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Research Article

DESIGN AND CHARACTERIZATION OF FLOATING MICROSPHERES FOR ORAL DELIVERY OF CEFIXIME

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ABSTRACT

Cefixime, a broad spectrum antibiotic has a short biological half-life and needs frequent dosing resulting in increased side effects. The objective of this study is to produce floating microspheres of Cefixime by solvent evaporation technique to increase entrapment capacity and sustained release. The prepared microspheres were characterized by percentage yield, particle size distribution, floating character, entrapment efficiency, *in vitro* drug release behaviour, scanning electron microscopy. The prepared floating microspheres were found to be discrete, spherical and free flowing. Fourier Transform Infrared Spectroscopic analysis shows the observation, that there is no interaction between the drug and other polymers**.** SEM studies showed that the microspheres were spherical and smooth surface. The floating behaviour of microspheres was found to be positive. The drug loaded microspheres showed 61.84% - 81.6% entrapment efficiency. Release of Cefixime from microspheres was studied in pH 1.2 using paddle type dissolution apparatus. From the release exponent in the Korsmeyer-Peppas model (n >1), it can be suggested that the mechanism of release of cefixime from floating microspheres was said to be non-fickian super case II model release.

Keywords: Cefixime, Floating microspheres, Eudragit S100, Eudragit rspo, Buoyancy.

INTRODUCTION

Drug administration per oral is usually preferred compared to all other ways of chemotherapy. As it is known that the drug release at a constant rate favours the maintenance of the required therapeutic level and eliminates significant variations in the drug concentration in the blood and tissues. The oral bioavailability of many drugs is limited by their unfavourable physicochemical characteristics and or absorption in defined part of the gastrointestinal tract. Extending the gastric retention improves the solubility for drugs that are less soluble in a high pH environment, reduces drug waste and enhances the bioavailability. Various approaches have been investigated to increase the retention of oral dosage form in the stomach, including floating systems, swelling and expanding systems, bioadhesive systems, modified shape systems, high density systems, and other delayed gastric emptying devices[1-2].

Cefixime is a third generation cephalosporin antibiotic used for treatment of susceptible infections, including gonorrhea, otitis media, pharyngitis, and lower respiratory-tract infections such as bronchitis and urinary-tract infections. CFT has poor solubility classified under BCS class IV and shows poor bioavailability with the range between 40–50 % and gets absorbed from upper GIT region due to narrow absorption window. The drug candidate with poor solubility and narrow absorption window are not best choice for oral route due to insufficient absorption in the absorption window[3]. Such that it is suitable to formulate and investigate under gastroretentive type drug delivery systems.

In this study the preparation of cefixime floating microspheres was accomplished using the solvent evaporation technique which is a simultaneous process that combines spherical agglomeration and microencapsulation of the drug. The technique was selected to prepare floating cefixime microspheres due to its simplicity, low cost, success with poor aqueous solubility drugs and the production of microspheres of relatively high drug loading. Eudragit RSPO and Eudragit S100, a methacrylate polymer was favoured as the retarding polymer in view of the many advantages that they possess. The objective of this study was to produce floating microspheres of cefixime by solvent evaporation technique to sustained release at the absorption area thereby enhance its bioavailability.

MATERIALS AND METHODS

Cefixime was received as a gift sample from Aravind remedies Pvt. Ltd, Chennai. Eudragit S100 and Eudragit RSPO Evonik Degussa India Pvt Ltd (Mumbai, India) were received as a gift sample from. All other chemicals and solvents used were of analytical grade and procured from an authorized dealer Sigma-Aldrich (Mumbai, India).

PREPARATION OF MICROSPHERES

Microspheres were prepared by solvent evaporation method[4-7]. The drug and polymers such as Eudragit S100 or Eudragit RSPO were mixed in the mixture of ethanol, dichloromethane and isopropyl alcohol at 8:5:2 ratios to get a clear solution. Tween 80 was used as a surfactant which was added to organic solution. These were dispersed into the 1% Polyvinyl Alcohol (PVA) solution which acts as a continuous phase. The solution was stirred for 1 hour at 800 rpm at room temperature. Then microspheres was filtered and washed completely thrice with water. The washed microspheres were then air dried at room

temperature for 3 hours and stored in dessicator over fused calcium chloride until further use. The effect of various formulation and processing factors on microspheres characteristics were investigated by changing drug polymer ratio and surfactant concentration.

