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FORMULATION AND EVALUATION OF FLOATING MICROSPHERE OF OFLOXACIN

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ABSTRACT

Floating microspheres have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time were prepared. Pale yellow, bitter, odorless, amorphous powder of ofloxacin was observed λ_{max} at 296nm. Drug ofloxacin was compatible and chemically stable as observed in FT-IR spectra. Five different formulations were prepared by o/w emulsion solvent evaporation method using different concentration of Ethyl Cellulose EC) and fixed amount (100mg) of ofloxacin and tween-80 (1%). Evaluation of floating microspheres formulations, **EC-4** has greater yield 95.43 % but its encapsulation efficiency was lower 74.6. **EC-1, EC-2, EC-4** and **EC-5** were possessed poor mircomeritic properties e.g. Carr's Index 39.65, 37.65, 29.31 and 30.44% respectively, Hausner's ratio 1.657, 1.604, 1.415 and 1438 respectively and angle of repose (θ) 31, 35, 28 and 29 respectively. Best formulation **EC-3** microsphere batch possessed yield (91.69%), particle size (676 µm), and encapsulating efficiency (98.2), Carr's Index (5.08%), Hausener's ratio (1.054) and 65.2 % *in-vitro* buoyancy which was excellent among all prepared formulations. Also drug release was 97.913 %. Kinetic modeling revealed that floating microsphere batch EC-3 was followed Higuchi model with regression value (R^2) 0.990.

KEYWORD: Floating Microsphere, Ofloxacin, Buoyancy, Floating Drug Delivery Systems.

INTRODUCTION

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time.[1,2,3,4] Floating microspheres loaded with drug in their outer polymer shell were prepared by a novel emulsion-solvent diffusion method.[5,6] The floating microspheres floated

continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *invitro.*[7,8,9] Floating microspheres improves patient compliance by decreasing dosing frequency.[10] Avoid gastric irritation, because of sustained release effect. Better therapeutic effect of short half-life drugs can be achieved.[11]

Ofloxacin is a quinolone/fluoroquinolone antibiotic. Ofloxacin is bactericidal and its mode of action depends on blocking of bacterial DNA replication by binding itself to an enzyme called DNA gyrase, which allows the untwisting required replicate one DNA double helix into two.[12]

MATERIAL AND METHODS

Femciclovir was obtained from Ranbaxy, Devas (M.P.), Ethyl Cellulose from Sulab, Varodara, Guar Gum from Titan Biotech Ltd. Bhiwadi, Heavy Liquid Paraffin from Himedia Labolatory, Mumbai, Tween 80 from J & K Scientifics. China, Sodium Aliginate and Calcium Chloride were purchased from Oxford Laboratory, Mumbai. All used solvents and chemicals were laboratory grade.

PREFORMULATION STUDY

Organoleptic Properties

The drug (ofloxacin) powder was examined for its organoleptic properties like color, odour and taste it was observed that.

Determination of Solubility

A fixed amount of drug was taken, and then solvent was added and observes the solubility visually. Solubility study should be performed for ofloxacin to determine in which solvent it is soluble, for that various solvents like water, methanol, 0.1N NaOH, 0.1N HCl, Ethanol 6.8pH & 7.4pH buffer was used, for determining the solubility the drug should be dissolved in individual solvent in 1:10 ratio (Drug: Solvent) and visually observed for its solubility.

Melting Point Determination

The Melting point was determined by the capillary method using Digital Melting point apparatus. The capillary tube was fused and filled by pressing the open end gently into pure drug sample and packed by tapping the bottom of the capillary on a hard surface so that the drug packed down into the bottom of the tube. When the drug was packed into the bottom of

the tube, the tube was placed into the slot of the apparatus, the apparatus was started and the temperature was noted at which the drug melt.

Analytical Estimation by UV Spectrophotometer

Determination of Wavelength of Maximum Absorbance (λ_{max})

10 µg/ml solution of Ofloxacin was scanned by UV spectrophotometer range from 200-400 nm using double beam visible spectrophotometer.

Preparation of Calibration Curve

Weigh accurately 10mg of Ofloxacin was dissolved in about 1 ml of solvent and volume was made upto 10 ml using same solvent the prepared solution was 1 mg/ml or 1000µg/ml.

From this stock solution 1 ml was pipette out in 10 ml calibrated volumetric flask filled upto 10ml prepared solution was 100 µg/ml and dilutions of 2, 4, 6, 8, 10 µg/ml was obtained from 100µg/ml solution. The absorbance of these solutions was taken on double beam U.V. spectrophotometer using λmax at 296 nm. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve. Same procedure was fallowed for every solvent.

