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DESIGN AND DEVELOPMENT OF FLOATING MICROSPHERES OF OFLOXACIN

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Abstract:

In the present study design and development of floating microspheres of ofloxacin. 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 = 0.032x – 0.003 with R^2 = 0.998. Partition coefficient was found 0.989. 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 between 78.6 to 98.2%. On the basis of various parameter of evaluation of floating microspheres formulations, ***F-4*** *has greater yield 95.43 % but its encapsulation efficiency was lower 74.6.* ***F-1, F-2, F-4*** *and* ***F-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 F-****3*** *were not suitable for further investigation. F-****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 also drug release was 97.913 %. Stability studies for 30 days was performed on three different temperatures (4, 25 & 45°C) and found that no significant variation in % drug release of optimized floating microspheres batch F-3 during whole study.*

KEYWORDS: *Residence time, Sustained release, therapy, drug release, bioavailability*

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INTRODUCTION:

Recently in the field of pharmaceutical technology, great efforts are being directed towards the refabrication of existing drug molecules in a fashion, capable of solving problem related to poor water solubility, poor bioavailability, dosing problem, stability, toxicity, etc. This trend of working has lead to development of new drug delivery system.

Even today, conventional drug delivery systems are primary pharmaceutical products commonly seen in prescriptions and 'over the counter' market place. They provide prompt release of the drug, but in order to achieve as well as maintain drug concentration within therapeutically achieved range, it is often necessary to administer it several times a day. Conventional drug therapy results in significant fluctuations of drug concentration in systemic circulation causing either lethal effect or no therapeutic action.

Basic goal of drug therapy is to provide therapeutic amount of drug to proper site in body to promptly achieve and then maintain desired drug concentration. This idealized objective points to two aspects most important to the drug delivery, namely spatial placement and temporal delivery of drug. Spatial placement relates to targeting a drug to specific organ or tissue while temporal delivery refers to controlling rate of drug delivery to that specific organ or tissue.

Despite tremendous advancement in drug delivery, oral route remains preferred route for administration. 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.
However, this approach is faced with several physiological difficulties such as inability to restrain and locate controlled drug delivery system within the desired region of GIT, due to variable gastric emptying and motility. Furthermore the relative brief gastric emptying time in humans which normally averages 2-3 hrs through major absorption zone i.e. stomach and upper part of intestine can result in incomplete drug release from drug delivery system leading to low bioavailability and thus reduced efficacy of administered dose.

Efforts to improve oral drug bioavailability have grown in parallel with pharmaceutical industry. As the number and chemical diversity of drugs has increased, new strategies are required to develop orally active therapeutics. The past two decades have been characterized by an increased understanding of causes of low bioavailability and great deal of innovation in oral delivery technologies, marked by an unprecedented growth of drug delivery industry.

It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in stomach for prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in GIT is to control gastric residence time.

Control of placement of drug delivery system in specific region of GIT offers advantage for variety of important drugs characterized by narrow absorption window in GIT or drugs with stability problem. These considerations have lead to development of unique oral controlled release dosage form with gastro retentive properties i.e. dosage form could be retained in the stomach for several hours and release the drug there in a controlled and prolonged manner, so that drug could be supplied continuously to its absorption site in the upper GIT.

To comprehend the considerations taken in design of gastro retentive dosage forms and to evaluate their performance, the relevant anatomy and physiology of GIT must be fully understood.

The GIT is essentially a tube about 9 meters long that runs through middle of body from mouth to anus and include throat(pharynx), oesophagus, stomach, small intestine(consisting of duodenum, jejunum and ileum) and large intestine(consisting of cecum, appendix, colon and rectum). In the living person it is shorter because the muscles along walls of GIT organs are in state of tone (sustained contraction).

MATERIALS AND METHOD:

MATERIALS: ofloxacin drug was obtained from Lupin Pharmaceuticals Mandideep, India; ethyl cellulose were obtained from NRI chemical store Bhopal (M.P). Tween 80 potassium dihydrogen phosphate, sodium hydroxide was obtained from Govindpura drug store Bhopal. All ingredients used were of analytical grade.

METHODS:

Preformulation Study

Preformulation studies were the first step in the rational development of dosage form of a drug substance.

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.

Table 1: various Solubility Terms

Descriptive terms	Parts of Solvent Required For Parts of Solute
Very Soluble	Less than 1
Freely Soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly Soluble	From 30 to 100
Slightly Soluble	From 100 to 1000
Very Slightly Soluble	From 1000 to 10000
Practically insoluble	More than 10000

Melting Point Determination

The Melting point was determined by the capillary method using Digital Melting point apparatus.

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 from200-400nm using double beam visible spectrophotometer.

Preparation of Calibration Curve

Preparation of stock solution

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.

Partition coefficient

In pharmaceutical sciences, a partition coefficient is the ratio of concentrations of a compound in the two phases of a mixture of two immiscible solvents at equilibrium.

