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FORMULATION AND EVALUATION OF MICROPARTICULATE DRUG DELIVERY SYSTEMS OF CEFIXIME

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Abstract : Oral controlled release drug administration offers a number of advantages in therapeutics like prolonged and efficient delivery of drugs, patient compliance, localization of therapy and minimization of undesirable local action within the gastrointestinal tract (GIT). But the drug absorption is unsatisfactory and highly variable in individuals due to physiological variability in gastrointestinal transit and gastric retention time (GRT). This problem can be overcome by the development of gastroretentive dosage forms (GRDF) which include floating drug delivery systems (FDDS). Floating microspheres are a type of FDDS which are buoyant in nature and have density less than that of the gastric fluid.

Cefixime is an orally active 3rd generation cephalosporin antibiotic active against enterobacteriaceae, *Haemophilus influenzae*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Moraxella catarrrhalis*, *Escherichia coli*, *Proteus mirabilis*, *Neisseria gonorrheae* and is resistant to many β lactamases. Cefixime with pKa value of 2.5 is a weak acid which will remain unionized at acidic pH and thus increases the absorption in the stomach region. After its oral administration, it is slowly and incompletely absorbed from the gastrointestinal tract which results in the poor bioavailability of 40-50%.

Keywords: Microsphere, cefixime, *Escherichia coli* , , UV spectroscopy, bacteriocidal ,HPMC,floating,

INTRODUCTION

The oral route is the most preferable and predominant route for drug delivery due to ease of administration and better patient compliance. It should ideally produce the required plasma levels and maintain it at steady state for a prolonged period of time. But the drug absorption is unsatisfactory and highly variable in the individuals even though excellent *in vitro* release patterns are shown by the oral dosage forms.1,2 The major reason for it is the physiological variability in gastrointestinal transit as well as gastric retention time (GRT).

To achieve gastric retention, the dosage form must resist premature gastric emptying. For this, the dosage form must be able to withstand in the stomach against the force caused by peristaltic waves. Furthermore, once its use is completed the dosage form should be removed from the body with ease. Table 1.1 explains the GIT transit time of various dosage forms.

NEED OF THE STUDY.

The aim of the present study is to formulate floating microspheres of cefixime in order to improve bioavailability by allowing the formulation to float in the stomach for a longer period of time and prolonging GRT. The matrix material used for drug encapsulation is alginate which is a pH sensitive, biocompatible and non toxic natural polymer along with cellulose copolymers like HPMC K4M, HPMC

K15M and ethyl cellulose for the formulation of alginate-cellulose floating microspheres. Chitosan which is another non-toxic, biocompatible and biodegradable natural polymer is also used along with sodium alginate for the preparation of alginate-chitosan floating microspheres.

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RESEARCH METHODOLOGY

Preparation of floating alginate-cellulose microspheres

The drug cefixime trihydrate (114.3 mg) equivalent to 100 mg of cefixime was dispersed in 5ml distilled water. This solution was added to 30 ml alginate solution (3%w/v) containing HPMC/ethyl cellulose. (Alginate: HPMC=9:1 w/w i.e. 30 ml alginate solution contains 0.9 gm alginate and 100 mg of HPMC/ ethyl cellulose). The gas forming agents such as calcium carbonate ($CaCO_3$) or sodium bicarbonate ($NaHCO_3$) were added to the solution with levels from 0:1 to 1:1 (gas forming agent/alginate, w/w i.e. the amount of $CaCO_3$ or $NaHCO_3$ was 0 gm, 0.205 gm, 0.450 gm, 0.605 gm and 0.9 gm respectively). The microspheres were formed by dropping the bubble free dispersion (30 ml) through 26G syringe needle into 100 ml of 0.5% (w/v) calcium chloride ($CaCl_2$) solution containing 10% (v/v) acetic acid. The dropping rate was adjusted to 30 drops/minute and falling distance was 5 cm. The solution containing suspended microspheres were stirred with a magnetic stirrer for 10 minutes to improve their mechanical strength and was allowed to complete the reaction to produce gas. Since the carbonate salts are insoluble at neutral pH, the divalent ions were only released in the presence of acid(fig.6.1). The fully formed microspheres were collected, washed with distilled water twice and subsequently air dried.113-115 Floating alginate microspheres of cefixime with different types of co-polymers such as HPMC K4M, HPMC K15M, and ethyl cellulose were prepared.

