

Preparation and Evaluation of Floating Microspheres of Cefdinir in Treatment of Otitis Media and Respiratory Tract Infections

Anjali Devi N*, Vijendar C, Anil Goud K, Anil Kumar D, Khaja M and Anil A

Department of Pharmaceutics, University College of Pharmaceutical Sciences, Kakatiya University, Warangal 506009, Telangana, India

Abstract

The main objective of the present investigation was to develop gastro retentive (floating) microsphere for Cefdinir. Cefdinir, Third-generation bactericidal cephalosporin antibiotic drugs has been chosen as a model drug in the formulation of floating drug delivery systems. It is a drug of choice in treatment of otitis media, soft tissue infections, and respiratory tract infections, including sinusitis, strep throat, community-acquired pneumonia and acute exacerbations of bronchitis. Three biocompatible polymers like HPMC, Ethyl cellulose and Eudragit were chosen in varying proportions with the drug. F5 formulation with drug: polymer (1:2) show excellent micromeritic properties, percent yield (87.22%), drug entrapment efficiency (92%), percent buoyancy (89%), and highest *in-vitro* drug release 98.9% within 12 h. In the stability studies no significant change in drug entrapment release characteristics of the microspheres.

Keywords: Cefdinir; Floating microspheres; Buoyancy; Hydroxy propyl methyl cellulose

Introduction

Comprehensive knowledge about GI dynamics such as gastric emptying, small intestine transit, colonic transit, etc. is the key for designing oral controlled release dosage forms. The rate and extent of drug absorption from different sites of GI tract and factors that govern the absorption further assist the design of dosage form.

Materials and methods

Materials

Cefdinir is a gift sample from Chandra labs, Hyderabad, India. Hydroxy propyl methyl cellulose, Ethyl cellulose, poly vinyl alcohol and Eudragit s100 are purchased from SD Fine Chemicals Ltd, Mumbai, India.

Methods

Preparation of floating microspheres of cefdinir: Floating microspheres were prepared by the solvent evaporation method. Various concentration of polymer in suitable solvents were mixed well with the Cefdinir in different ratios of polymer and this pasty mass was introduced into 50ml of aqueous saline phase containing 0.04% (20 mg) polyvinyl alcohol (PVA) and 10% (5 ml) ethanol. The system was stirred using Propeller at 300 rpm at room temperature for 2-3 h. The drug loaded floating microspheres formed were filtered, washed and dried in a hot air oven at 60°C (Table 1).

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cefdinir	600	600	600	600	600	600	600	600	600
HPMC	600	1200	1800	-	-	-	-	-	-
Eudragit S100	-	-	-	600	1200	1800	-	-	-
Ethyl cellulose	-	-	-	-	-	-	600	1200	1800
NaHCO ₃	600	1200	1800	600	1200	1800	600	1200	1800
Water (ml)	Q.s	Q.s	Q.s	-	-	-	-	-	-
Dichloromethane: Ethanol (2:1) (ml)	-	-	-	Q.s	Q.s	Q.s	-	-	-
Ethanol (ml)	-	-	-	-	-	-	Q.s	Q.s	Q.s

Table1: Formulation of cefdinir floating microspheres.

Drug- excipient compatibility study: Prior to the development of the dosage forms the preformulation study was carried out. FTIR spectra were recorded with a Thermo Nicolet, Japan. In the range 400-4000 cm⁻¹ using a resolution of 4 cm⁻¹ and 16 scans. Samples were diluted with kbr mixing powder, and pressed to obtain self-supporting disks. Liquid samples formulations were analyzed to form a thin liquid film between two kbr disks.

Evaluation of Floating Microspheres

Micromeritic studies

The prepared microspheres are characterized by their micromeritic properties, such as microsphere size, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose (Table 2).

In vitro buoyancy studies

The *in vitro* buoyancy was determined by floating lag time, and total floating time. The microspheres were placed in a 100ml beaker containing 0.1N HCl. The time required for the microspheres to rise to the surface and float was determined as floating lag time (FLT) and the duration of the time the microspheres constantly float on the dissolution medium was noted as the total floating time respectively (TFT) [1-3].

$$\% \text{Buoyancy} = Q_f / (Q_f + Q_s) \times 100$$

Where Q_f and Q_s are the weight of the floating and settled microspheres respectively.