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 polymersolution. This solution was added slowly to a beaker having 300 ml of watercontaining 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 werecollected by decantation then filtration anddried at room temperature.Compositions of various formulations are shown in table.

Evaluation of Ofloxacin Microsphere

6.3.3.1 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.

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

6.3.3.2. 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.

6.3.3.3 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.

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: 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 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.

In-vitro Release Studies of Microsphere

In-vitro release studies were carried out using USP type I apparatus at 37±0.5° 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 14h 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 2: 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.

7.1.4 Solubility study: Solubility of Ofloxacin was determined in various aqueous and non aqueous solvents.

Table 3: 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

7.1.3 Melting point

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

Table 4: 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.

7.1.5 Determination of Wavelenth of Maximum Absorbance (λmax)

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

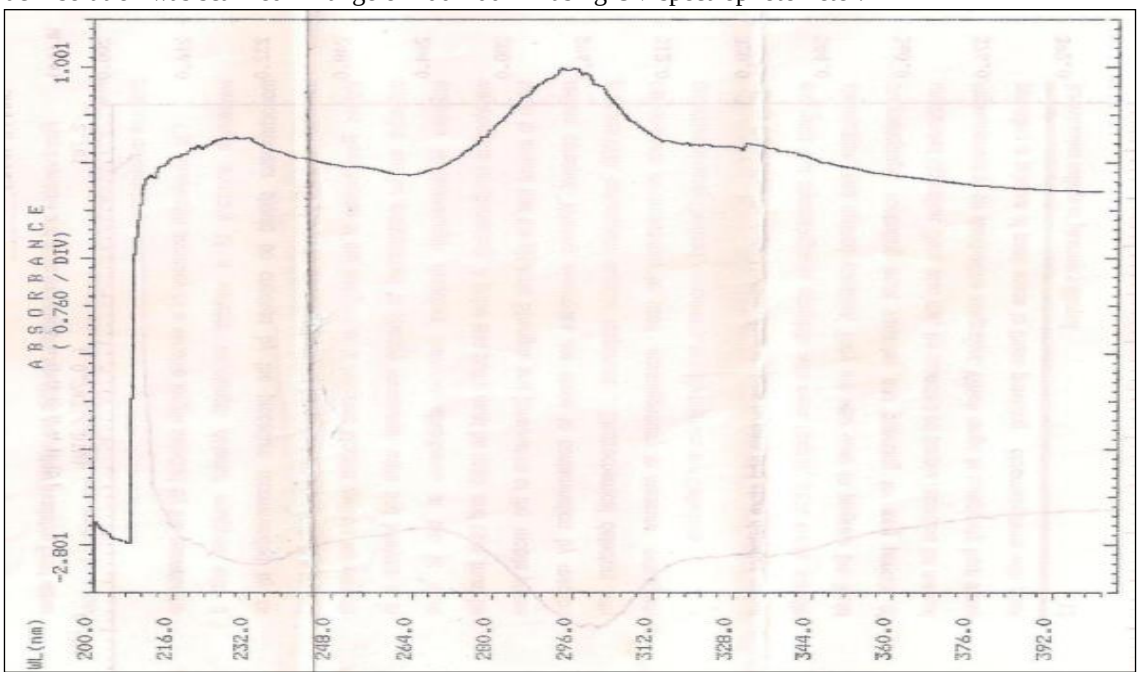

Fig no.1: UV spectrogram of Ofloxacin for λmax determination

Table 5: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 6: 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