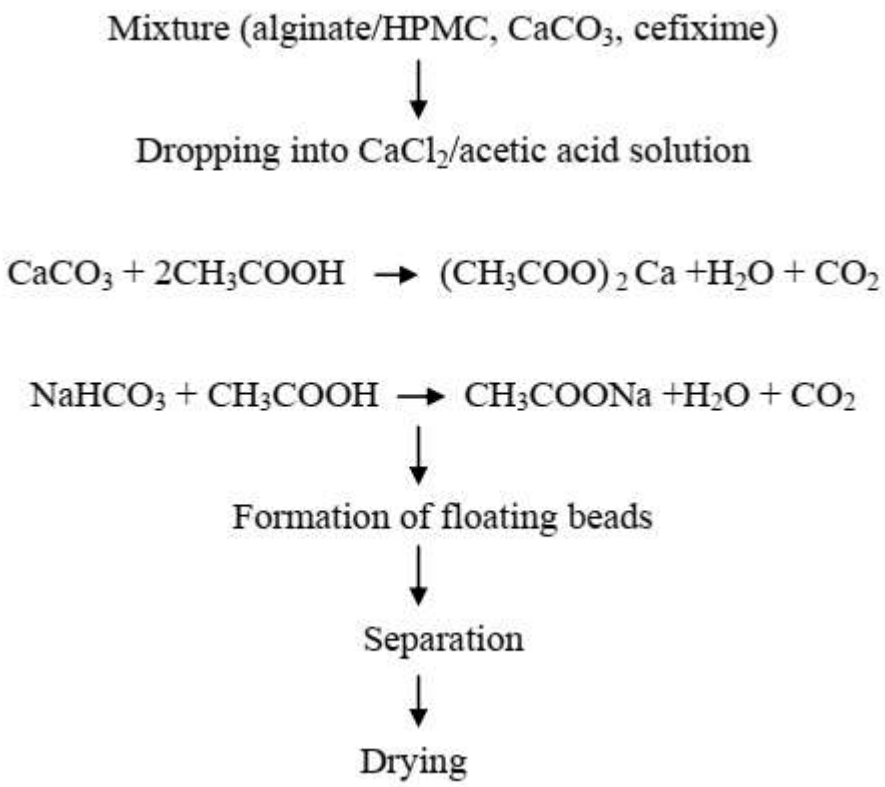

Fig. 1: Schematic representation of formation of floating microspheres

Table 1: Formulation of floating alginate microspheres with HPMC K4M as copolymer

Formulation code	Cefixime (mg)	Concentration of Sodium alginate (%)	HPMC K4M (mg)	$CaCl_2$ (%w/v)	$CaCO_3$: Alginate	$NaHCO_3$: Alginate
H1	100	3	100	0.5	0:1	-
H2	100	3	100	0.5	0.25:1	-
H3	100	3	100	0.5	0.5:1	-
H4	100	3	100	0.5	0.75:1	-
H5	100	3	100	0.5	1:1	-
H6	100	3	100	0.5	-	0.25:1
H7	100	3	100	0.5	-	0.5:1
H8	100	3	100	0.5	-	0.75:1
H9	100	3	100	0.5	-	1:1

Table 2: Formulation of floating alginate microspheres with HPMC K15M as copolymer

Formulation code	Cefixime (mg)	Concentration of Sodium alginate (%)	HPMC K15M (mg)	$CaCl_2$ (%w/v)	$CaCO_3$: Alginate	$NaHCO_3$: Alginate
M1	100	3	100	0.5	0:1	-
M2	100	3	100	0.5	0.25:1	-
M3	100	3	100	0.5	0.5:1	-
M4	100	3	100	0.5	0.75:1	-
M5	100	3	100	0.5	1:1	-
M6	100	3	100	0.5	-	0.25:1
M7	100	3	100	0.5	-	0.5:1
M8	100	3	100	0.5	-	0.75:1
M9	100	3	100	0.5	-	1:1

Table 3: Formulation of floating alginate microspheres with ethyl cellulose as copolymer