***Corresponding author:** Anjali Devi N, Department of Pharmaceutics, University College of Pharmaceutical Sciences, Kakatiya University, Warangal 506009, Telangana, India, Tel: 9701142628; E-mail: anjali_nippani@yahoo.com

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Swelling index studies

The swelling behaviour of a dosage unit was measured by studying its weight gain. The swelling index of microspheres was determined by placing the microspheres in the basket of dissolution apparatus using dissolution medium 0.1N HCl at $37 \pm 0.5^\circ\text{C}$. After 0.5, 1, 2, 3, 4, 5, and 6 h, each dissolution basket containing microspheres was withdrawn, blotted with tissue paper to remove the excess water and weighed on the analytical balance (Schimdzu, AX 120). Swelling index was calculated by using the following formula [4,5].

$$\text{Swelling index} = \frac{(\text{Wet weight of microspheres} - \text{Dry weight of microspheres})}{\text{Dry weight of microspheres}}$$

Drug entrapment efficiency

The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl (pH-1.2) repeatedly [6,7]. The extract was transferred to a 100ml volumetric flask and the volume was made up using 0.1N HCl (pH-1.2). The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically (UV 1700, Shimadzu, Japan) at 220 nm against appropriate blank (Table 3).

$$\text{Drug entrapment efficiency (\%)} = \frac{\text{Amount of drug actually present} \times 100}{\text{Theoretical drug load expected}}$$

In-vitro release study

The drug release study was performed for microsphere containing quantity equivalent to 300mg of Cefdinir by using USP dissolution apparatus Type I in 900 ml of 0.1N HCl dissolution media (pH-1.2) at 100 rpm and 37°C temperature. 10 ml of sample was withdrawn at predetermined time interval for 12 hours and same volume of fresh medium was replaced to maintained sink condition. Withdrawn samples were assayed spectrophotometrically at 220 nm. Drug release was also performed for pure drug (Table 4) [8-10].

Formulation	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose
F5	0.44	0.52	15.48	1.18	28.52

Table 2: Micro particulate analysis.

S.No	Formulation code	% Yield	% Buoyancy	% Drug entrapment efficiency	%Swelling Index	Lag time	Floating time
1	F1	80	63	62.66	33.32	12 m	8 h
2	F2	83.33	67	72	35.66	10 m	8 h
3	F3	85	75	89	30.91	7 m	8 h
4	F4	86	79	56	32.33	6 m	10 h
5	F5	87.22	89	92	38.11	3 m	>12 h
6	F6	80	85	72	38.18	3 m	>12h
7	F7	88	70	80	36.55	7 m	10 h
8	F8	82	76	82	37.32	8 m	10 h
9	F9	80	84	67	35.66	4 m	>12h

Table 3: Percentage yield and percentage drug entrapment efficiency of the prepared microspheres.

Release Kinetics				
	ZERO	HIGUCHI	PEPPAS	FIRST
	1	2	3	4
	Q Vs T	Q Vs \sqrt{T}	Log C Vs Log T	Log % Remain Vs T
Slope(n)	6.85	24.73	1.18	-0.06
R2	0.9850	0.9365	0.69	0.91

Table 4: In vitro drug release kinetics data for Formulation F5.

Release kinetics

The matrix systems were reported to follow the Pappas release rate and the diffusion mechanism for the release of the drug [11-14]. To analyse the mechanism for the release and release rate kinetics of the dosage form, the data obtained fitted, Zero order, First order, Higuchi matrix, Pappas and Hixson Crowell model. By comparing the r-values obtained, the best-fit model was selected.

Stability studies

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light, and enables recommended storage conditions [6,15].

Results and Discussion

Compatibility studies

Drug polymer compatibility studies were carried out using Fourier Transform Infra Red spectroscopy to establish any possible interaction of Cefdinir with the polymers used in the formulation [16,17]. The FT-IR spectra of the formulations were compared with the FTIR spectra of the pure drug (Figures 1 and 2).

Pre-formulation parameters

Optimized formulation for bulk density, tapped density, % compressibility, hausner's ratio and angle of repose. The results of % compressibility, hausner's ratio and angle of repose were found to be <16, <1.25 and <30 respectively.