CHARACTERISATION OF FLOATING CEFIXIME MICROSPHERES

Practical Yield

Microspheres harvested and dried at room temperature were weighed and yield of microspheres preparation was calculated using the formula

Percentage yield = (Amount of microspheres obtained / Theoretical yield) X 100.

Determination of Drug Entrapment Efficiency

Accurately weighed 50 mg of drug loaded microspheres were crushed and addedto 10 ml of ethanol and dissolve thoroughly using magnetic stirrer for 30 min and it was filtered prior to the further process[8]. An aliquot of sample was diluted with ethanol and analysed for drug entrapment by spectrophotometer at 291 nm. The amount of drug entrapped in microspheres is calculated by using the formula (Amount of drug actually present / Theoretical drug loaded) X 100.

Floating Microspheres Particle Size Analysis

The size of the prepared microspheres was measured by the optical microscopy method using a calibrated stage micrometer. Approximately 100 microspheres were counted for particle size in random direction.

Fourier Transform Infrared Spectroscopy

Infrared spectra of the drug, polymer and microspheres were recorded using a Fourier transform infrared spectroscopy (FTIR) spectrophotometer (FTIR-8400, Shimadzu, Japan) utilizing potassium bromide discs[9]. Samples were prepared by gently grounding the powder with KBr. The data region was 4000–400 cm^{-1}.

MICROMERITICS PROPERTIES

Microspheres were characterized for their micromeritic properties viz., bulk density, tapped density, Carr index, Hausner's ratio, angle of repose, particle size and shape.

Bulk and Tapped Density

Accurately weighed quantities of prepared microspheres were carefully poured intothe10 ml graduated cylinder. The initial volume was measured without disturbing the cylinder. The tapping method was adapted to find out the tapped density. The graduatedcylinder was tapped for 100 times with an interval of 2 seconds onto a hard wood surface from a height of 1 inch. After that the volume was measured. Bulk and tapped density were calculated by the following equation.

$$\text{Bulk Density} = W/V_o$$

$$\text{Tapped Density} = W/V_F$$

W= Weight of microspheres, V_o= Bulk Volume, V_F = Final Volume

Compressibility Index

The Carr index is an indication of the compressibility of solids. The Carr index is frequently used in pharmaceutics as an indication of the flowability of a powder. Compressibility parameter evaluates the flow property of powder by comparing the bulk density and tapped density. Carr's index was calculated by using following formula. A Carr's index greater than 25 is considered to be an indication of poor flowability.

Carr's index = ((Tapped density - bulk density)/ Tapped density) X 100

Hasuner's Ratio

Hausner's ratio is an important character to determine the flow property of powder and granules.Huasner's ratio gives an indication of the degree of densification which may arise from variation of the feed hopper. A lower value of indicates better flow and vice versa.

Hausner's Ratio = Tapped density/ Bulk density

Angle of Repose

Angle of repose is defined as the maximum possible angle between the surface of a powder pile or granules and the horizontal plane. Angle of repose of microspheres was determined by fixed funnel method. The granules were allowed to flow through a funnel fixed to a stand at a definite height. The angle of repose (Θ) was then calculated by measuring the height (h) and radius (r) of the formed granules heap and incorporating these values into the under mentioned formula.

$$\Theta = \tan^{-1}(h/r)$$

SCANNING ELECTRON MICROSCOPY

The ultra structural features were analyzed by JEOL Scanning Electron Microscope. Prior to the analysis of the samples, dry microspheres were placed on an electron microscope brass stub and coated with gold in an ion sputter. Images of the sample microspheres were taken by random scanning of the stub.

IN VITRO BUOYANCY

To assess the floating properties, 100 mg of microspheres were carefully spread over the surface of a USP dissolution apparatus filled with 900ml of 0.1N Hydrochloric acid containing 0.02% tween 80[10]. The use of tween 80 was to mimic the wetting effect of the natural surface active agents in the gastrointestinal tract. The medium was agitated with a paddle rotating at 100 rpm for 12 hours. 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 sum of remained and settled mass of the microspheres.Density values of the formulated microspheres were less than that of the gastric fluid (-1.004 g/cm^3) which substantiates their floating behavior.