Formulation code	Cefixime (mg)	Concentration of Sodium alginate (%)	Ethyl cellulose (mg)	$CaCl_2$ (%w/v)	$CaCO_3$: Alginate	$NaHCO_3$: Alginate
E1	100	3	100	0.5	0:1	-
E2	100	3	100	0.5	0.25:1	-
E3	100	3	100	0.5	0.5:1	-
E4	100	3	100	0.5	0.75:1	-
E5	100	3	100	0.5	1:1	-
E6	100	3	100	0.5	-	0.25:1
E7	100	3	100	0.5	-	0.5:1
E8	100	3	100	0.5	-	0.75:1
E9	100	3	100	0.5	-	1:1

Evaluation of floating alginate-cellulose microspheres

Determination of percentage yield

The prepared batches of all the microspheres were accurately weighed. The weighed quantity of prepared microspheres was divided by the total amount of the drug and all the polymers used in the formulation of microspheres, which gave the total % yield of all the microspheres.116, 117 The procedure was done in triplicate and the mean value of % yield was calculated using the formula:

$$\text{Percentage Yield} = \frac{\text{Weight of the dried microspheres X 100}}{\text{Total weight of polymers and drug}}$$

Determination of drug entrapment efficiency

The drug content in the microspheres was determined by pulverizing the drug loaded microspheres (equivalent to 100 mg of the drug) followed by immersing them in 1000 ml simulated gastric fluid (pH 1.2 buffers) with agitation at room temperature for 24 hours. From this, 1 ml of the solution was transferred to 10 ml volumetric flask and diluted with pH 1.2 buffer to make up the volume. The solution was filtered through Whatmann No.1 filter paper and the drug concentration was determined spectrophotometrically at wave length of 284 nm using UV spectrophotometer (UV 1800, Shimadzu, Kyoto, Japan). The filtered solution from the empty microspheres was taken as blank. All samples were analyzed in triplicate.118

Encapsulation efficiency (EE %) = WA/WTX100

EE: Encapsulation efficiency; WA: Actual drug content; WT: Theoretical drug content.

Study of particle size and morphology of microspheres

Particle size analysis plays an important role in determining the release characteristics and floating property. The size of the microspheres was determined using an optical microscope fitted with an ocular micrometer and stage micrometer. The diameters of about 100 microspheres were randomly measured and the average particle size was determined using the Edmondson's equation.119

$$d_{mean} = \sum nd / \sum n$$

where 'n' stands for the number of counted microspheres and 'd' for the mean size range.

***In vitro* evaluation of floating ability (buoyancy) of microspheres**

The floating properties of the microspheres were evaluated using a dissolution vessel filled with 1000 ml simulated gastric fluid (pH 1.2) containing 0.02% of Tween 80. Paddle rotation speed was at 100 rpm and temperature was maintained at 37±0.50C. For each batch of microspheres, 50 individual microspheres were placed in the dissolution vessel. Both the number of floating microspheres NF (observed visually) and the floating duration FT (which is the time during which the microspheres remain buoyant on test solution) were then determined at fixed time intervals during a 24 hours period. Experiments were performed in triplicate and the percentage of floating microspheres were calculated according to the equation.

$$F\% = [N_F / N_T] \times 100$$

where, N_F = Number of floating Microspheres

N_T = Total number of the microspheres.

***In vitro* drug release studies**

Preparation of standard curve in pH 1.2 buffers: Accurately weighed 114.3 mg of cefixime trihydrate equivalent to 100 mg of cefixime was transferred to 100 ml standard flask. 5 ml of methanol was added to dissolve it, made up to 100 ml with pH 1.2 buffer. From this stock solution 10 ml sample was transferred to 100 ml standard flask and was again made up to 100 ml with pH 1.2 buffer. From this 0.2, 0.4, 0.6, 0.8, 1, 1.2, 1.4, 1.6, 1.8, & 2 ml were transferred to 10 ml standard flask, was made up to 10 ml and the absorbance of each solution was noted at 284 nm.