Partition coefficient

10 mg of drug take into separating funnel and 25 ml of water and 25 ml of n-octanol mix the solution by shaking then this mixture stand for 2hr. and separate the two immiscible layers and collect into separate beakers. These separated solutions scanned by UV Spactrophotometer and obtain its absorbance.

FT-IR Spectra Analysis

FT-IR Spectroscopy can be used to investigate and predict any physicochemical interactions between different components, in a formulation and therefore it can be applied to selection of suitable chemically compatible excipients. While selecting the ingredients, we would choose those which are stable, compatible and therapeutically acceptable. The aim of compatibility study was to test, whether there is any interaction between the excipients and the drug and compatibility between the drug and excipients.

Levels of investigation

IR Spectrum = Pure drug (Ofloxacin)

IR Spectrum = Ofloxacin + Excipients

IR Spectrum = Ofloxacin + Excipients

Method of Preparation of Microspheres

Preparation of Ofloxacin Microsphere with Ethyl Cellulose by Solvent evaporation method

Ofloxacin microspheres were prepared by solvent evaporation technique. Polymer Ethyl Cellulose was dissolved in dichloromethane:ethanol (1:1). Ofloxacin was dispersed in polymer solution. This solution was added slowly to a beaker having 300 ml of water containing 0.1 % w/w tween-80 under constant stirring (1000 rpm) there after emulsifier added. When stable emulsion formed organic solvents were evaporated by stirring. After evaporation of solvents, formed microspheres were collected by decantation then filtration and dried at room temperature. Compositions of various formulations are shown in table.

Evaluation of Ofloxacin Microsphere

Percentage Yield

The yield of microsphere was determined by comparing the whole weight of microspheres formed against the combined weight of the copolymer and drug.

$$\% \textbf{ Yield } = \frac{\text{Actual weight of Microsphere}}{\text{Total weight of excipient and Drug}} \text{ X } 100$$

Particle Size Analysis

The size of the prepared microspheres was measured by the optical microscopy method using a calibrated stage micrometer. The average size of 100 particles was determined.

Entrapment Efficiency

Ofloxacin microsphere was digested in 100ml distilled water by warming. The solution was then sonicated for 15 minutes, filtered & 1ml of filtrate was made up to 10ml with distilled water. The solution was analyzed in UV spectrophotometer to determine amount of entrapped in microsphere.

Scanning Electron Microscopy (SEM)

The surface morphology of microsphere was investigated using scanning electron microscopy (SEM) by mounting on stubs using double-sided adhesive tapes. The stubs were then vaccum-coated with gold-palladium alloy using coat sputter JFC 1600 (JEOL, Japan) and the microspheres were observed and examined using SEM (JEOL JSM 6390 A).

Micromeritic properties

Bulk Density: The bulk density is defined as the mass of powder divided by bulk volume. The bulk density was calculated by dividing the weight of the samples in grams by the final volume in cm^3.

$$\text{Bulk Density} = \frac{\text{Mass of microsphere}}{\text{Volume of microsphere}}$$

Tapped Density: Tapped density is the volume of powder determined by tapping by using a measuring cylinder containing weighed amount of sample. The cylinder containing known amount of microspheres was tapped for about 1 minute on a tapped density apparatus until it gives constant volume.

$$\text{Tapped Density} = \frac{\text{Mass of microsphere}}{\text{Tapped volume of microsphere}}$$

Carr's Compressibility Index: This is an important property in maintaining uniform weight. It is calculated using following equation,

$$\textbf{Carr's or compressibility index} = 1 - \frac{\text{Bulk density}}{\text{Tapped desity}}$$

Lower the compressibility values indicate better flow.

Hausner's index: A similar index like percentage compressibility index has been defined by Hausner's. Values less than 1.25 indicate good flow, whereas greater than 1.25 indicates poor flow. Added glidant normally improve flow of the material under study. Hausner's ratio can be calculated by formula,

$$\textbf{Hausner's Index} = \frac{\text{Tappeddensity}}{\text{Bulk desity}}$$

Angle of Repose (θ): Inter particle forces between particles as well as flow characteristics of powders are evaluated by angle of repose. Angle of repose is defined as the maximum angle possible between the surface and the horizontal plane. The angle of repose of each powder blend is to be determined by glass funnel method. Powders are to be weighed accurately and passed freely through the funnel so as to form a heap. The height of funnel is so adjusted that the tip of the funnel just touched the apex of the heap. The diameter of the powder cone so formed was measured and the angle of repose was calculated using the following equation:

$$\tan\theta = \frac{h}{r}$$

Where, θ = angle of repose; h = height of the pile and; r = radius of the powder cone respectively.