IN VITRO RELEASE STUDY

The United States pharmacopoeia paddle type dissolution test apparatus was used for *in vitro* release studies. The release profile of cefiximefloating microspheres was examined in 900 ml of 0.1 N hydrochloric acidwith 0.02% of tween 80to mimic the gastric fluid content. Sample of dissolution fluid was withdrawn and filtered through membrane (0.45 µm) at different time intervals for 12 hours and replaced by an equal volume of fresh pre warmed dissolution fluid maintaining sink condition throughout the experiment. After suitable dilution the aliquots were analyzed for drug quantification at 291 nm.Drug release data obtained from *in vitro* dissolution studies of all the batches were evaluated using different mathematical models to find out the release kinetics of drug from the microspheres[11].

Table 1: Formulation parameters for floating microspheres of Cefixime

S.no	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1	Cefixime: Eudragit S100	1:2	1:3	1:2	1:3	-	-	-	-
2	Cefixime: Eudragit RSPO	-	-	-	-	1:2	1:3	1:2	1:3
3	Tween 80	0.05%	0.05%	0.1%	0.1%	0.05%	0.05%	0.1%	0.1%

Table 2: Characteristics of floating microspheres

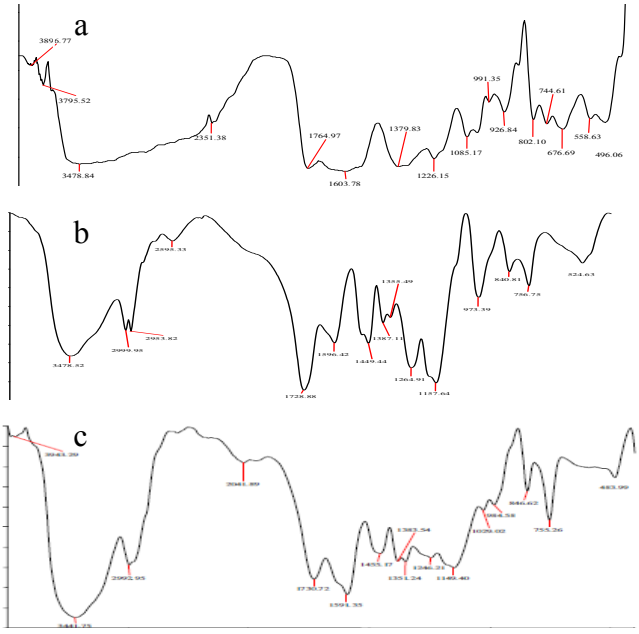
Formulation Code	Yield (%)	DEE (%)	Particle Size (µm)	*In vitro* Buoyancy (%)
F1	77.50	61.84	66.57	78
F2	80.00	65.42	57.71	74
F3	66.60	66.72	61.66	74
F4	76.25	68.60	53.70	69
F5	76.60	76.02	57.30	65
F6	83.30	81.60	55.97	69
F7	78.75	77.29	56.57	62
F8	83.75	79.54	52.80	64

Table 3: Micromeritics Properties of Microspheres

Characteristics	F1	F2	F3	F4	F5	F6	F7	F8
Angle of repose (^{0})	20.45	22.09	24.00	20.91	26.29	26.51	26.41	27.86
Bulk density (g/ml)	0.055	0.119	0.100	0.130	0.106	0.236	0.167	0.144
Tapped density (g/ml)	0.065	0.142	0.121	0.162	0.128	0.284	0.192	0.161
Hausner' ratio	1.18	1.20	1.21	1.24	1.20	1.20	1.14	1.11
Carr's index	15.55	16.66	17.35	19.55	16.67	17.19	14.81	10.53

