performed by keeping the sample at Accelerated Condition. The optimized formulation was analyzed at initial, third and sixth month. The formulation was evaluated for parameters like yield, *in vitro* drug release, *in vitro* buoyancy and drug entrapment efficiency at storage condition at 40 ± 5ºC/75 ± 5% RH.[26]

RESULTS AND DISCUSSIONS

Analytical Method

a. λ_{max} of Ketoprofen

The sample 100 µg/ml was prepared and scanned between 200 – 400 nm. The drug showed maximum absorption at 254 nm so the λ_{max} was found to be 254 nm.

b. Calibration Curve of Ketoprofen

The various concentration of drug (10 µg/ml, 20 µg/ml, 30 µg/ml, 40 µg/ml, 50 µg/ml) was prepared and the standard graph was plotted. Standard calibration curve data of Ketoprofen is given in Table No. 2. From Fig. No. 1 y intercept and R^2 value was found to be 0.014 and 0.998 respectively.

c. Compatibility Studies

1. FTIR

The results are given in the Table No. 3. FTIR spectrum of Ketoprofen is given in Fig. No.2. FTIR spectrum of Ketoprofen and excipients are given in Fig. No.3. The FTIR spectrum of Ketoprofen and excipients was compared with the FTIR spectrum of Ketoprofen. It was observed that there were no significant changes in characteristic peaks indicating compatibility between Ketoprofen and the excipients.

2. DSC

DSC of Ketoprofen is given in Fig. No. 4. DSC of solid dispersion of Ketoprofen is given in Fig. No. 5. DSC of Ketoprofen and excipients are given in Fig. No. 6. The DSC thermogram of solid dispersion of Ketoprofen and physical mixture of Ketoprofen remains almost same compared to the DSC thermogram of Ketoprofen indicating the compatibility of drug and the excipients.

Table No. 1: Formulation of solid dispersion of Ketoprofen as floating microspheres

Ingredients	F1	F2	F3	F4	F5	F6	F7
Solid dispersion of Ketoprofen(g)	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Ethyl Cellulose(g)	2.5	2.6	2.7	2.8	2.9	3.0	3.1
HPMC K4M(g)	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Dichloromethane(ml)	20	20	20	20	20	20	20
Methanol(ml)	20	20	20	20	20	20	20
Water(ml)	100	100	100	100	100	100	100
Tween 80 (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table No. 2: Standard calibration curve data of Ketoprofen

Sl. No.	Concentration (µg/ml)	absorbance
1	0	0
2	10	0.158
3	20	0.301
4	30	0.437
5	40	0.581
6	50	0.734

Table No. 3: Functional groups and observed peak values of FTIR spectrum

Sl. No.	Drug and Excipients	Functional Groups			
		Ar.H (cm^{-1})	C-H deformation of aromatic rings (cm^{-1})	C-H deformation (cm^{-1})	C=C stretching of aromatic ring (can be assigned as the presence of Keto group) (cm^{-1})
1	Ketoprofen	778.72	860-690	1282.18	1444.43
2	Ketoprofen+ HPMC K4M+ EC + Urea	710.04	860- 690	1282.06	1447.43

Table No. 4: *In vitro* dissolution studies of Ketoprofen and solid dispersion of Ketoprofen

SI. No.	Time (min)	% Cumulative drug release	
		Ketoprofen	Solid Dispersion
1	0	0	0
2	5	9.6	57.3
3	10	9.7	58.6
4	15	12.0	59.2
5	20	18.0	63.3
6	25	16.8	65.8
7	30	22.5	70.6
8	45	27.3	70.9
9	60	31.5	75.0
10	90	43.5	79.3
11	120	48.0	80.2

Table No. 5: Particle size of floating microspheres of Ketoprofen

Sl. No.	Formulation	Particle size (µm) *Mean ± S.D
1	F1	81.7 ± 0.100
2	F2	82.1 ± 0.150
3	F3	83.2 ± 0.150
4	F4	85.1 ± 0.200
5	F5	86.1 ± 0.100
6	F6	88.0 ± 0.150
7	F7	89.1 ± 0.100