Angle of repose affects particle size distribution, as larger the particle size, it will flow freely and vice-versa. It is a helpful parameter to monitor quality of powdered or granular pharmaceutical formulations. For good flowing materials then, angle of repose should be less than 30°.

***In- vitro* buoyancy of Microsphere**

300mg of Microspheres were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 ml of 0.1 N hydrochloric acid containing 0.02% tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.

***In-vitro* Release Studies of Microsphere**

In-vitro release studies were carried out using USP type I apparatus at 37 ± 0.5^{o} C in 900ml of 0.1N HCl for 24h. Microspheres equivalent to 20mg drug was placed into the baskets (tied using muslin cloth), and rotated at 100rpm 5ml sample was withdrawn at various time intervals like 0, 1, 2, 4, 6, 8, 10, 12 and 14 h and filtered, analyzed by UV spectrophotometrically.

RESULT AND DISCUSSION

Pre formulation studies

Organoleptic Properties

These tests were performed as per procedure given in experimental work part. The results are illustrated in following table:

Table No.: Organoleptic Properties of drug Ofloxacin.

Test	Specification	Observations
Color	Pale yellow	Complies
Taste	Bitter	Complies
Odor	Odorless	Complies

The results of table indicate that drug Ofloxacin complies with specifications.

Solubility study

Solubility of Ofloxacin was determined in various aqueous and non aqueous solvents. The drug was found to be freely soluble in methanol, Phosphate buffer (pH 6.8) and practically insoluble in dichloromethane, ether and sparingly soluble in ethanol.

Table No.: Solubility profile of Ofloxacin in different solvent.

Sr. No.	Solvent	Solubility
1	Distilled water	Soluble
2	Ethanol	Freely Soluble
3	Methanol	Freely Soluble
4	0.1N HCl	Soluble
5	Phosphate buffer (pH 6.8)	Soluble

The solubility evaluation of Ofloxacin been done only on visual inspection of solution of drug and solvent in which the solubility of drug is to be determined.

Melting point

It was determined as per procedure given in experimental work part. The results are illustrated in following table.

Table 7.3: Melting point of drug Ofloxacin.

Sr. No	Material	Melting point	Specification
1.	Ofloxacin	156^0C	158^0C

The result of table indicates the drug Ofloxacin was pure one.

Determination of Wavelenth of Maximum Absorbance (λmax)

Ofloxacin solution was scanned in range of 200-400 nm using UV spectrophotometer:

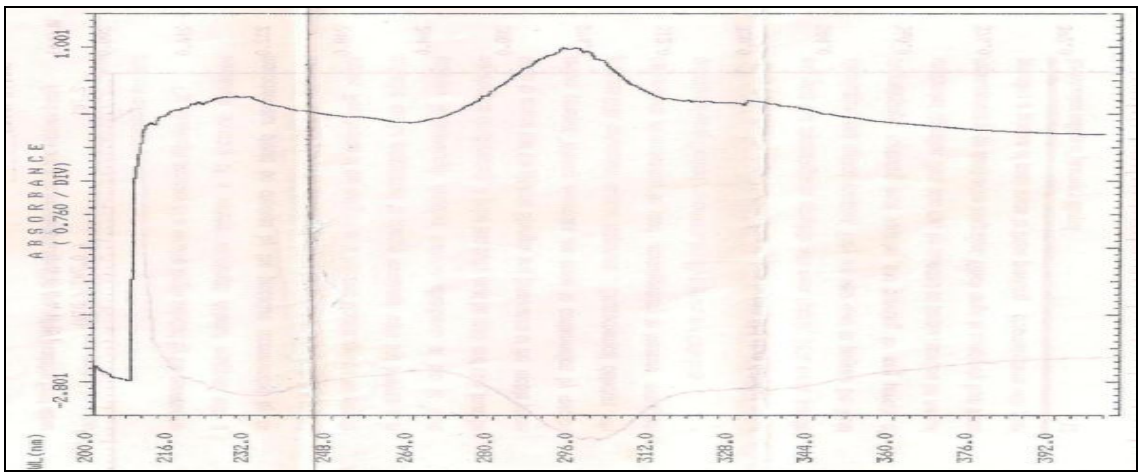

Fig no.: UV spectrogram of Ofloxacin for λmax determination.

Table no.: Wavelenth of Maximum Absorbance.

Conc. (µg/mL)	Scanning range(nm)	λ_{max}
10	200-400	296.0

Preparation of the Calibration Curves of Oloxacin

Table no.: Linearity of Ofloxacin in 0.1N HCl.