Evaluation of Microspheres

Percentage yield

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The percentage yield of optimized formulation (F5) is 87.22%.

Drug entrapment efficiency

Percentage Drug entrapment efficiency of cefdinir arranged from 62 to 89% for microspheres containing HPMC as polymer, 56 to 92% for microspheres containing Eudragit S 100 as polymer and 67 to 82% for microspheres contains Ethyl cellulose as polymer. F5 formulation shows 92% of entrapment efficiency.

In-vitro drug release studies

Dissolution studies of all the formulations were carried out using dissolution apparatus. The dissolution studies were conducted

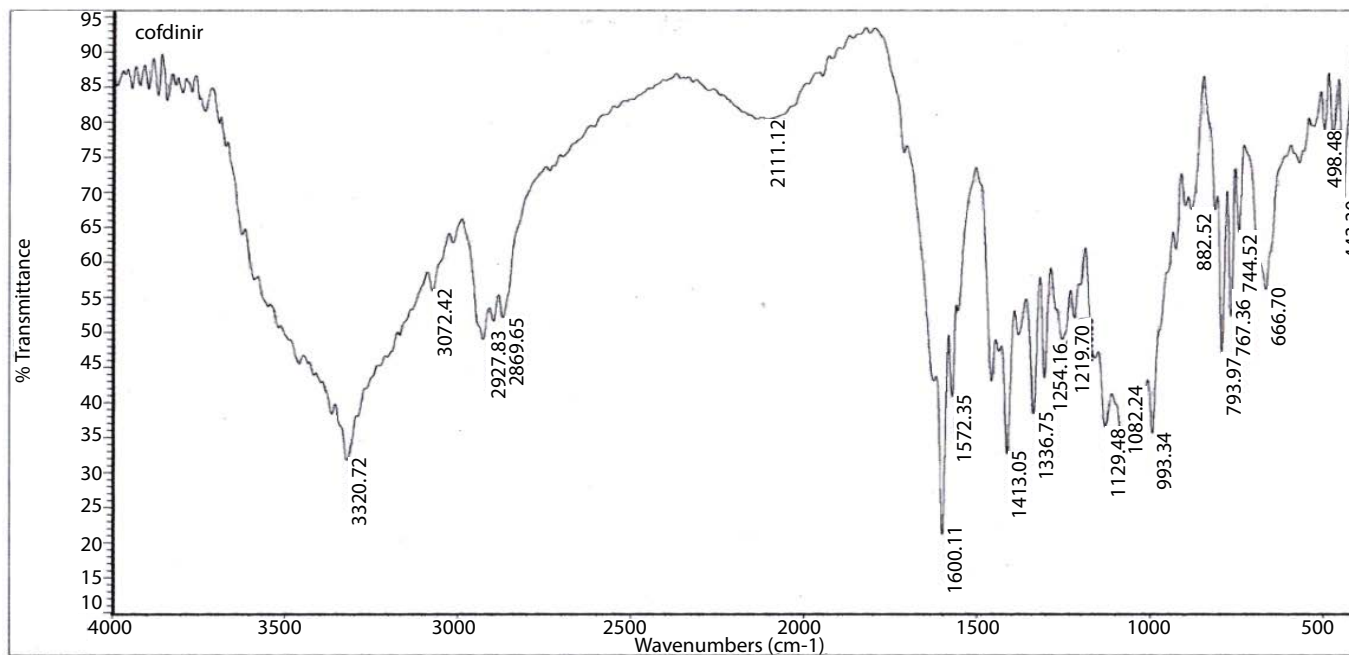


Figure 1: FTIR Spectra of pure drug.