*Each reading is an average of 3 determinations

Table No.6: Micromeritic properties of Ketoprofen floating microspheres

Sl. No.	Formu-lation	Bulk density* (g/cc) *Mean ± S.D	Tapped density (g/cc) *Mean ± S.D	Compressibility Index (%) *Mean ± S.D	Hausner's ratio *Mean ± S.D	Angle of repose (^{0}) *Mean ± S.D
1	F1	0.243 ± 0.003	0.282 ± 0.0015	12.61 ± 0.015	1.140 ± 0.002	29.60 ± 0.200
2	F2	0.251 ± 0.001	0.287 ± 0.002	14.22 ± 0.0152	1.131 ± 0.001	26.40 ± 0.305
3	F3	0.253 ± 0.004	0.291 ± 0.001	14.58 ± 0.015	1.171 ± 0.003	25.40 ± 0.152
4	F4	0.291 ± 0.001	0.340 ± 0.001	14.71 ± 0.064	1.172 ± 0.001	27.06 ± 0.015
5	F5	0.301 ± 0.001	0.341 ± 0.0015	13.77 ± 0.015	1.161 ± 0.002	29.14 ± 0.225
6	F6	0.309 ± 0.002	0.351 ± 0.009	12.49 ± 0.015	1.142 ±0.005	27.92 ± 0.055
7	F7	0.420 ± 0.100	0.481 ± 0.001	12.39 ± 0.01	1.143 ±0.001	28.13 ± 0.030

*Each reading is an average of 3 determinations

Table No.7: % Yield, *In Vitro* Buoyancy and Drug Entrapment Efficiency of Ketoprofen Floating Microspheres

Sl. No.	Formulation	Yield (%) *Mean ± S.D	*In vitro* Buoyancy (%) *Mean ± S.D	Drug entrapment efficiency (%) *Mean ± S.D
1	F1	77.30 ± 0.077	83.23 ± 0.208	75.4 ± 0.378
2	F2	76.01 ± 0.877	80.20 ± 0.100	78.4 ± 0.100
3	F3	87.28 ± 0.253	86.16 ± 0.378	80.9 ± 0.493
4	F4	60.36 ± 0.321	70.00 ± 0.100	75.1 ± 0.250
5	F5	58.50 ± 0.121	66.60 ± 0.152	76.6 ± 0.150
6	F6	55.78 ± 0.077	56.80 ± 0.100	77.2 ± 0.152
7	F7	53.3 ± 0.297	49.70 ± 0.608	79.1 ± 0.208

Table No. 8: *In vitro* dissolution studies of floating microspheres of Ketoprofen

Sl. No.	Time (hr)	% Cumulative drug release						
		F1	F2	F3	F4	F5	F6	F7
1	0	0	0	0	0	0	0	0
2	1	42.45	45.92	52.4	37.2	34.3	28.4	28.2
3	2	49.53	49.13	55.3	38.8	36.0	31.4	29.6
4	3	51.30	52.35	61.2	43.4	39.1	34.4	35.6
5	4	56.6	55.5	62.6	46.5	43.8	40.4	38.6
6	5	60.1	62.32	67.0	49.6	46.9	46.4	40.0
7	6	67.2	63.0	72.8	55.8	53.2	50.9	43.0
8	7	68.9	65.6	78.7	58.9	54.7	52.4	47.5
9	8	70.7	67.2	84.5	61.0	57.9	53.9	50.4

Table No. 9: Regression Co-efficient values and release exponent values of F3

Formulation	**Zero order (r^2)**	**First order (r^2)**	**Higuchi model (r^2)**	**Hixson Crowell (r^2)**	**Korsmeyer Peppas (n)**
F3	**0.883**	**0.899**	**0.9717**	**0.889**	**1.1427**

Table No. 10: Stability studies of floating microspheres of Ketoprofen

Months	**Yield (%)**	**Drug entrapment Efficiency (%)**	***In vitro* Buoyancy (%)**
Initial	87.28 ± 0.253	80.9 ± 0.493	86.16 ± 0.378
Third	87.20	80.7	86.13
Sixth	87.20	80.7	86.13

Table No. 11: Comparison of stability studies of *in vitro* drug release of Ketoprofen floating microspheres

Months	**Time (hr)**								
	0	1	2	3	4	5	6	7	8
Initial	0	52.4	55.3	61.2	62.6	67.0	72.8	78.7	84.5
Third	0	51.0	54.0	60.0	62.0	66.0	71.0	78.0	84.0
Sixth	0	51.0	54.0	60.0	62.0	66.0	71.0	78.0	84.0

