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DEVELOPMENT AND CHARACTERIZATION OF MOUTH DISSOLVING TABLETS OF DOMPERIDONE

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ABSTRACT: 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 λmax 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. 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 µmand encapsulation efficiency between78.6 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 possessedyield (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 F-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 F-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 & 45ºC) and found that no

significant variation in % drug release of optimized floating microspheres batch F-3 during whole study.

KEYWORDS: Sustained release, drug, floating, Evaluation, therapy

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.

MATERIALS AND METHODS:

Materials: Chemical Used

Table 6.1: The Material Used in the Preformulation Studies

S No	Material Used	Manufacturer
1.	Ofloxacin	Ranbaxy, Devas
2.	Ethyl Cellulose	Sulab, Varodara
3.	Ethanol (95%)	Jiangsu Huaxi International Trade co.Ltd.China
4.	Guar Gum	Titan Biotech Ltd.Bhiwadi
5.	Heavy Liquid Paraffin	Himedia Labolatory,Mumbai
6.	Tween 80	J & K Scientifics. China
7.	n-Hexane	Rankem, Mumbai
8.	Sodium Aliginate	Oxford Laboratory, Mumbai
9.	Calcium Cloride	Oxford Laboratory, Mumbai

Equipment Used

Table 6.2: List of equipments and their company/suppliers

S. No.	Equipments / Instruments	Menufacturer
1.	Ultra sonicator	EI instruments,Ahmedabad
2.	FT-IR	Brooker's,
3.	Hot Air Oven	Khera instruments, New Delhi
4.	Melting Point Apparatus	EI instruments,Ahmedabad
5.	Mechanical Stirrer	Remi,Bombay
6.	Optical Microscope	Lyzer, Ambala, Hariyana
7.	pH meter	Khera instruments, New Delhi
8.	Digital Weighing Balance	EI instruments,Ahmedabad
9.	UV (Double beam) spectrometer – 2203	Systronics, Ahmedabad
11.	Analytical SEM-JSM-6390A	JEOL

METHODS:

Preformulation Study

Preformulation studies were the first step in the rational development of dosage form of a drug substance. The objective of preformulation studies is to develop a portfolio of information about the drug substance, which is useful to develop formulation.

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.

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 from200-400nmusing 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 wasmade upto 10 ml using same solvent the prepared solution was 1 mg/ml or 1000µg/ml.

Preparation of dilutions from stock solution

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.

Partition coefficient

In pharmaceutical sciences, a partition- (P) or distribution coefficient (D) 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 usinga 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 entrappedin microsphere.

Micromeritic properties

Bulk Density: 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 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 0.1NHCl 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 No.1 : 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.

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

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. In present study, 0.1N HCl and ethanol were selected as solvents for the further studies of microspheres and phosphate buffer pH 6.8 were utilized as dissolution medium for microspheres.

Melting point

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

Table no. 3- Melting point ofdrug 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:

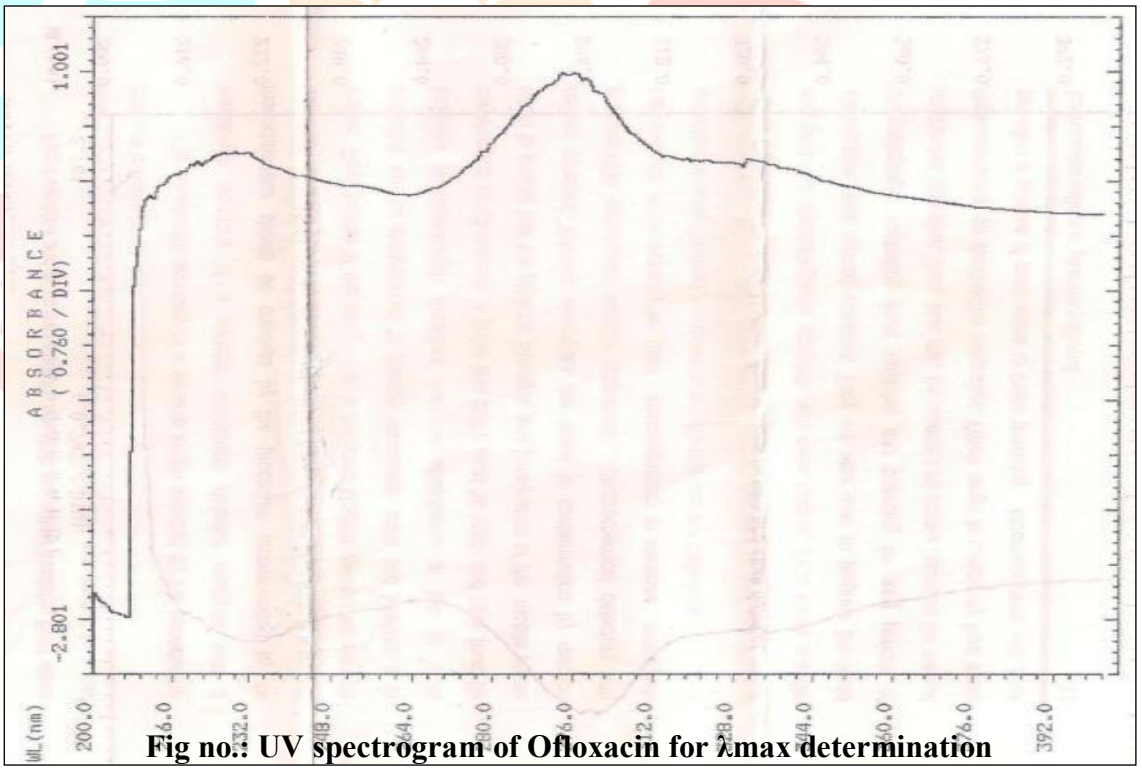

Fig no.: UV spectrogram of Ofloxacin for λmax determination

Table no. 4:Wavelenth of Maximum Absorbance

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

Preparation of the Calibration Curves of Oloxacin

Table no. 5: Linearity of Ofloxacin in 0.1N HCl

Conc. (ug/ml)	0	5	10	15	20	25
Absorbance	0	0.157	0.281	0.475	0.603	0.776

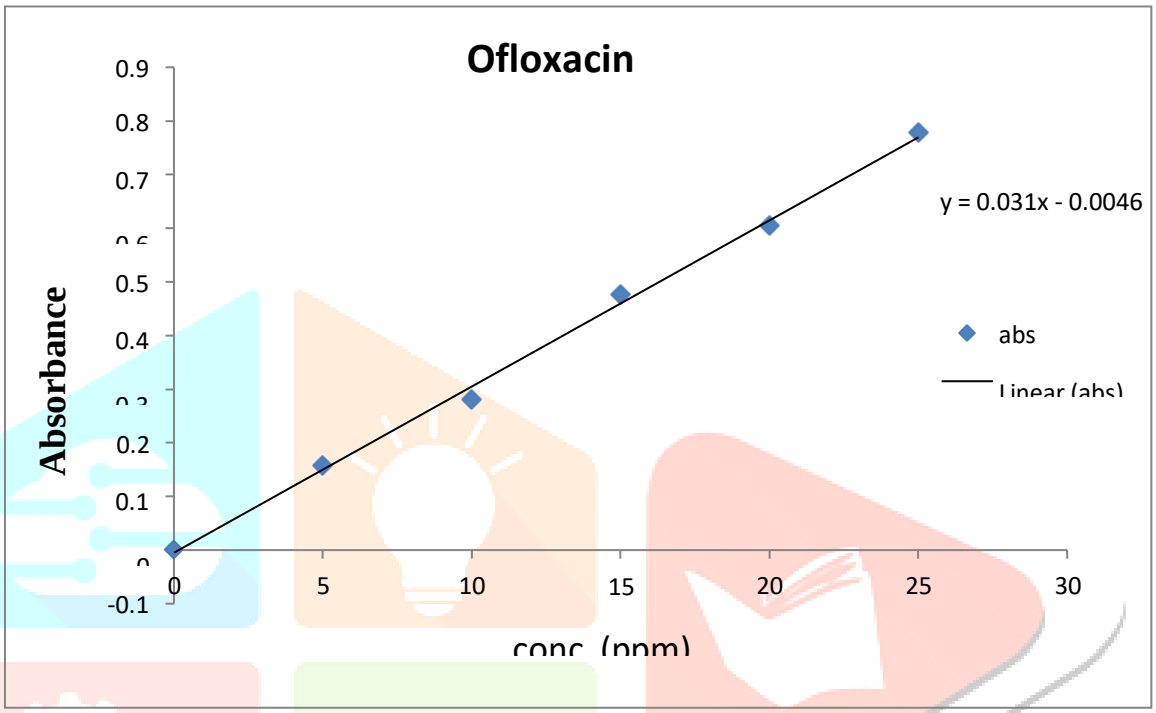

Fig. no.: Standard Calibration Curve of Pure Ofloxacin

7.1.7 Partition Co-efficient

Table no. 6: Partition Co-efficient

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

Partition coefficient = 16.309/ 16.488= 0.989

Preparation of floating Microsphere

Table no. 7:-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. 8:- Evaluation of prepared floating Microsphere