Conc. (ug/ml)	0	5	10	15	20	25
Absorbance	0	0.158	0.280	0.476	0.604	0.777

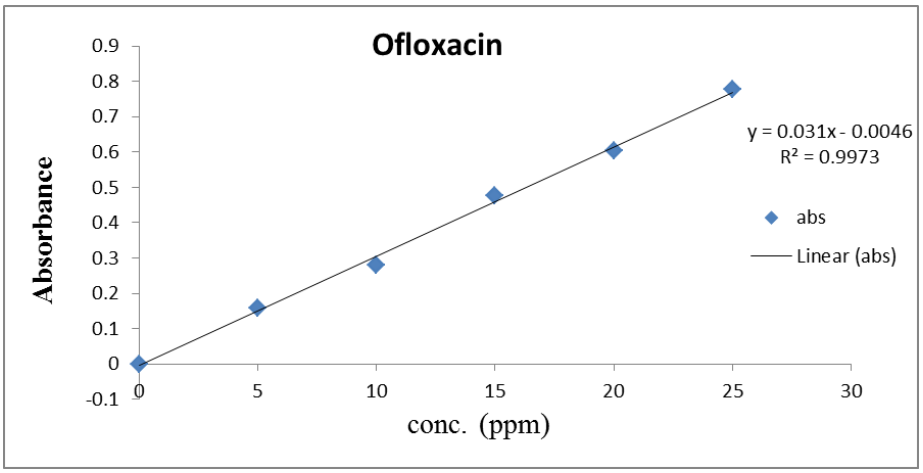

Fig. no.: Standard Calibration Curve of Pure Ofloxacin.

Regression Equation

$$Y = mx + c,$$

$Y = 0.031x - 0.004$

Y= abs. of unknown sample

m= slope = 0.031

X= Conc. in µg/ml

c= Intercept .004

r^2= 0.997

7.1.7 Partition Co-efficient

Table7.7: Partition Co-efficient.

Sr. No.	Solvents	Absorbance
1.	Water	1.378
2.	n- Octanol	1.363

Partition coefficient = concentration of n- Octanol/ concentration in water

Concentrtion in n-Octanol: Y= 0.084x – 0.007

1.363= 0.084x – 0.007

X= 1.363+0.007/ 0.084= 16.309

Concentrtion in water: Y= 0.084x – 0.007

1.378=0.084x – 0.007

X= 1.378+0.007/ 0.084=16.488

Partition coefficient = 16.309/ 16.488= 0.989

Drug excipient compatibility study

Physical Compatibility Study

Table no.: Physical Compatibility Study of Ofloxacin with polymer.

Sr. no.	Material	Storage at room temperature	Storage at 45^0C -50^0C	Storage at 2^0C -8^0C
1	Pure Drug (10mg)	Stable, No change in color	Stable, No change in color	Stable, No change in color
2	Ofloxacin+ EC	Stable, No change in color	Stable, No change in color	Stable, No change in color

Compatibility Study by FT-IR

FTIR Peaks of Ofloxacin

Table no.: Interpretation of FT-IR spectrogram.

Standarded Peaks(Cm^{-1})	Observed Peaks(Cm^{-1})	Peak Assigned
3050-3000	3050	O-H str
3000-2840	2800	CH_3str
1650-1600	1630	C=C str
1750-1700	1720	C=O str (acid)
1392-1366	1350	N-H str
1050-1000	1025	C-F str

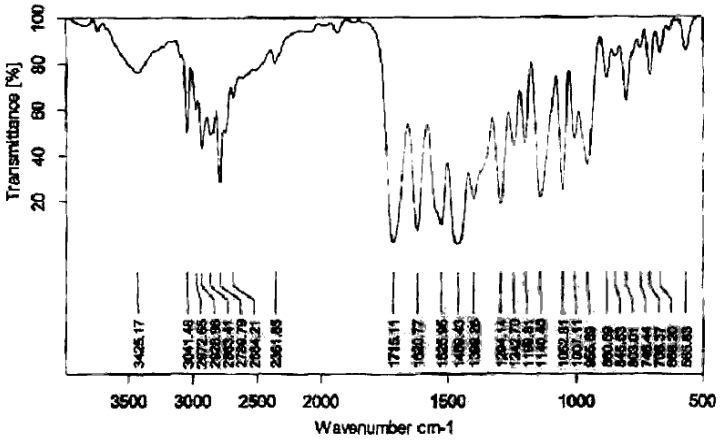

Fig. no.: FT-IR spectrogram of Ofloxacin.

Preparation of floating Microsphere

Table 6.4: Composition of various Formulations using EC.

