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DEVELOPMENT AND EVALUATION FLOATING MICROSPHERE OF OFLOXACIN

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ABSTRACT

Gastric emptying is a complex process, one that is highly variable and that makes in vivo performance of drug delivery systems uncertain. A controlled drug delivery system with prolonged residence time in the stomach can be of great practical importance for drugs with an absorption window in the upper small intestine. The main limitations are attributed to the inter- and intra-subject variability of gastro-intestinal (GI) transit time and to the non-uniformity of drug absorption throughout the alimentary canal. Floating or hydrodynamically controlled drug delivery systems are useful in such applications. Various gastroretentive dosage forms are available, including tablets, capsules, pills, laminated films, floating microspheres, granules and powders. Floating microspheres have been gaining attention due to the uniform distribution of these multiple-unit dosage forms in the stomach, which results in more reproducible drug absorption and reduced risk of local irritation. Such systems have more advantages over the single-unit dosage forms. 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 to replicate one DNA double helix into two. Notably the drug has 100 times higher affinity for bacterial DNA gyrase than for mammalian. Ofloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria.

INTRODUCTION

Oral controlled release dosage forms have been developed over past three decades. These drug delivery system have a great potential of solving problems associated with conventional multiple dosing system like strict adherence to timely dosing, flip flop plasma concentration, associated side effects due to systemic accumulation of drug. Thus, there are numerous advantages such as improved efficacy, reduced toxicity, improved patient compliance and convenience, reduction in health care cost, etc.

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. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. FDDS can be divided into non-effervescent and effervescent systems.

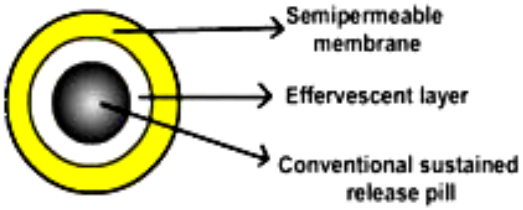

Figure 1: Multiple unit type floating pill with different layers

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 to replicate one DNA double helix into two. Notably the drug has 100 times higher affinity for bacterial DNA gyrase than for mammalian. Ofloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria.

Ofloxacin acts on DNA gyrase and toposiomerase IV, enzymes which, like human topoisomerase, prevents the excessive supercoiling of DNA during replication or transcription. By inhibiting their function, the drug thereby inhibits normal cell division.

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RESEARCH ENVISAGED

An attempt is being made to develop and characterize floating microspheres, which afteroral administration could prolong gastric residence time and increase drug bioavailability.

Oral delivery of drug is most preferable route of drug delivery due to ease of administration, patient compliance and flexibility of formulation, etc. From immediate release to site specific delivery, oral dosage forms have really progressed. Several difficulties have been faced in designing controlled release systems for better absorption and enhanced bioavailability. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for dosage form and controlled drug release. Preparation remains buoyant in stomach content due to its lower density than that of gastric fluid. It is well accepted fact that it is difficult to predict the real. *in-vivo* time of release with solid, oral controlled release dosage forms. Thus drug absorption in gastrointestinal tract may be very short and high variable in certain circumstances. Gastric emptying of multiparticulate floating system would occur in consistent manner with reduced intersubject variability in absorption. On each subsequent gastric emptying, sunken particles will spread out over large area of absorption site, increasing the opportunity for drug release and absorption.

MATERIAL AND METHOD

The API Ofloxacin was obtained from Ranbaxy,Devas, Ethyl Cellulose was obtained from Sulab, Varodara, Ethanol (95%) was obatined from Jiangsu Huaxi International Trade co.Ltd.China, Guar GumTitan from Biotech Ltd.Bhiwadi, Heavy Liquid Paraffin from Himedia Labolatory,Mumbai, Tween 80 from J & K Scientifics. China, n-Hexane Rankem,from Mumbai, Sodium Aliginate and Calcium Cloride from Oxford Laboratory, Mumbai.

Pre formulation Study

Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients. Preformulation investigations was designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and Pharmacokinetic- biopharmaceutical properties of the resulting product. Which includes Organoleptic Properties, Determination of Solubility, Melting Point Determination, Analytical Estimation by UV Spectrophotometer, Partition coefficient, etc. Observation of all these methods are shown below:

Table no.1: Organoleptic Properties of drug Ofloxacin

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

Table no.2: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

Table no.3:Melting point of drug Ofloxacin

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

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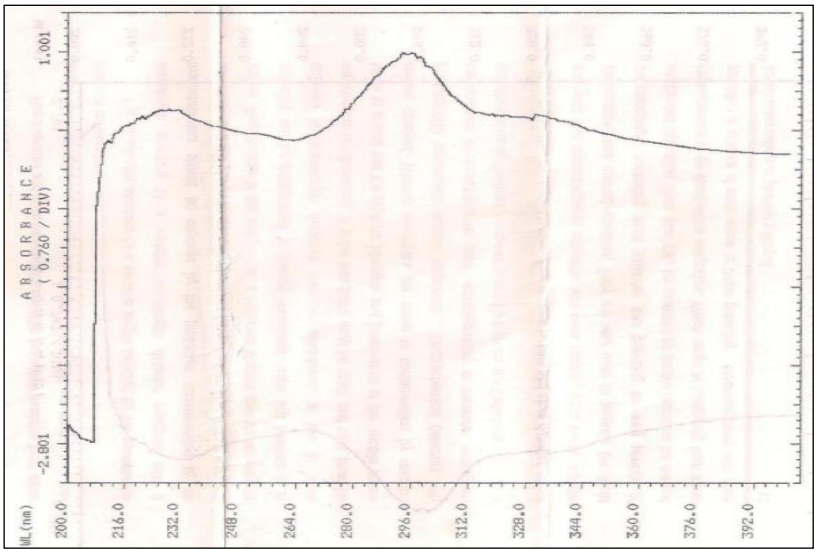