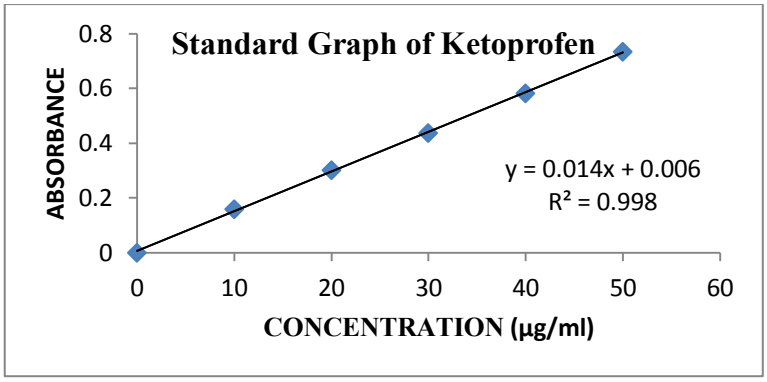

Fig. No. 1: Standard Graph of Ketoprofen

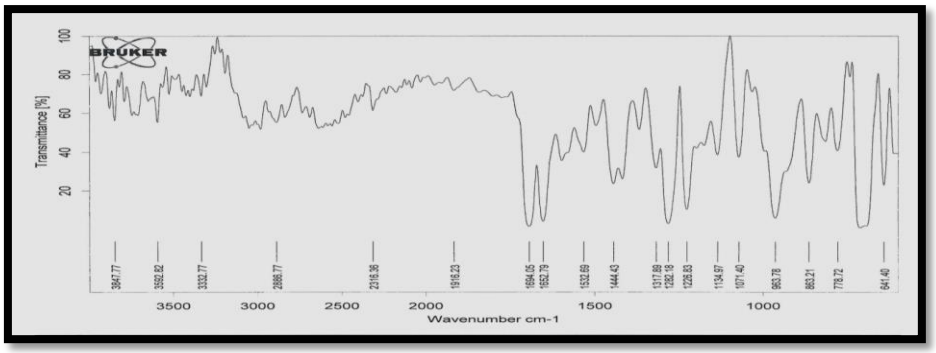

Fig. No. 2: FTIR Spectrum of Ketoprofen

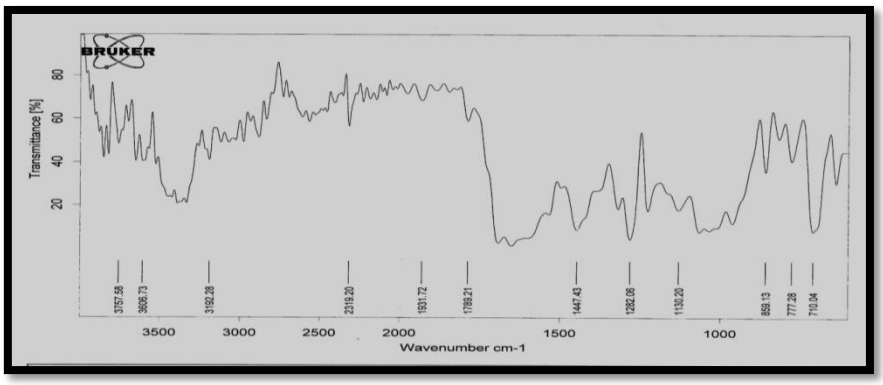

Fig. No. 3: FTIR spectrum of Ketoprofen+ HPMC K4M +EC + Urea

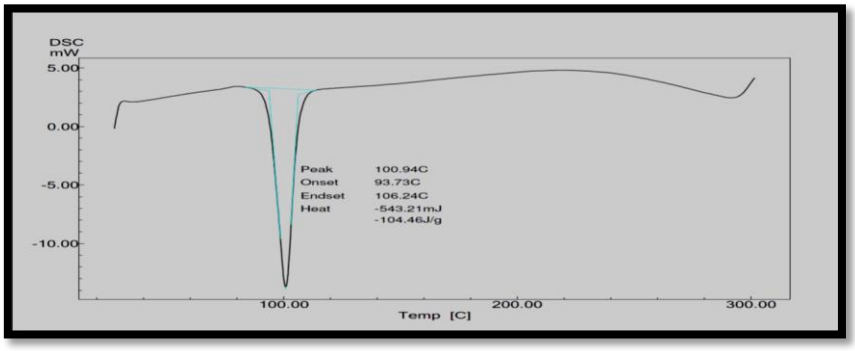

Fig. No. 4: DSC of Ketoprofen