Batch code	Yield(%)	Mean Particle size(µm)	Encapsulation Efficiency (%)
EC1	94.27±0.045	643±0.016	89.80±0.025
EC2	92.45±0.038	663±0.012	92.70±0.038
EC3	91.68±0.052	676±0.007	98.20±0.059
EC4	95.42±4.7	463+2.6	78.6±1.3
EC5	93.23±2.6	521±4.4	86.2±2.0

Micromeritic properties of floating Microspheres

Table no. 8 : 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	0.103	0.166	38.65 %	1.647	30
EC2	0.105	0.171	36.65 %	1.614	34
EC3	0.111	0.117	06.08 %	1.044	16
EC4	0.122	0.172	28.31 %	1.425	27
EC5	0.127	0.183	29.44 %	1.428	28

In-vitro drug release study

Table no. 10 : 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	15.249	17.62	19.6	27.7	21.68
2	27.835	30.68	31.12	33.365	28.726
4	31.34	38.68	44.64	36.435	40.876
6	43.566	46.7	47.692	40.781	47.227
8	49.931	58.22	58.405	47.39	48.932
10	59.57	64.62	69.276	57.3	53.785
12	75.541	81.18	72.72	65.998	60.489
16	80.49	84.6	80.681	70.937	66.403
18	83.273	87.56	85.011	76.827	71.808
20	87.329	92.18	92.092	83.162	74.621
24	91.565	94.46	96.913	95.241	80.533

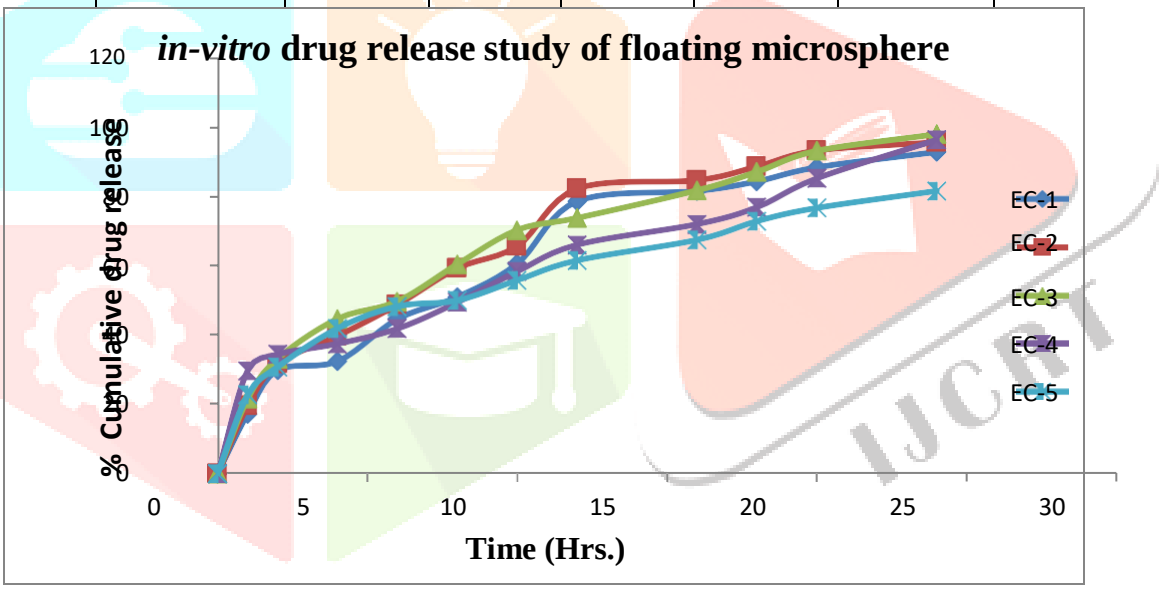

Fig. no.: in-vitro drug release study of floating microspheres

Stability Studies

Table no. 11 : Stability studies of optimized floating microsphere batch EC-3

Time (Days)	% Drug release		
	4 ºC	25 ºC	45 ºC
0	96.1	96.1	96.1
15	96.1	96.1	92.32
30	93.02	96.1	94.06

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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