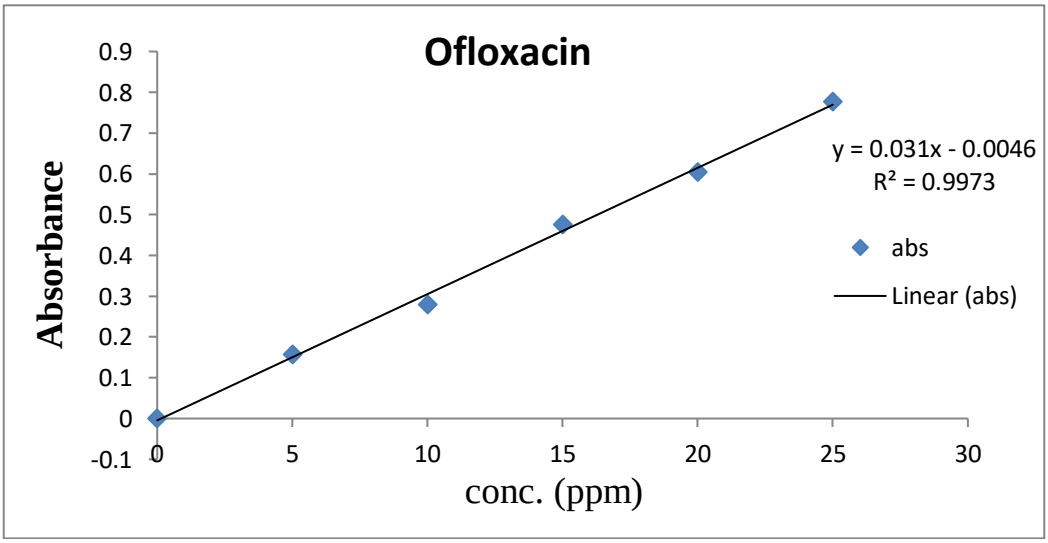

Fig. no.2: Standard Calibration Curve of Pure Ofloxacin

Partition Co-efficient

Table 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

Partition coefficient = 16.309/ 16.488= 0.989

Preparation of floating Microsphere

Table 8:Composition of various Formulations using EC

Formulation code	Ofloxacin	Ethyl Cellulose	Tween-80
F1	100	100	0.1%
F2	100	200	0.1%
F3	100	300	0.1%
F4	100	400	0.1%
F5	100	500	0.1%

Evaluation of prepared floating Microsphere

Table 9:Evaluation of prepared floating Microsphere

Batch code	Yield(%)	Mean Particle size(µm)	Encapsulation Efficiency (%)
F1	94.28±0.045	644±0.016	89.80±0.025
F2	92.46±0.038	663±0.012	92.70±0.038
F3	91.69±0.052	676±0.007	98.20±0.059
F4	95.43±4.7	463+2.6	78.6±1.3
F5	93.24±2.6	521±4.4	86.2±2.0

Micromeritic properties of floating Microspheres

Table 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)
F1	0.102	0.169	39.65 %	1.657	31
F2	0.106	0.170	37.65 %	1.604	35
F3	0.112	0.118	05.08 %	1.054	17
F4	0.123	0.174	29.31 %	1.415	28
F5	0.128	0.184	30.44 %	1.438	29

On the basis of various parameter of evaluation of floating microspheres formulations, **F-4** has greater yield 95.43 % but its encapsulation efficiency was lower 74.6. F-**1, F-2, F-4** and **F-5** were possessed poor mircomeritic properties e.g. Carr's Index, Hausner's ratio and angle of repose (θ) that indicates irregular shape, improper size distribution and poor to very poor flow properties of the prepared microsphere, hence, all formulations except **F-3** were not

suitable for further investigation. Only, **F-3** microsphere batch having 98.20±0.059 encapsulation efficiency was taken for further studies.

In-vitro drug release study

Table 11: *in-vitro*% cumulative drug release of floating microspheres

Time (hrs)	F-1	F-2	F-3	F-4	F-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

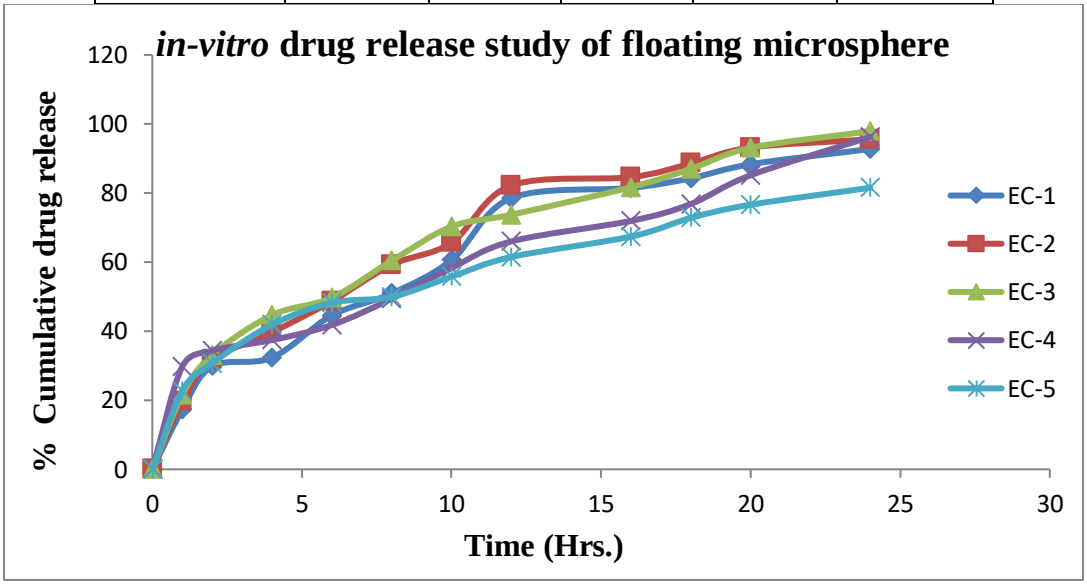

Fig. no.3: In-vitro drug release study of floating microspheres

STABILITY STUDIES

Table 12: Stability studies of optimized floating microsphere batch F-3

Time (Days)	% Drug release		
	4 ºC	25 ºC	45 ºC
0	97.91	97.91	97.91
15	97.91	97.90	93.31
30	94.01	97.90	95.05

SUMMARY AND 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.

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