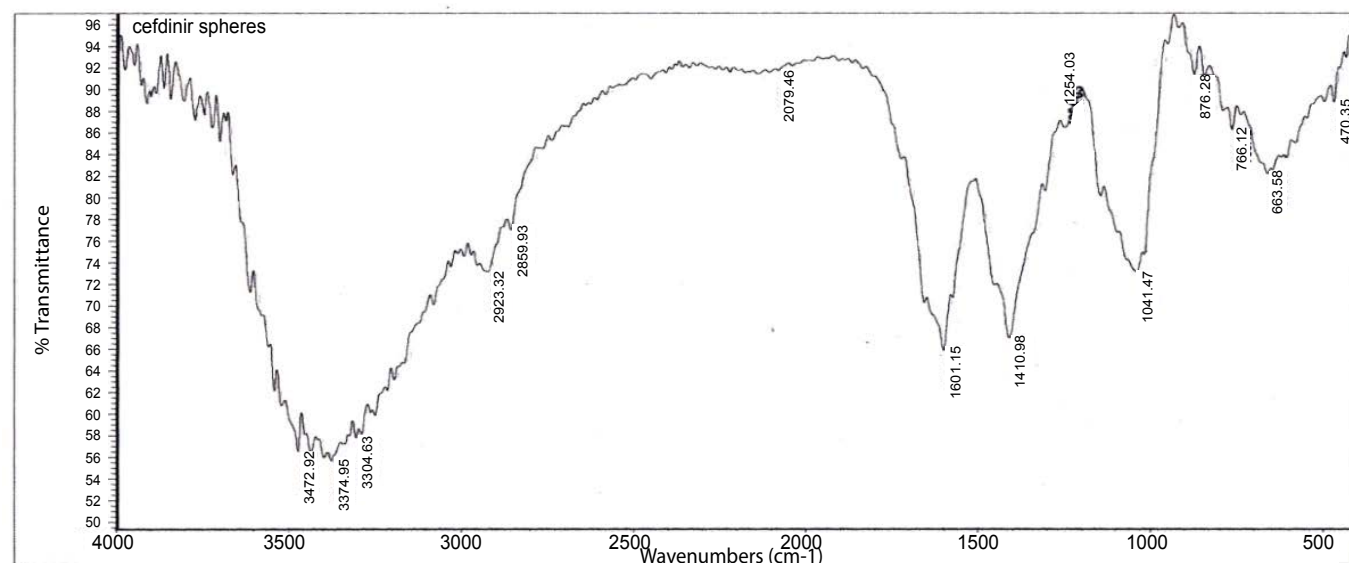


Figure 2: FTIR spectra of optimized formulation.

by using dissolution media, pH 1.2. The plots of Cumulative percentage drug release vs Time. F5 formulation shown significant release 98.95% within 12 h (Figure 3).

In-vitro drug release kinetics

The *in-vitro* drug dissolution data obtained was fitted to various mathematical

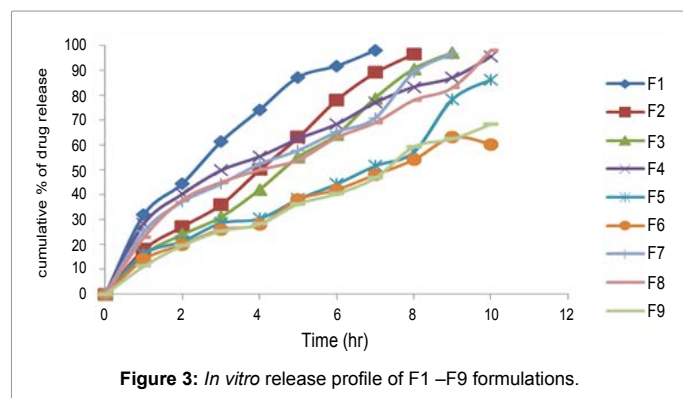
Models such as zero order, First order, Higuchi matrix, and Krosmeier-Peppas model. The kinetic data analysis of all the formulations reached higher coefficient of determination with the Zero order ($R^2 = 0.985$).

Stability studies of cefdinir optimized formulation

The optimized formulation of Cefdinir (F5) was subjected to short-term stability testing by storing the microspheres at room temperature 25°C/60% RH and also subjected to accelerated stability testing by storing the microspheres at temperature 40°C/70% RH.

Conclusion

The present study has been a satisfactory attempt to formulate floating microspheres of cefdinir with a view of improving its oral bioavailability and giving a controlled release of the drug. The floating



microspheres of drug with HPMC and Ethyl cellulose were buoyant while those with Eudragit S 100 showed greater buoyancy (89%) percent yield (87.22%), drug entrapment efficiency (92%), and highest *in vitro* drug release 98.9% within 12 hours. The formulations f5 best fitted into zero order. Microspheres were stable and compatible at the room and temperature and humidity in storage for 90 days. In stability studies no significant change in the drug entrapment, release characteristics of the microspheres.

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