The dissolution studies of microspheres equivalent to 100 mg of cefixime were performed using USP dissolution type apparatus II (paddle type). The drug release study was carried out using 900 ml of pH 1.2 buffer, maintained at 37± 0.50C. The speed of stirrer was maintained at 100 rpm. An aliquot of 5 ml of the solution was withdrawn at predetermined time intervals and perfect sink condition was established during the dissolution study period by replacing with an equivalent volume of the fresh dissolution medium. The sample solution was filtered through Whatman No.1 filter paper and analyzed for the concentration of cefixime using a UV spectrophotometer (UV 1800, Shimadzu, Kyoto, Japan) at wavelength of 284 nm. The amount of cefixime released was calculated from the calibration curve of the same dissolution medium. All experiments were performed in triplicate.

IV. RESULTS AND DISCUSSION

Analysis of cefixime trihydrate

Analytical data of cefixime trihydrate is given in table 4.

Table 4: Analytical results of cefixime trihydrate

Sl .No.	Tests	Analytical values
1.	Melting point	224.34oC
2.	Assay	98.30 % w/w
3.	Water content	11%

Identification of the drug

FTIR spectroscopic method

The spectrum of pure drug showed characteristic peaks at 1780-1710 cm-1 (C=O stretching of lactam), 1690-1630 cm-1 (C=O stretching of amide), 1565- 1700 cm-1(C=N stretching of oxime), 1540-1380 cm-1 (N=O stretching of oxime) and 1340-1300 cm-1 (-NH_2 of carbamate). The spectrum of drug cefixime is shown in fig.2.. The spectral peaks comply with the spectrum given in IP 2014.

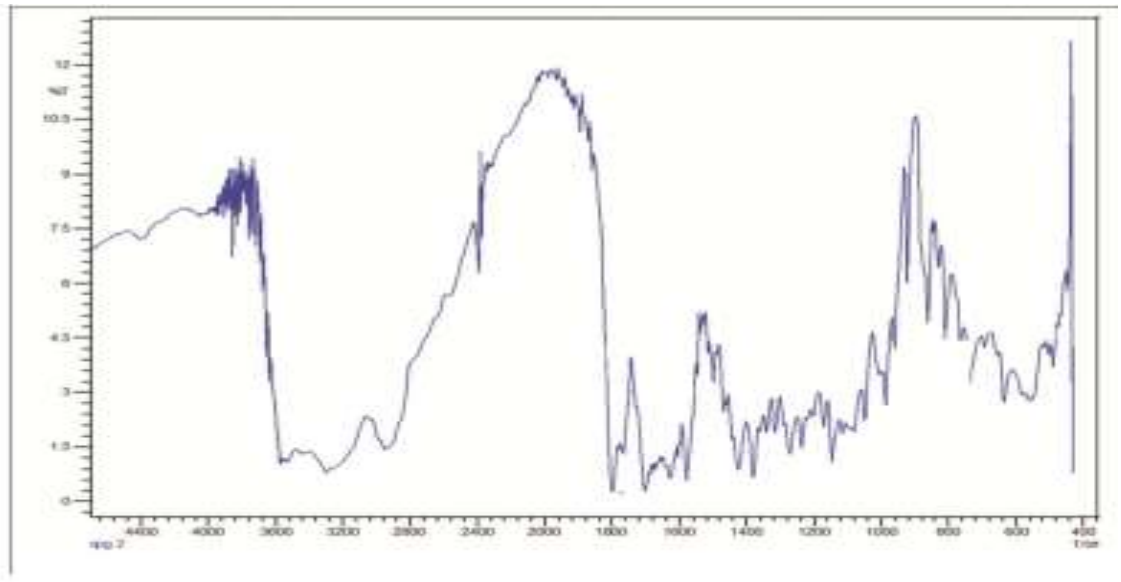

FIG. 2: FTIR SPECTRUM OF PURE DRUG CEFIXIME

UV- Visible spectroscopy

The UV spectrum of cefixime trihydrate in methanol showed characteristic peak at 287 nm as reported earlier.106 The spectrum is shown in fig. 7.2. A calibration curve of concentration against absorbance was plotted (fig.3) and the curve showed linearity in the range of 2-14 µg/ml. The method showed good reproducibility and the results are shown in table 5.