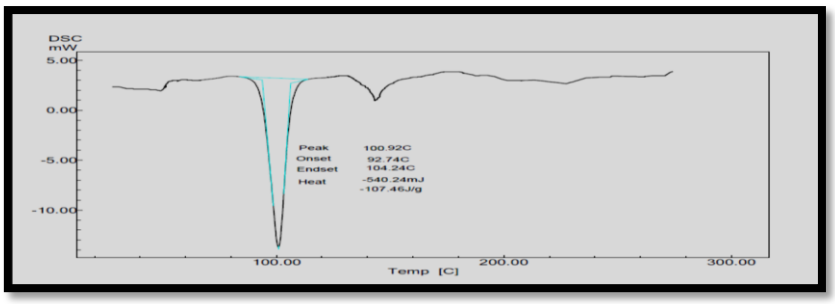

Fig. No. 5: DSC of Solid Dispersion of Ketoprofen

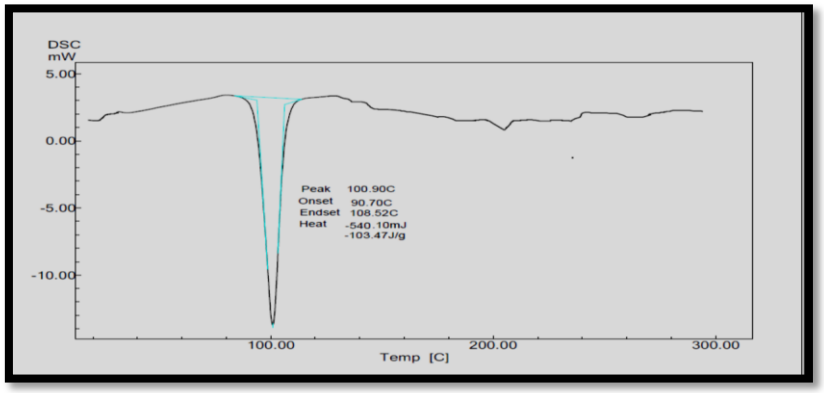

Fig. No. 6: DSC of Ketoprofen +HPMC K4M+ EC+ Urea

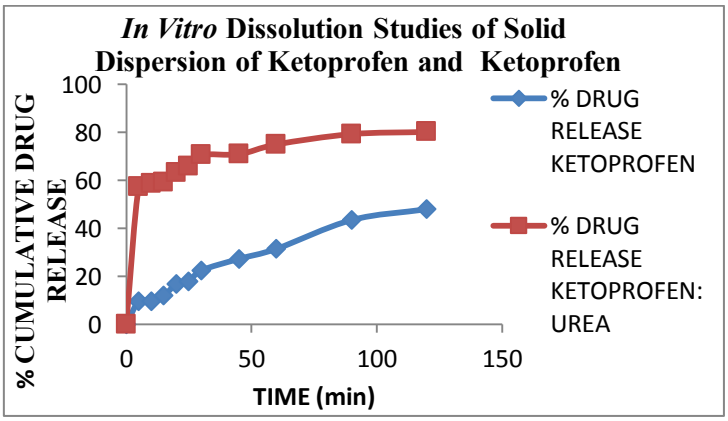

Fig. No. 7: *In vitro* dissolution studies of solid dispersion of Ketoprofen and Ketoprofen