Figure 2: UV spectrogram of Ofloxacin for λmax determination

Table no.4:Wavelenth of Maximum Absorbance

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

Table no.5: 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

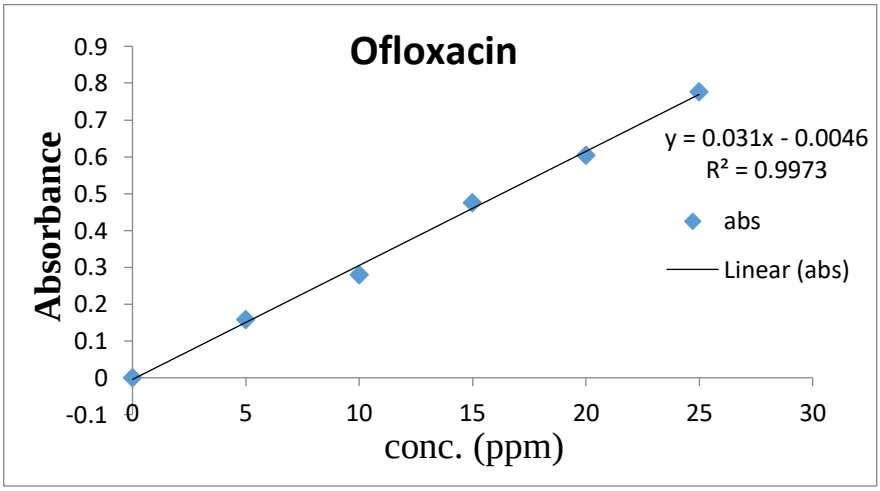

Figure 3: Standard Calibration Curve of Pure Ofloxacin

Table no.6: Partition Co-efficient

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

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Table no.7: 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

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:

Table no.8: 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%

Table no.9: 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

Table no.10: evaluation of micromeritic properties of floating microsphere

Batch Code	Bulk Density g/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

Table no.11: 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

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Table no.12 : *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

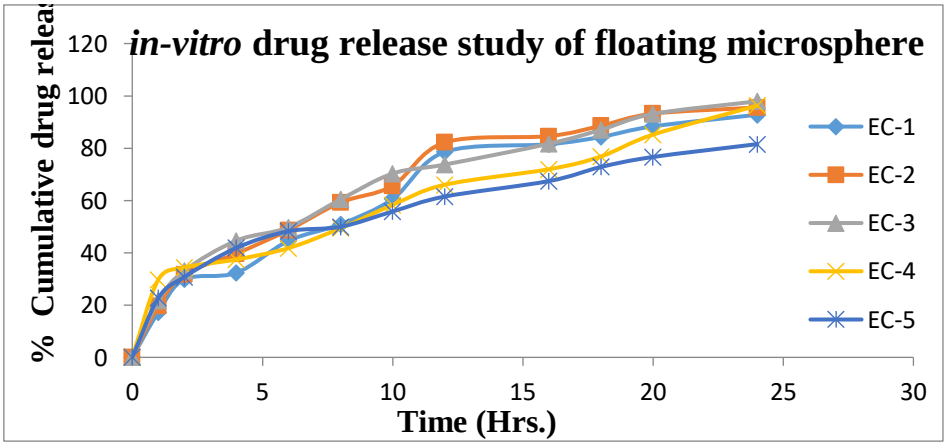

Fig. no.4: in-vitro drug release study of floating microspheres

Table no.13: *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

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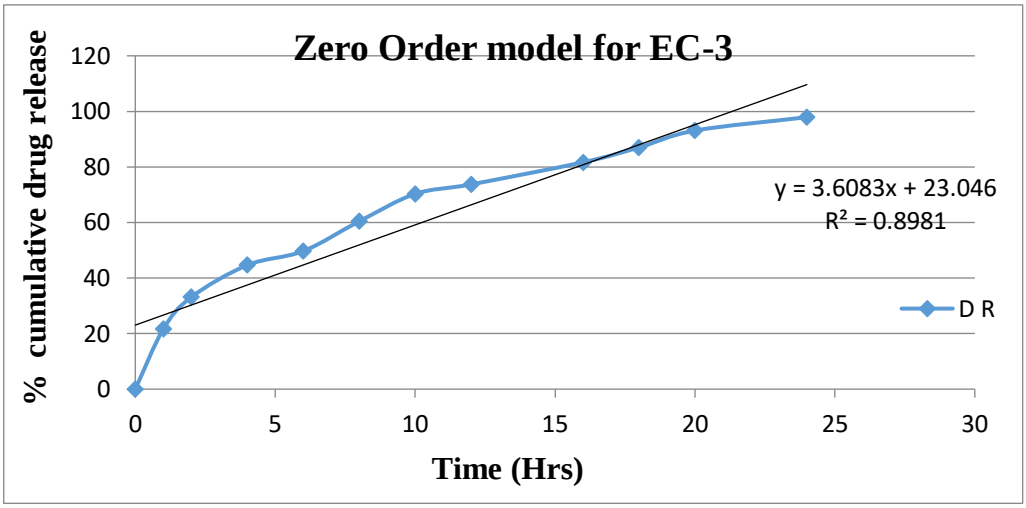

Figure 5: zero order model

Table no.14: 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

DISCUSSION AND RESULT

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 156^0C 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.

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. Ofloxacinhas 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.

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