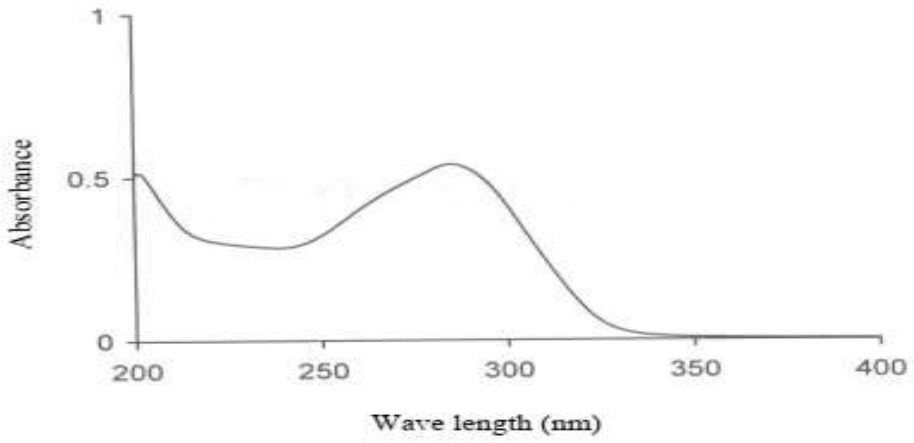

Fig. 3: UV spectrum of cefixime

Table 5: UV absorbance of different concentrations of cefixim

Concentration (µg/ml)	Absorbance
2	0.198
4	0.257
6	0.412
8	0.567
10	0.638
14	0.898

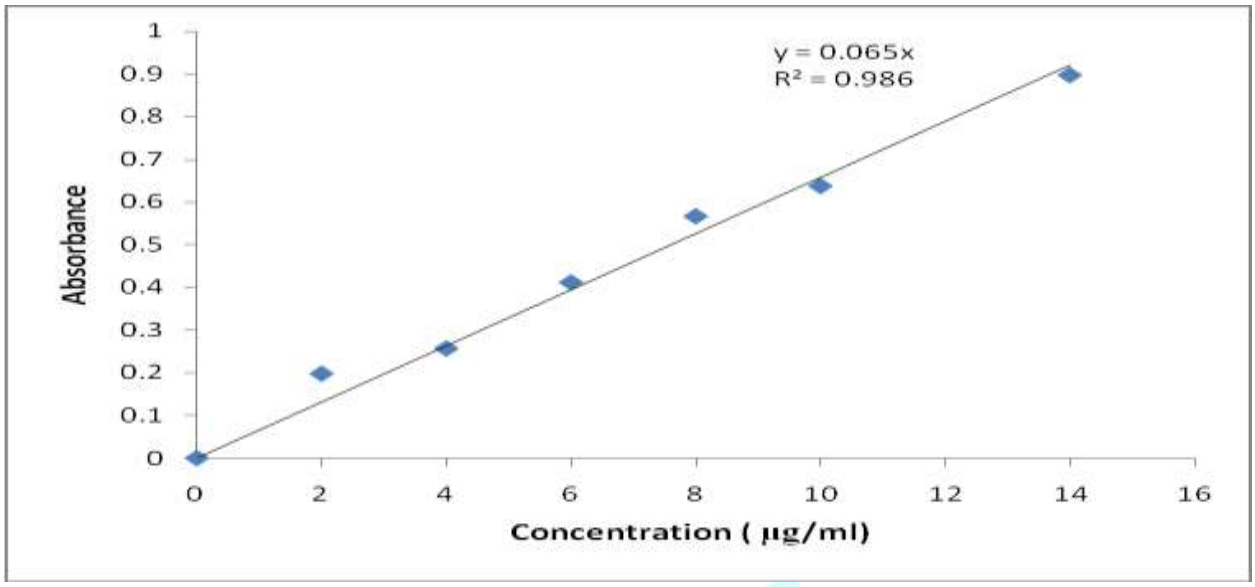

Fig. 6: Calibration curve of cefixime in methanol

Drug excipient compatibility studies

In this work, drug polymer compatibility studies were carried out by fourier transform infrared spectroscopy and differential scanning calorimetry.