Fig. No. 8: Microscopic view of floating microspheres of Ketoprofen

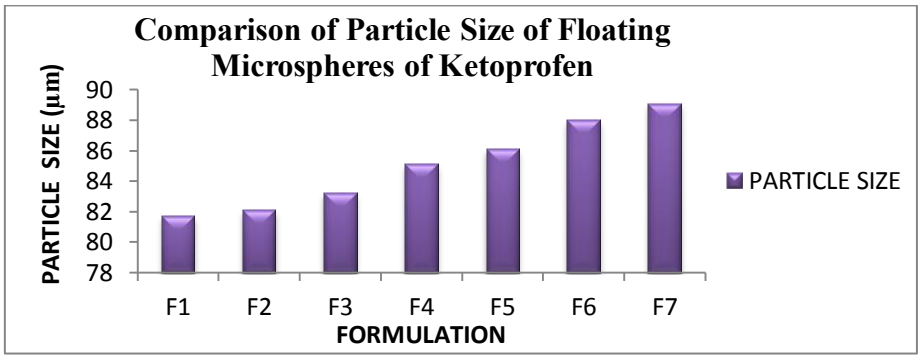

Fig. No. 9: Comparison of particle size of floating microspheres of Ketoprofen

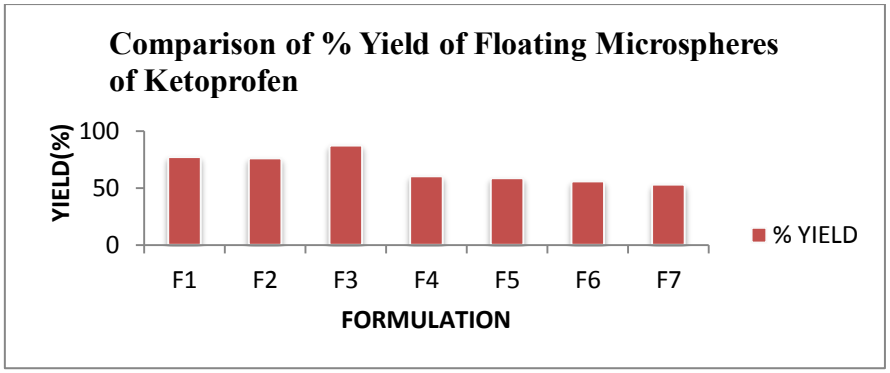

Fig. No. 10: Comparison of % yield of floating microspheres of Ketoprofen

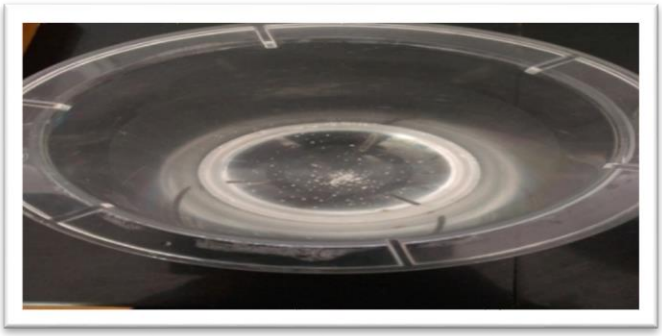

Fig. No 11: Top view of *in vitro* buoyancy of floating microspheres of Ketoprofen

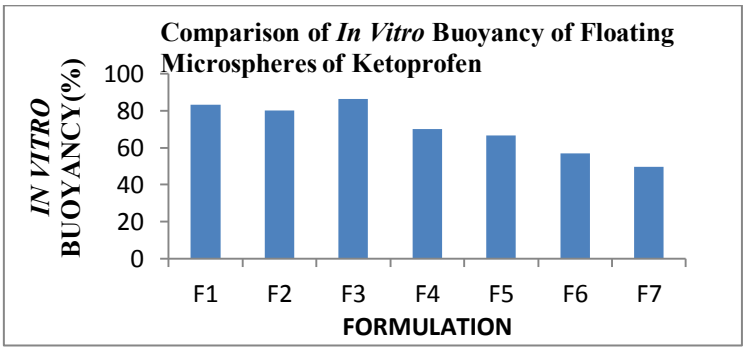

Fig. No. 12: Comparison of *in vitro* buoyancy of floating microspheres of Ketoprofen