Formulation code	Ofloxacin	Ethyl Cellulose	Tween-80
EC1	100	100	0.1%
EC2	100	200	0.1%
EC3	100	300	0.1%
EC4	100	400	0.1%
EC5	100	500	0.1%

Evaluation of prepared floating Microsphere

Table no.: Evaluation of prepared floating Microsphere.

Batch code	Yield (%)	Mean Particle size(µm)	Encapsulation Efficiency (%)
EC1	94.28±0.045	644±0.016	89.80±0.025
EC2	92.46±0.038	663±0.012	92.70±0.038
EC3	91.69±0.052	676±0.007	98.20±0.059
EC4	95.43±4.7	463+2.6	78.6±1.3
EC5	93.24±2.6	521±4.4	86.2±2.0

Micromeritic properties of floating Microspheres

Table no.: Evaluation of micromeritic properties of floating microsphere.

Batch Code	Bulk Densityg/cm^3	Tapped Density g/cm^3	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ)
EC1	0.102	0.169	39.65 %	1.657	31
EC2	0.106	0.170	37.65 %	1.604	35
EC3	0.112	0.118	05.08 %	1.054	17
EC4	0.123	0.174	29.31 %	1.415	28
EC5	0.128	0.184	30.44 %	1.438	29

***In-vitro* buoyancy studies**

Table no.: Percentage buoyancy studies.

Formulation	% Buoyancy			
	6 Hrs.	12 Hrs.	18 Hrs	24 Hrs
EC1	90.4 ± 0.224	91.3 ± 0.520	80.3 ± 0.120	68.2 ± 0.111
EC2	89.3 ± 0.322	78.4 ± 0.621	69.3 ± 0.021	51.4 ± 0.733
EC3	93.9 ± 0.663	82.1 ± 0.123	71.7 ± 0.221	65.2 ± 0.191
EC4	73.6 ± 0.812	62.2 ± 0.413	51.5 ± 0.271	41.1 ± 0.505
EC5	78.5 ± 0.632	74.4 ± 0.102	61.9 ± 0.621	51.2 ± 0.353

On the basis of various parameter of evaluation of floating microspheres formulations, **EC-1, EC-2, EC-4** and **EC-5** were possessed poor mircomeritic properties. Hence, all formulations except **EC-3** were not suitable for further investigation. Only, **EC-3** microsphere batch having 65.2 % buoyancy was taken for further studies.

***In-vitro* drug release study**

Table no.: *In-vitro* % cumulative drug release of floating microspheres.

Time (hrs)	EC-1	EC-2	EC-3	EC-4	EC-5
0	0	0	0	0	0
1	17.249	19.62	21.6	29.7	22.68
2	29.835	31.68	33.12	34.365	30.726
4	32.34	39.68	44.64	37.435	41.876
6	44.566	48.7	49.692	41.781	48.227
8	50.931	59.22	60.405	49.39	49.932
10	60.57	65.62	70.276	58.3	55.785
12	78.541	82.18	73.72	65.998	61.489
16	81.49	84.6	81.681	71.937	67.403
18	84.273	88.56	87.011	76.827	72.808
20	88.329	93.18	93.092	85.162	76.621
24	92.765	95.56	97.913	96.241	81.533

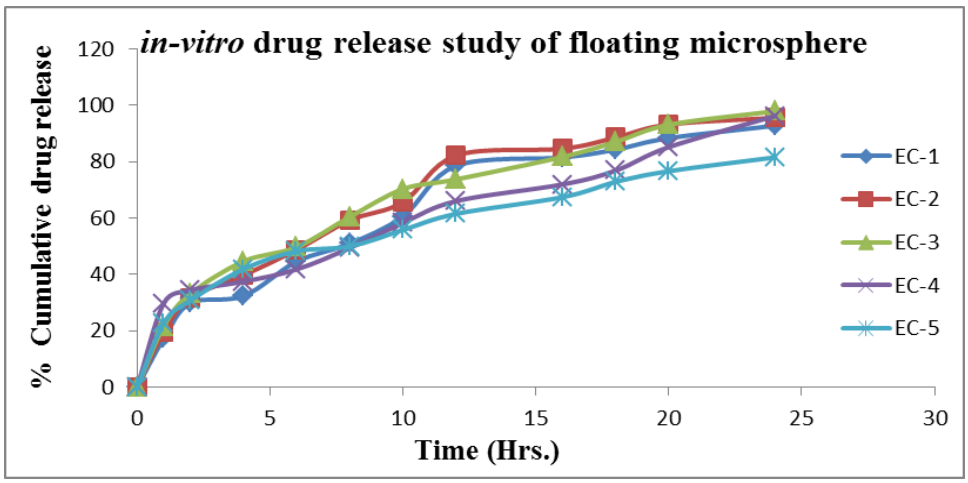

Fig. no.: in-vitro drug release study of floating microspheres.