Fourier transform infrared (FTIR) spectral studies

The spectrum of pure drug showed characteristic peak at 1780-1710 cm^{-1} (C=O stretching of lactam), 1690-1630 cm^{-1} (C=O stretching of amide), 1565- 1700 cm^{-1}(C=N stretching of oxime), 1540-1380 cm^{-1}(N=O stretching) and 1340- 1300 cm^{-1}(-NH_2 of carbamate) (fig.7.).

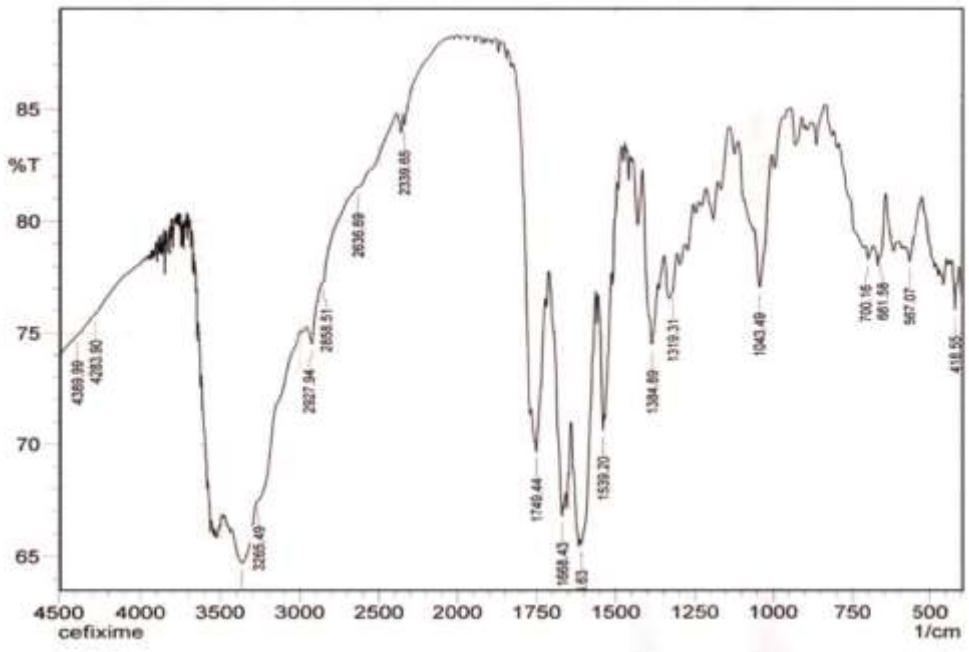

Fig. 7: FTIR Spectrum of pure drug cefixime

Differential scanning calorimetry (DSC)

The DSC thermogram of the pure drug cefixime, The characteristic peak of cefixime at 250.10^{o}C provided the endothermic melting value of the pure drug The minor changes observed in peak value of drug is not an indication of any potential incompatibility. The minor changes in the peak values revealed no interaction

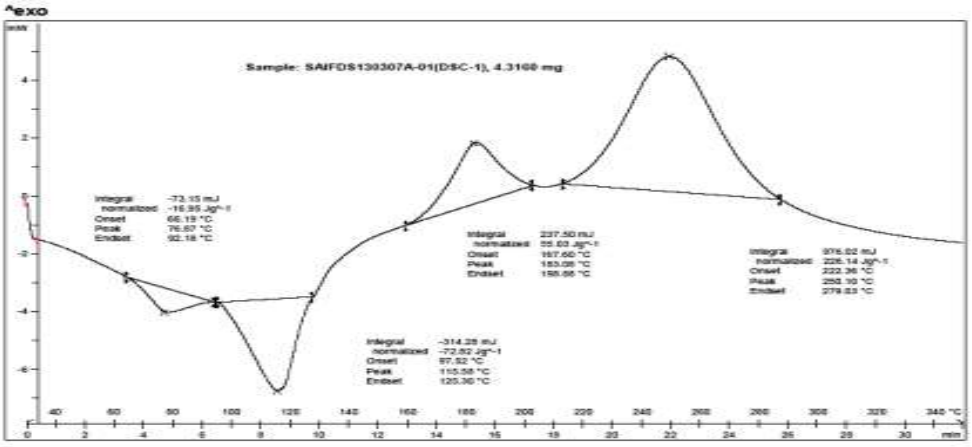

Fig. 8: DSC thermogram of pure drug cefixime

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