Table 4: Correlation Coefficient values of different release models

	F1	F2	F3	F4	F5	F6	F7	F8
Zero order	0.981	0.969	0.985	0.959	0.994	0.963	0.981	0.981
First order	0.961	0.928	0.989	0.938	0.965	0.899	0.971	0.965
Hixon- crowell	0.935	0.945	0.991	0.950	0.981	0.925	0.989	0.981
Higuchi equation	0.846	0.803	0.880	0.852	0.860	0.824	0.919	0.901
Korsmeyer – peppas	0.897	0.876	0.861	0.744	0.842	0.766	0.795	0.741
Korsmeyer – Peppas (n values)	1.274	1.153	1.236	1.026	1.275	1.117	1.238	1.123



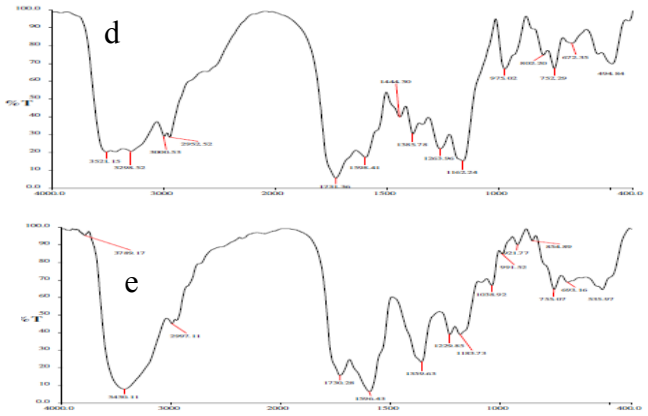


Figure 1: FTIR Spectra of (a) CEFIXIME (b) EUDRAGIT S100 (c) EUDRAGIT RSPO (d) EUDRAGIT S100 microspheres (e) EUDRAGIT RSPO microspheres