***In-Vitro* Release Profile of optimized Ofloxacin floating Microsphere batch EC-3**

Time (hr.)	S.R.T.	Log T.	Abs.	Conc. (µg)	Amt. in 5ml	Amt. in 900ml	Correction factor	C.R	Log % C.R	Drug remaining	Log% drug release
0	0	0	0	0	0	0	0	0	0	100	2
1	1	0	0.745	24.166	0.120	21.6	-	21.6	1.334	78.4	1.894
2	1.141	0.301	1.141	36.944	0.184	33.12	0.120	33.12	1.521	66.76	1.824
4	2	0.602	1.539	49.722	0.248	44.64	0.304	44.64	1.652	55.056	1.74
6	2.449	0.777	2.048	66.388	0.273	49.14	0.552	49.692	1.696	50.308	1.701
8	2.828	0.903	2.381	76.944	0.331	59.58	0.825	60.405	1.781	39.591	1.597
10	3.162	1.000	2.483	80.277	0.384	69.12	1.156	70.276	1.846	29.724	1.473
12	3.464	1.079	2.747	88.611	0.401	72.18	1.54	73.72	1.86	26.18	1.419
16	4	1.204	2.925	94.166	0.443	79.74	1.941	81.681	1.912	18.319	1.263
18	4.242	1.255	3.102	100.27	0.470	84.6	2.411	87.011	1.939	12.989	1.113
20	4.472	1.301	3.446	111.38	0.501	90.18	2.912	93.092	1.968	6.908	0.839
24	4.898	1.380	3.253	105.27	0.525	94.6	3.|413	97.913	1.990	2.087	0.319

Kinetic Modeling of ofloxacin release data of floating microsphere batch EC-3

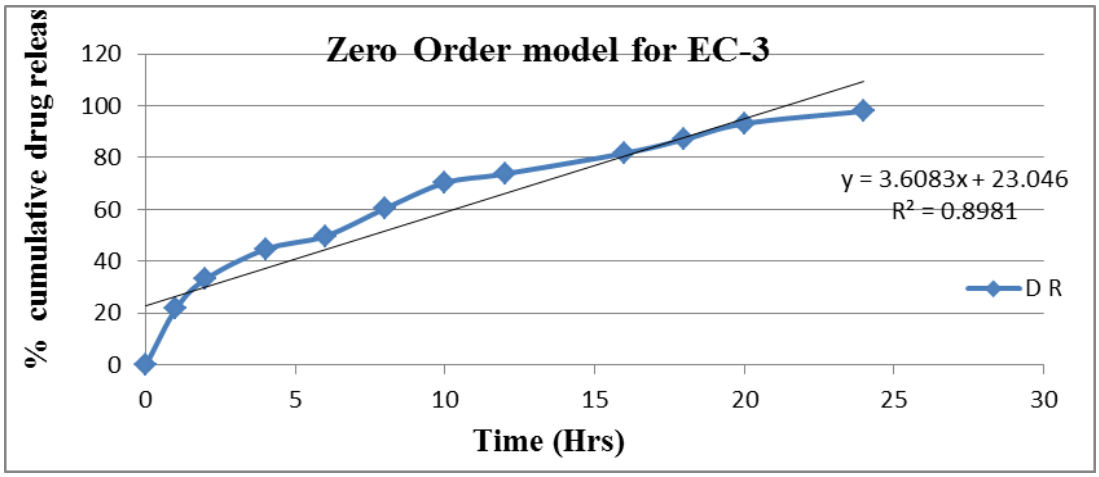

Fig. no.: Zero order model for EC-3.