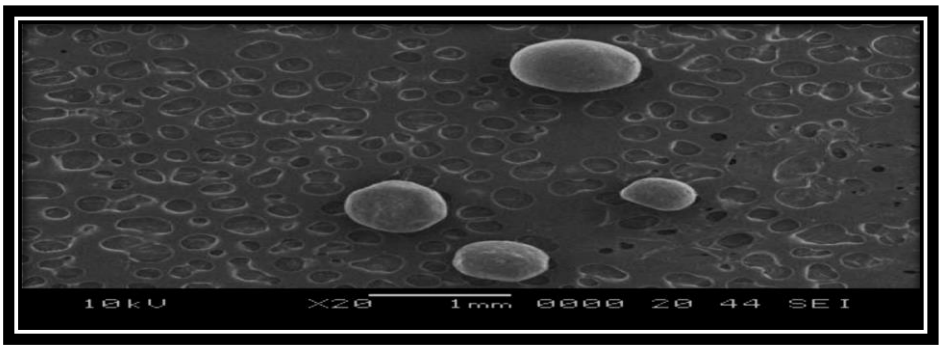

Fig. No. 13: SEM of floating microspheres of Ketoprofen

Fig. No. 14: *In vitro* dissolution studies using paddle

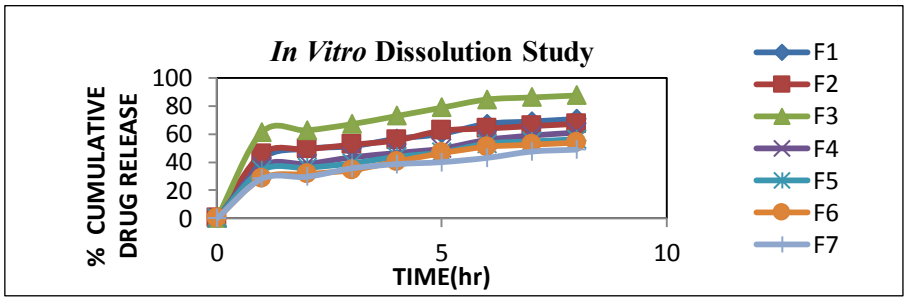

Fig. No. 15: *In vitro* dissolution study of floating microspheres of Ketoprofen

Fig. No. 16: F3- The optimized formulation of Ketoprofen floating microspheres

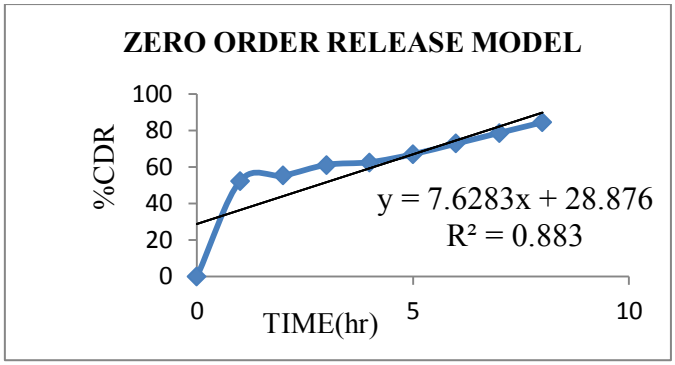

Fig. No. 17: Zero Order Kinetics of F3

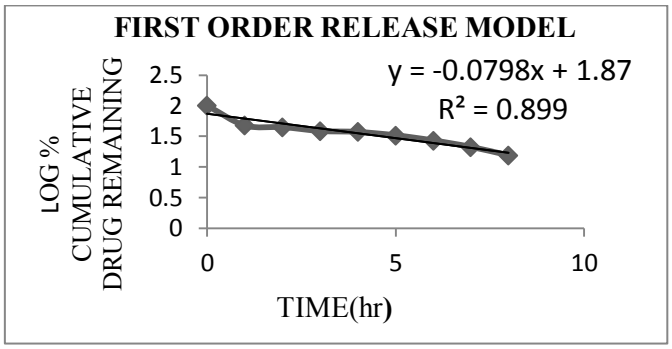

Fig. No. 18: First Order Kinetics of F3

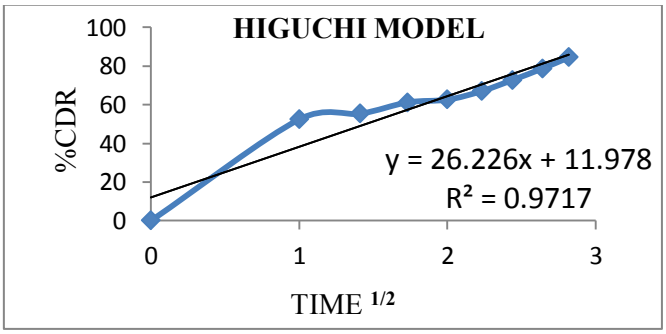

Fig. No.19: Higuchi Model of F3

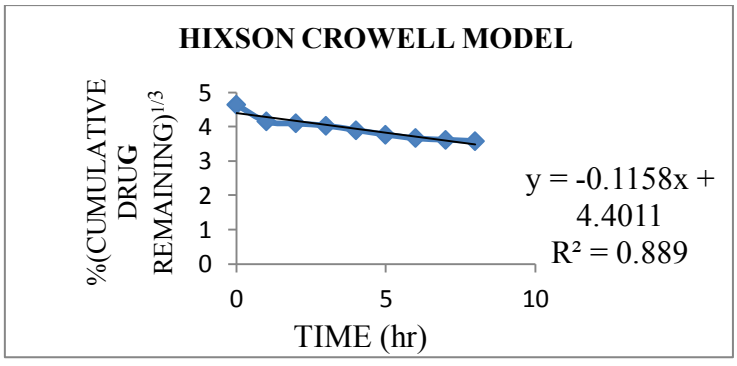

Fig. No.20: Hixson Crowell Model of F3

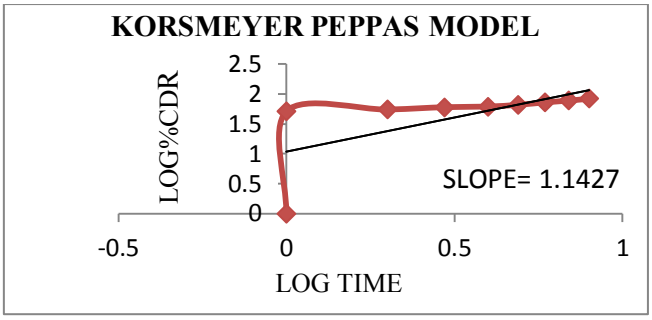

Fig. No 21: Korsmeyer Peppas Model of F3

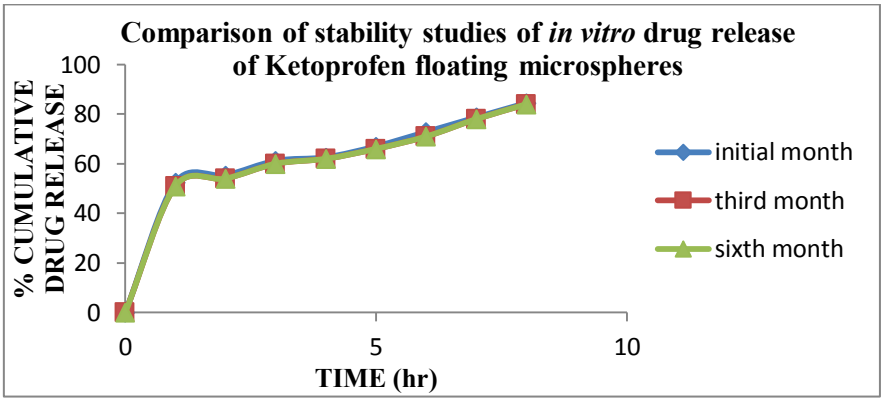

Fig. No. 22: Comparison of stability studies of *in vitro* drug release of Ketoprofen floating microspheres

EVALUATION OF SOLID DISPERSION OF KETOPROFEN

Determination of Yield: The % yield of solid dispersion of Ketoprofen was found to be 80.2 ± 0.1%. (Mean ± S.D)*
*Reading is an average of 3 determinations.

Determination of Solubility

The solubility of solid dispersion of Ketoprofen in phosphate buffer pH 7.2 was found to be 1.71 ± 0.01 mg/ml.(Mean ± S.D)*
*Reading is an average of 3 determinations.

Drug Content

The drug content of solid dispersion of Ketoprofen was found to be 89.2 ± 0.1%. (Mean ± S.D)*
*Reading is an average of 3 determinations.

***In Vitro* Drug Release**

Solid dispersion of Ketoprofen showed better *in vitro* drug release compared to Ketoprofen. The results are given in Table No.4. It is graphically represented in Fig. No.7.