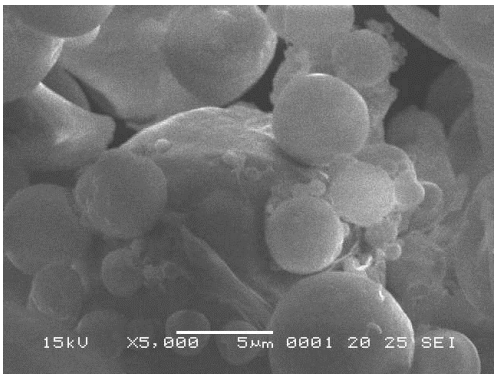


Figure 2: SEM Image of Cefixime loaded Eudragit S100 Microspheres

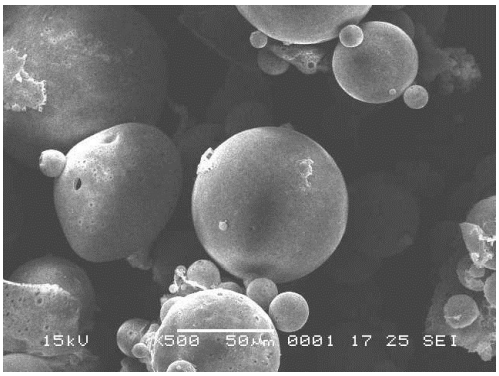


Figure 3: SEM Image of Cefixime loaded Eudragit RSPO Microspheres

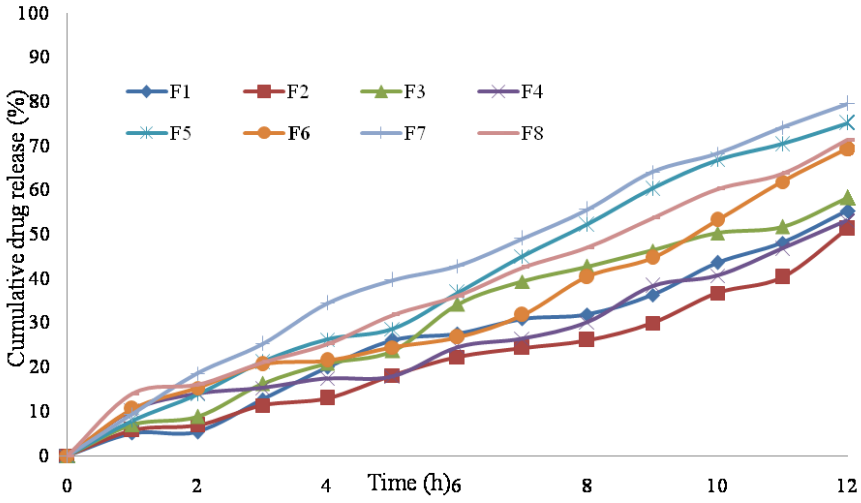


Figure 4: *In vitro* release profiles of Cefixime floating microspheres

RESULTS AND DISCUSSION

PREPARATION OF MICROSPHERES

In the present work the microspheres of Cefixime with Eudragit S100 or Eudragit RSPO were prepared as shown in Table 1, by oil in water type emulsion solvent evaporation technique using ethanol, dichloromethane and isopropyl alcohol and PVA system. The effect of polymer concentration on the production yield, entrapment efficiency, particle size distribution, floating behavior, in vitro drug release, surface characteristics and drug polymer interaction were studied.

Practical Yield

The floating microspheres of cefixime were prepared by solvent evaporation method.The percentage yields of floating microspheres were found to be 66.6%-83.75%. The practical yields of all the batches were found to be high exhibits the suitability of the formulation parameters which show in Table 2.The prepared floating microspheres were found to be discrete, spherical and free flowing.

Determination of Drug Entrapment Efficiency

The highest entrapment efficiency (81.6%) was achieved for microspheres with Eudragit RSPO drug ratio of 1:3. The viscosity of the polymer solution at higher drug loading was very high and is responsible for the formation of microspheres[12]. Keeping the drug polymer ratio constant there was a significant decrease in encapsulation efficiency of Cefixime with increasing the concentration of surfactant for secondary emulsification. This may be due to the fact that the increase miscibility of organic solvent with continuous phase which may increase the extraction of Cefixime into the processing medium.

Particle Size Analysis

Keeping the solvent mixture constant and varying the polymer ratio influenced the particle size. The mean arithmetic diameter varied between52.80 - 66.57 µm. Increasing the polymer load led to a more viscous solution with the constant solvent mixture. Thus the viscous polymeric solution when poured into the aqueous phase larger droplets which yields larger particle size of floating microspheres[13].

FOURIER TRANSFORM INFRARED SPECTROSCOPY

Drug-Excipients compatibility was carried out by FTIR analysis (Figure 1). IR spectrum of pure drug Cefixime is characterized by 558 cm^{-1} (CH_3 stretching), 1764 cm^{-1} (C=O stretching of aromatic nucleus), 3478 cm^{-1}(N-H stretching of aromatic nucleus), 1603 cm^{-1} (C=C stretching), 926 cm^{-1} (C-H bending), 1085 cm^{-1} (C-N stretching). IR spectrum of Eudragit S 100 has the bands of C=O vibrations of the carboxylic acid groups at 1728 cm^{-1} as well as further ester vibrations at 1157, 1264 cm^{-1}. The wide absorption range of the associated OH groups between 2595 and 3478 cm^{-1}. Important peaks in Eudragit RSPO spectrum are 1149 cm^{-1}(C–CO–C– stretching), 1383 cm^{-1} (CH_3– asymmetric bending), 1455 cm^{-1}(CH_2– symmetric bending) and 1730 cm^{-1}(C=O stretching).Comparing the spectra of Cefixime with microspheres, no much difference was shown in the position of the absorption bands of the drug. The spectra can be simply regarded as the superposition of those of Cefixime and polymers used for the preparation of microspheres. This observation ruled out the possibility of chemical interaction and complex formation between these components. The results of this observation were concluded that there is no interaction between the Cefixime and polymers of Eudragit S100 and Eudragit RSPO.

