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FORMULATION, DEVELOPMENT AND EVALUATION OF FLOATING MICROSPHERE OF CEFUROXIME AXETIL

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ABSTRACT

The present study involves preparation and evaluation of floating microspheres using Cefuroxime axetil as a model drug for improving the drug bioavailability by prolongation of gastric retention time. Ethyl cellulose, hydroxyl propyl methyl cellulose microspheres loaded with Cefuroxime axetil were prepared by solvent diffusion evaporation method. The microspheres had smooth surfaces with free-flowing and good-packing properties. Percentage yield of different formulation was determined by weighing the Microspheres after drying. The percentage yield of different formulation was in range of 62.23±0.85–73.32±0.65%. The maximum Percentage yield was found in formulation F3, 73.32±0.65 as compare to all formulation tables 2. The drug entrapment efficacies of different formulations were in range of 63.23±0.65- 76.56±0.65% w/w table 3. The maximum percentage yield, drug entrapment, percentage buoyancy and floating lag time was found to be formulation F3 in floating microsphere. When the regression coefficient values were compared, it was observed that an 'r^2' value of microsphere was maximum zero order i.e 0.958 hence indicating drug releases from formulations was found to follow zero order for floating microsphere. It was concluded that developed floating microspheres of Cefuroxime axetil offers a suitable and practical approach for prolonged release of drug over an extended period of time and thus oral bioavailability, efficacy and patient compliance is improved.

KEYWORDS: Cefuroxime axetil, Solvent diffusion evaporation method, Ethyl cellulose, Hydroxyl propyl methyl cellulose.

INTRODUCTION

Microspheres constitute an essential piece of these particulate medication conveyance frameworks by uprightness of their little size and productive bearer limit. Microspheres are the bearer connected medication conveyance framework in which molecule estimate is ranges from 1-1000 µm extend in distance across having a center of medication and completely external layers of polymer as covering material. Be that as it may, the accomplishment of these microspheres is restricted because of their short habitation time at site of assimilation. It would, in this way be worthwhile to have implies for giving a private contact of the medication conveyance framework with the engrossing layer. Microspheres have focal points like proficient retention and upgraded bioavailability of the medications because of a high surface to volume proportion, a substantially more cozy contact with the bodily fluid layer and particular focusing of medications to the ingestion site (Parmar *et al.*, 2010). Microspheres incorporate microparticles and microcapsules (having a center of medication) of 1-1000µm in distance across and comprising either totally of a floating polymer or having an external covering of it, individually. Microspheres, as a rule, can possibly be utilized for focused and controlled discharge sedate conveyance; however coupling of floating properties to microspheres has extra preferences e.g. effective assimilation and bioavailability of the medications because of high surface to volume proportion, a considerably more personal contact with the mucous layer, particular focusing of medications to the ingestion site.

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content, increases gastric residence and fluctuation in plasma concentration. It also reduces chances of striking and dose dumping and produces prolonged therapeutic effect. Drug (ketoprofen) given through this form (Najmuddin *et al.*, 2012). Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation. Cefuroxime axetil is Broad-spectrum cephalosporin antibiotic resistant to beta-lactamase. It has been proposed for infections with gram-negative and gram-positive organisms, gonorrhea, and haemophilus. Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric

contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation.

MATERIAL AND METHODS

Material

Cefuroxime axetil was obtained as a gift sample from Pharmaceutical Company. Dichloromethane, ethanol and isopropyl alcohol were purchased from E. Merck (India) Ltd., Mumbai. Ethyl cellulose, hydroxyl propyl methyl cellulose was purchased from Loba Chem. Pvt. Ltd, Mumbai. Double distilled water was prepared freshly and used whenever required. All the chemicals used in this work were of analytical grade.

Methods

Preparation of Floating microsphere of Cefuroxime axetil

Floating microspheres loaded with Cefuroxime axetil were prepared using solvent diffusion-evaporation method using HPMC and EC in different ratio like 1:0.5, 1:1.5, 1:2 w/w (Patel *et al.*, 2006). Drug and polymer in proportion of drug and polymers were dissolved in 1:2 mixture of solvent system of ethanol and dichloromethane. This clear solution was poured slowly in a thin stream into the aqueous solution of 1% polyvinyl alcohol. The emulsion was continuously stirred for 3 h at a speed of 500 rpm at 27±2°C. The floating microspheres were collected by decantation, while the non-floating microspheres were discarded. The microspheres were dried overnight at 40±2°C and stored in desicator (Patel et al., 2006).

Table 1: Formulations of the floating microspheres prepared.