EVALUATION OF FLOATING MICROSPHERES

Micromeritic Properties

a. Particle Size

Particle sizes of 7 formulations were determined and reported in Table No. 5. The microscopic view of floating microspheres of Ketoprofen is given in Fig. No.8. It is graphically represented in Fig. No.9. The particle size was affected by increase in ethyl cellulose concentration. The particle size increased as the ethyl cellulose concentration increased. This increased the viscosity of polymer which in turn decreased stirring efficiency. The polymer rapidly precipitated leading to hardening and thus avoiding particle size reduction during solvent evaporation.

b. Bulk Density, Tapped Density, Compressibility Index, Hausner's Ratio and Angle of Repose

The results are given in Table No. 6. All the results showed good flow property.

Percentage yield, *In Vitro* Buoyancy, Drug Entrapment Efficiency

The results are shown in Table No. 7. The yield of floating microspheres decreased as the concentration of ethyl cellulose increased. It is graphically represented in Fig. No.10. As the concentration of the polymer increased, viscosity of the solution increased affecting the stirring speed and resulting in decreased percentage yield. *In vitro* buoyancy was decreased as the ethyl cellulose concentration increased. Top view of *in vitro* buoyancy of floating microspheres of Ketoprofen is given in Fig. No.11. It is graphically represented in Fig. No.12. As the polymer concentration increased, the density of the floating microspheres increased resulting in decreased *in vitro* buoyancy The drug entrapment efficiency of 7 formulations was determined.The drug entrapment efficiency increased as the ethyl cellulose concentration increased due to increase in viscosity of the solution.

SEM

SEM revealed the morphology of the floating microspheres. It was found that the floating microspheres were spherical in shape. SEM of Ketoprofen floating microspheres is given in Fig. No. 13.

***In Vitro* Drug Release Studies**

In vitro drug release decreased as the ethyl cellulose concentration increased because increased density of the polymer matrix at higher concentrations resulted in an increased diffusional path length. This might be resulted in decrease of overall drug release from the polymer matrix. The results are given in Table No.8. *In vitro* dissolution studies using paddle is given in Fig. No.14. It is graphically represented in Fig. No.15. Based on *in vitro* drug release studies the best formulation was selected as F3. It is shown in Fig. No. 16.

KINETIC MODELLING OF DISSOLUTION PROFILES

1. Zero and First Order Kinetics: The release kinetics data indicates that the release of drug best fits to first order release kinetics because R^2 values are higher in case of first order kinetics. Zero order is graphically represented in Fig. No. 17 and First order in Fig. No. 18.

3. Hixson Crowell Model and Higuchi Model: The R^2 values best fits to Higuchi model. Hence the formulations follow diffusion. Higuchi model is graphically represented in Fig. No. 19 and Hixson Crowell in Fig. No.20.

5. Korsmeyer Peppas Model

The drug release behavior was found to be super case II transport which indicated that in addition to diffusion other release mechanism including matrix erosion and polymer relaxation is involved. It is graphically represented in Fig. No. 21. When the formulation is exposed to gastrointestinal fluids, the surface of the formulation is wetted and hydrophilic polymer hydrated to form a gel layer around the drug, this will lead to relaxation and swelling of the polymer contributing diffusion mechanism. This phenomenon may also result in initial burst release due to the presence of drug in the solid dispersion contributing to erosion of matrix. The regression coefficient values and release exponent values are given in Table No.9.

STABILITY STUDIES

The optimized formulation F3 was subjected to stability study. Initial third and sixth month studies were done and results are given in Table No. 10 and 11. The change in yield, drug entrapment efficiency, *in vitro* buoyancy and *in vitro* drug release was determined. *In vitro* drug release studies at initial third and sixth month are graphically represented in Fig. No. 22. No significant change in yield, drug entrapment efficiency, *in vitro* buoyancy and *in vitro* drug release was observed. Thus the formulation was found to be stable.

CONCLUSION

The various studies of solid dispersion of Ketoprofen show reduced gastric bleeding. The solid dispersion of Ketoprofen as floating microspheres reduces gastric bleeding. Due to its advantage of reduced side effects, sustained release, prolonged pain relief and improved patient compliance, it is better alternative when compared to available Ketoprofen tablets and capsules. This product can be manufactured in large scale and commercialized for the treatment of arthritic patients.

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