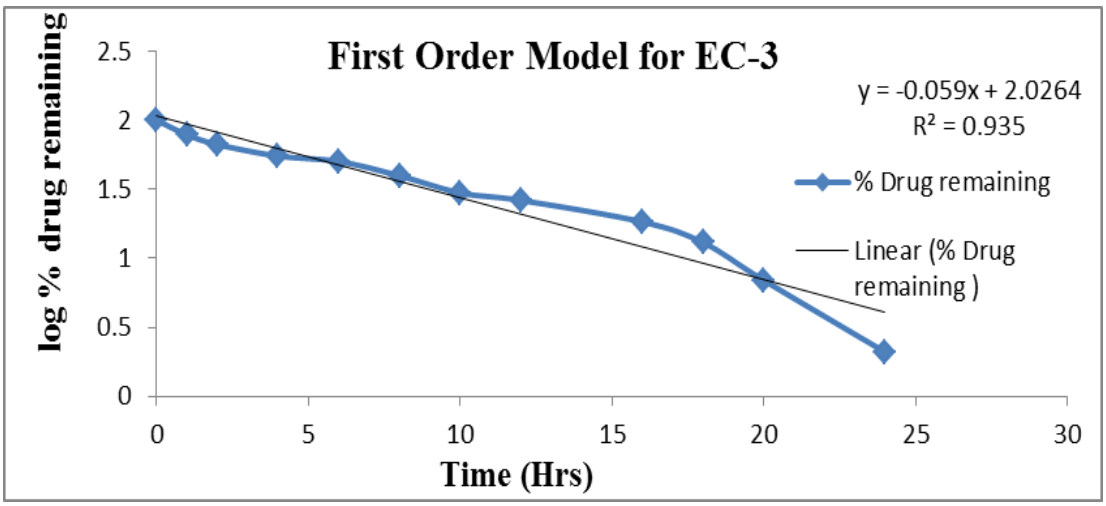

Fig. no.: Fisrt order model for EC-3.

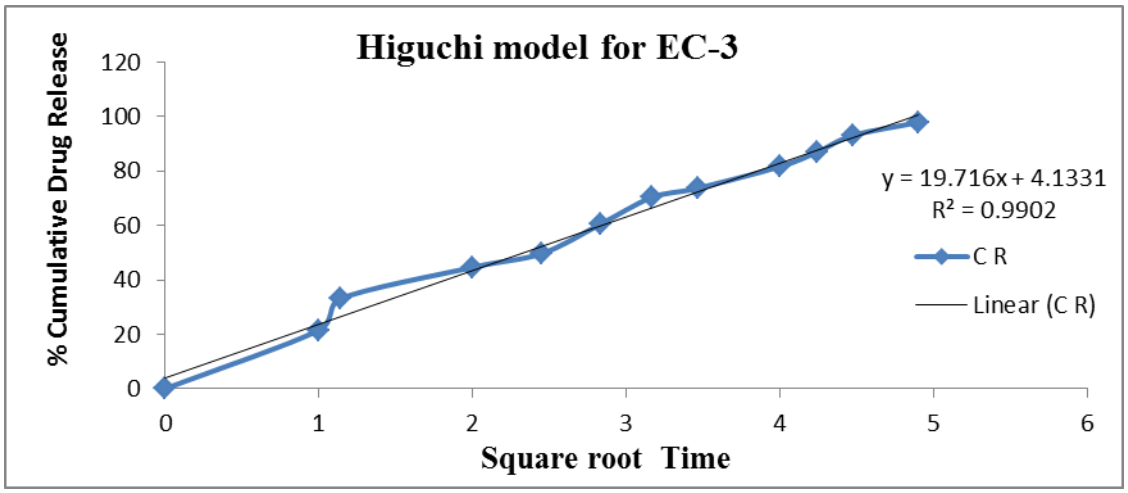

Fig. no.: Higuchi model for EC-3.

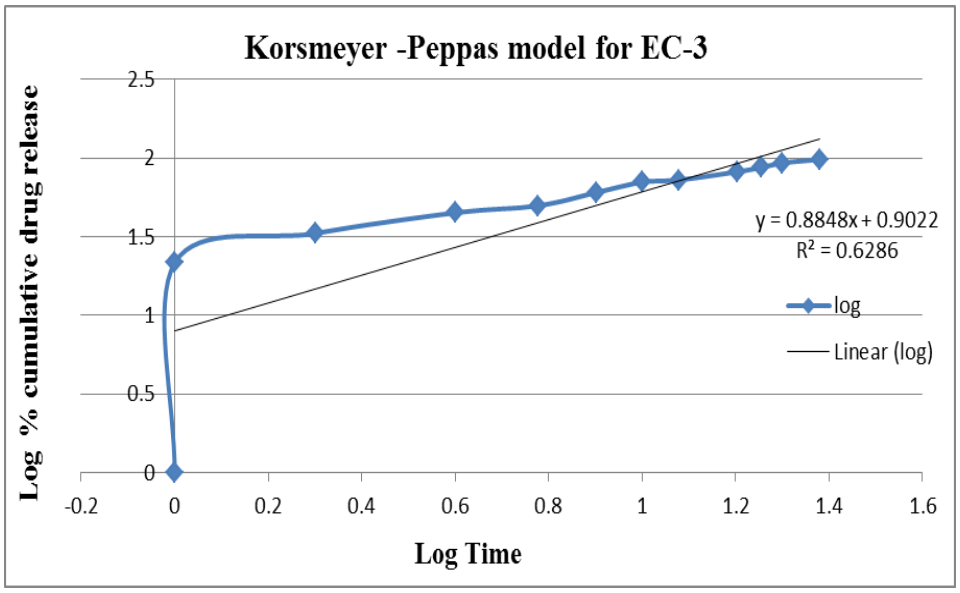

Fig. no.: Korsmeyer- Peppas model for EC-3.