Sr. No	Formulation Code	Cefuroxime axetil (mg)	HPMC (mg)	EC (mg)
1.	F1	100	100	50
2.	F2	100	100	150
3.	F3	100	100	200
4.	F4	100	100	100
5.	F5	100	150	100
6.	F6	100	200	100

Evaluation of microspheres

Percentage Yield

The prepared microspheres with a size range of 1µm to 1000µm were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres (Harsha, 2012).

$$\% \text{ Yield } = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} x\ 100$$

Drug Entrapment

The various formulations of the Floating microspheres were subjected for drug content. 10 mg of Floating microspheres from all batches were accurately weighed and crushed. The powder of microspheres were dissolved in 10 ml 0.1 N HCl and centrifuge at 1000 rpm. This supernatant solution is than filtered through whatmann filter paper No. 44. After filtration, from this solution 0.1 ml was taken out and diluted up to 10 ml with 0.1 N HCl. The percentage drug entrapment was calculated using calibration curve method.

Floating behavior: Ten milligrams of the floating microspheres were placed in 0.1 N HCl (100 mL). The mixture was stirred at 100 rpm in a magnetic stirrer. After 12 h, the layer of buoyant microsphere was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in desiccators until a constant weight was obtained. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles (Amin *et al.*, 2013).

$$\text{Percent buoyancy} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} x\ 100$$

Measurement of mean particle size

The mean size of the microspheres was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyzer (Horiba Instruments) at a scattering angle of 90°. A sample (0.5mg) of the microspheres suspended in 5 ml of distilled water was used for the measurement (Srivastava *et al.*, 2005).

Determination of zeta potential

The zeta potential of the drug-loaded microspheres was measured on a zeta sizer (Horiba Instruments) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25°C in triplicate.

6.3.6 *In-vitro* release studies

The drug release rate from Floating microspheres was carried out using the USP type II (Electro Lab.) dissolution paddle assembly. A weighed amount of Floating microspheres

equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCI (pH=1.2) maintained at 37 ± 0.5°C and stirred at 55rpm. One ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. The collected samples analyzed spectrophotometrically at 282.0 nm to determine the concentration of drug present in the dissolution medium.

RESULTS AND DISCUSSION

Percentage yield of different formulation was determined by weighing the Microspheres after drying. The percentage yield of different formulation was in range of 62.23±0.85–73.32±0.65%. The maximum Percentage yield was found in formulation F3, 73.32±0.65 as compare to all formulation tables 2. The drug entrapment efficacies of different formulations were in range of 63.23±0.65- 76.56±0.65% w/w table 3. The maximum percentage yield, drug entrapment, percentage buoyancy and floating lag time was found to be formulation F3 in floating microsphere. The results of measurement of mean particle size of optimized formulation F3 of floating microsphere was found 198.3 nm figures 1.

Results of zeta potential of optimized formulation F3 of floating microsphere was found -35.8 mV figure 2**.** The optimized formulation of both batches subjected to further studies. The *In vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, in order to determine the mechanism of drug release. When the regression coefficient values were compared, it was observed that an 'r^2' value of microsphere was maximum zero order i.e 0.958 hence indicating drug releases from formulations was found to follow zero order for floating microsphere table 5 & 6.

Table 2: Percentage Yield for Different Formulation.

Formulation	Percentage Yield
F1	69.98±0.98
F2	70.12±0.95
F3	73.32±0.65
F4	65.56±0.58
F5	62.23±0.85
F6	66.56±0.32

(Mean of 3 replicate, Mean±SD)

Table 3: Drug Entrapment for Different formulations.

Formulation	Drug entrapment (% w/w) of prepared microsphere
F1	65.56±0.95
F2	69.98±0.65
F3	75.56±0.23
F4	62.23±0.54
F5	59.98±0.52
F6	63.32±0.45

(Mean of 3 replicate, Mean±SD)

Table 4: Percentage Buoyancy and floating lag time of floating microsphere.

Formulation	Floating Lag Time (Sec.)	Percentage Buoyancy
F1	45±3	55.65±0.65
F2	49±2	66.65±0.69
F3	32±4	76.65±0.52
F4	45±3	56.65±0.47
F5	43±2	65.56±0.32
F6	48±3	73.21±0.45

(Mean of 3 replicate, Mean±SD)