MICROMERITICS PROPERTIES

The formulated microspheres were characterised for micromeritics[14]. These values are shown in Table 3. The bulk and tapped densities of the formulations had values less than 1 g/ml. The bulk density ranged from 0.055 to 0.236 g/ml and the tapped density ranged from 0.065 to 0.284 g/ml. Flow properties of microspheres were evaluated by measuring the angle of repose and compressibility index. While evaluation of flowability of dry solid microspheres exhibits satisfactory flowability and performance. All the batches were shown satisfactory values for angle of repose. The better flow property of microspheres indicates that the microspheres produced were non aggregated. These results suggest that they can be easily handled and filled into a capsule. Hausner values less than 1.25 have been reported to indicate good flow characteristics for solids. The Hausner values obtained for the microspheres are below this cut off value indicating that the microspheres exhibit variations in the flowability of the various batches of the microspheres. A Carr index value of 5-15% is indicative of excellent flow, 12-16% is good flow, and 18-21% is fair flow. Thus the all the batches exhibits satisfactory level of compressibility index.

SCANNING ELECTRON MICROSCOPY

Surface morphology of the microspheres were investigated and revealed by scanning electron microscopy (SEM). The microphotographs of surface view of microspheres were shown in Figure 2&3. SEM indicated that the microspheres produced by the emulsion solvent evaporation method are spherical with smooth surface, not aggregated which is responsible for the characteristic patterns of drug release. Their smooth surface indicated that Cefixime was embedded in the core, as the drug particles were not present on the surface. The shell of microspheres showed some porous structure. These pores impart floating nature to the microspheres. It may be caused by the evaporation of solvent entrapped within the shell of microspheres after forming a smooth and dense skin layer.

IN VITRO BUOYANCY

Floating behavior of the all batches of microspheres was studied. The purpose of preparing floating microspheres is to extend the gastric residence time of a drug. As revealed by morphology characteristics the floating behavior of the microspheres, was due to the porous surface resulted due to evaporation of organic solvent used while preparation. The microsphere posses low apparent particle density and thus imparts the buoyancy properties. The *in vitro* buoyancy study results were satisfactory during the experiments.

IN VITRO RELEASE STUDY

There is significant difference in the release rate from formulation prepared from different polymers of Eudragit. The type of polymer significantly influenced the drug release rate in the order Eudragit RSPO >Eudragit S 100.

The dissolution profile of cefixime from Eudragit S100 and Eudragit RSPO in 0.1 N HCl containing 0.02% Tween 80 are shown in Figure 4. It was observed that the release rate of cefixime from Eudragit RSPO increased than the Eudragit S100. Cefixime release rate from Eudragit S100 microspheres was very slow and incomplete for F1, F2, F3, F4 formulation such as 55.33%, 51.30%, 58.33%, and 53.16% respectively at 1.2 pH for 12 hours. This is due to the polymer Eudragit S100 is pH dependent type. The curves of dissolution rate profile for F5, F6, F7, F8 indicates that increasing the drug to polymer ratio resulted in thicker coated walls and greater impeding of the release of cefixime such as 75.09%, 69.28%, 79.51%, and 71.25% respectively for the 12 hour study period.

Comparison of the dissolution rate of all formulation indicated a sustained effect due to the encapsulation of the drug with acrylic polymers. Increasing the drug to polymer ratio resulted in a decrease in dissolution rate as a result of increase in coat thickness surrounding the drug particles, thereby increasing the distance travelled by the drug through the polymer coat.

Release mechanism

To investigate the drug-release kinetics, data were fitted to various kinetic models such as zero-order, first-order, Higuchi equation, Korsmeyer–Pappas equation, and Hixson–Crowell equation[15]. The regression analysis was done for all eight batches and the values were shown in TABLE 4.

Regression analysis was performed and regression values r^2 was used as an indicator of the best fitting for each of the models was considered. The zero order plots were found to be 0.959-0.994. To confirm the exact mechanism of drug release the data were fitted according to korsmeyer empirical equation to describe general drug release behaviour from controlled release polymer matrices. In the present study the mechanism of release of cefixime from batches F1 to F8 was, indicates a Non-fickian super case II controlled drug release. From the release exponent in the Korsmeyer-Peppas model[16] (n >1), it can be suggested that the mechanism that led to the release of cefixime with Non-fickian super case II release.

CONCLUSION

The core aim of this study was to develop floating microspheres of cefixime using Eudragit S100 and Eudragit RSPO polymers employing simple solvent evaporation technique as method of preparation of floating microspheres. Floating microspheres were successfully formulated and the characterized parameters results were satisfactory.

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