Table no.: i*n-vitro* curve fits for various release systems for optimized.

Model	Equation	R^2
Zero order	y = 3.608x + 23.04	0.898
First order	y = -0.059x + 2.026	0.935
Higuchi	y = 19.71x + 4.133	0.990
Korsmeyer –Peppas	y = 0.884x + 0.902	0.628

Stability Studies

Table no.: Stability studies of optimized floating microsphere batch EC-3.

Time (Days)	% Drug release		
	4 ^oC	25 ^oC	45 ^oC
0	97.1	97.1	97.1
15	97.1	97.1	93.32
30	94.02	97.1	95.06

DISCUSSION

During the Preformulation studies it is found that the organoleptic properties of Ofloxacin comply as reported. Pale yellow, bitter, odorless, amorphous powder of ofloxacin was soluble in water, 0.1N HCl and Phosphate buffer (pH 6.8) and freely soluble in ethanol and methanol. Melting point was observed at 156 ^{0}C and λ_{max} at 296nm. Standard calibration curve was prepared using concentration range 5- 25 ug/ml and linearity equation as y = 0.031x – 0.004 with R^2 = 0.997. Partition coefficient was found 0.989. Drug ofloxacin was also compatible with used excipients, physically stable, no color change reaction observed at 2^0C - 8^0C, room temperature and 45^0C -50^0C, also chemically stable as observed in FT-IR spectra.

Five different formulations were prepared by o/w emulsion solvent evaporation method using different concentration of Ethyl Cellulose EC) and fixed amount (100mg) of ofloxacin and tween-80 (1%). Evaluation of prepared floating microsphere were found yield between 91.69 to 95.43%, mean particle size between 463 to 676 µm and encapsulation efficiency between78.6 to 98.2%. On the basis of various parameter of evaluation of floating microspheres formulations, **EC-4** has greater yield 95.43 % but its encapsulation efficiency was lower 74.6. **EC-1, EC-2, EC-4** and **EC-5** were possessed poor mircomeritic properties e.g. Carr's Index 39.65, 37.65, 29.31 and 30.44% respectively, Hausner's ratio 1.657, 1.604, 1.415 and 1438 respectively and angle of repose (θ) 31, 35, 28 and 29 respectively that indicates irregular shape, improper size distribution and poor to very poor flow properties of the prepared microsphere. Hence, all formulations except **EC-3** were not suitable for further investigation. **EC-3** microsphere batch possessed yield (91.69%), particle size (676 µm), encapsulating efficiency (98.2), Carr's Index (5.08%), Hausener's ratio (1.054) and 65.2 % *in-vitro* buoyancy which was excellent among all prepared formulations. Also drug release was 97.913 %. SEM analysis also indicated that floating Microsphere batch EC-3 had smooth surface and regular in shape. *In-vitro* drug release data was further expended for kinetic modeling. Kinetic modeling revealed that floating microsphere batch EC-3 was followed Higuchi model with regression value (R^2) 0.990.

Stability studies for 30 days was performed on three different temperatures (4, 25 & 45^oC) and found that no significant variation in % drug release of optimized floating microspheres batch EC-3 during whole study.

CONCLUSION

Floating microspheres of ofloxacin were prepared by novel o/w emulsion solvent evaporation technique using Ethyl cellulose polymers order to retain drug in body for longer period of time. Ofloxacin has short half life of 9 h. The drug requires a novel gastroretentive drug delivery system which can provide an extended period of time in stomach and improve oral bioavailability. Floating microspheres were characterized for floating ability, compatibility study, particle size and shape, entrapment efficiency, *in-vitro* drug release. Due to their low density, these multi particulate drug delivery systems showed good floating ability and remained in gastric environment for more than 24 hrs, required for sustained therapeutic activity. Major advantages of the system include ease of preparation, good floating ability, high encapsulation efficiency and sustained drug release over 24 hours. From this study, it

was concluded that formulation of floating microspheres of ofloxacin offers prolonged gastric residence time and continuous release of the medication over an extended period of time thus oral bioavailability of the drug and subsequent efficacy is improved.

CONFLICTS OF INTEREST

There are no conflicts of interests.

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