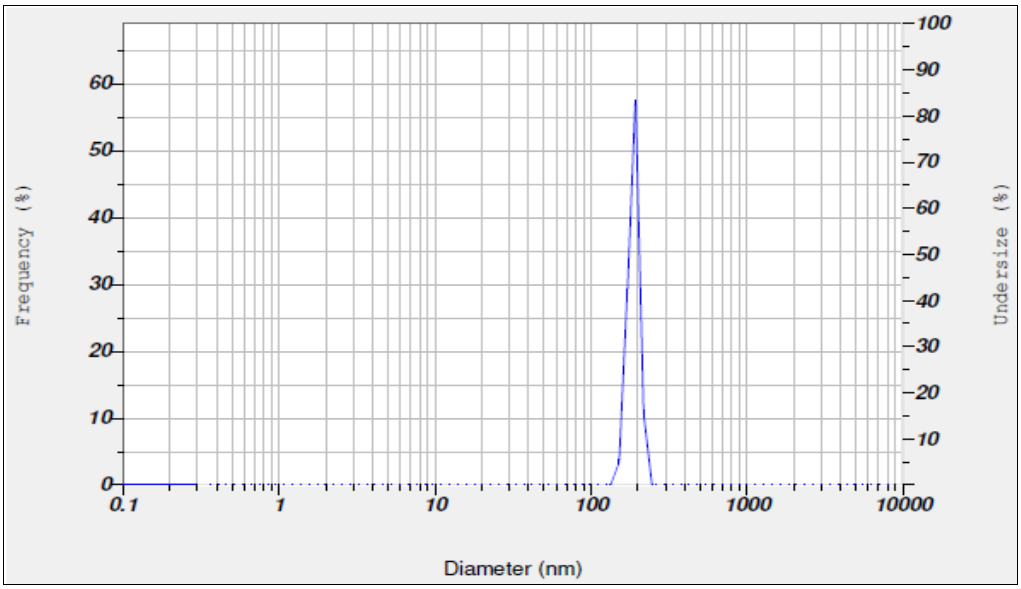

Figure 1: Particle size data of optimized microsphere formulation F3.

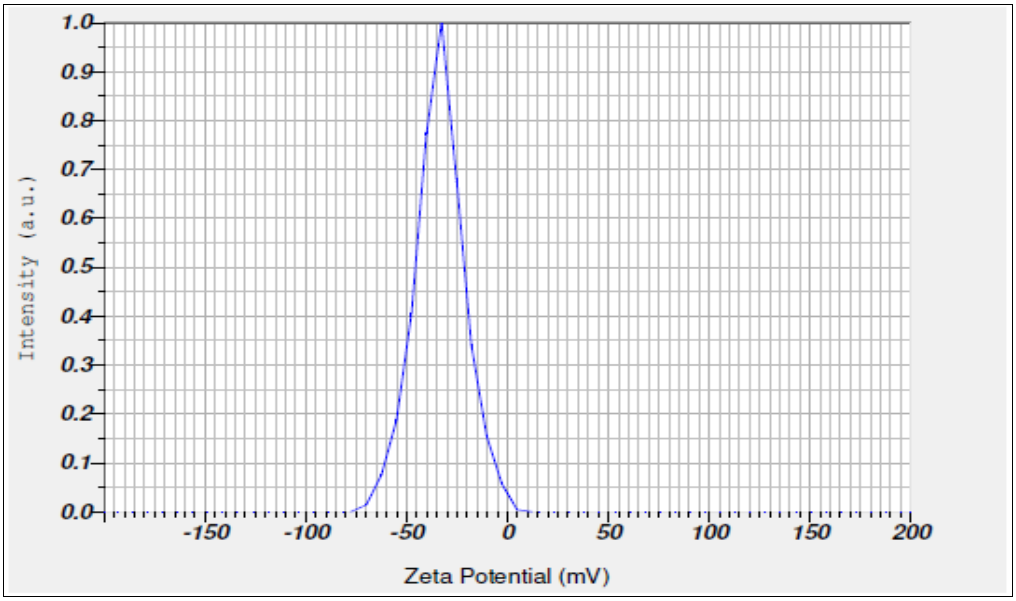

Figure 2: Zeta potential data of floating microsphere F3.

Table 5: Release Study data of formulation F1-F6.

Time	Percentage Drug Release					
(hr)	F1	F2	F3	F4	F5	F6
0.5	30.25	29.98	25.56	20.23	15.56	12.56
1	41.25	39.98	30.56	26.65	23.32	20.32
2	52.36	46.65	42.23	31.25	33.32	32.45
4	69.98	63.32	60.32	46.65	45.56	43.25
6	85.56	80.56	75.56	53.32	51.48	49.98
8	90.23	92.23	82.56	63.32	56.65	55.65
10	99.89	99.23	89.98	72.23	65.56	63.32
12	-	-	98.85	85.56	73.32	74.45

Table 6: Comparative study of regression coefficient for selection of optimized Formulation F3.

Release Kinetics	Zero order	First order
R^2	0.958	0.866

CONCLUSION

Floating microspheres of Cefuroxime axetil were prepared by solvent diffusion-evaporation method, using various biodegradable polymers such as ethyl cellulose and Hydroxypropyl Methylcellulose. Major advantages of the system include ease of preparation, good floating ability, high encapsulation efficiency and sustained drug release over several hours. From this study it was concluded that formulation of floating microspheres of Cefuroxime axetil 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. This

delivery system can play a beneficial role in the absorption of acidic active pharmaceutical ingredients with decrease in dosing frequency.

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