Acta Pharmaceutica Sciencia
52: 101-104 (2010)

Development of floating microspheres to improve oral bioavalibity of cefpodoxime proxetil

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Abstract

The objective of the present study was to develop floating microspheres of Cefpodoxime Proxetil (CP) in order to achieve an extended retention in the upper GIT, to protect the prodrug from enzymatic attack which may enhance the absorption and improve the bioavailability. The microspheres were prepared by non aqueous solvent evaporation method using different ratios of Cefpodoxime Proxetil, hydroxyl propyl methyl cellulose (HPMC K4M) and ethyl cellulose (1:1:1, 1:1:2,1:1:3,1:1:4,1:1:5 and 1:1:6), in the mixture dichloromethane and ethanol at ratio of (1:1), with tween80 as the surfactant. The floating microspheres were characterized by and results obtained are Particle size analysis (75-600 μm), buoyancy percentage (68.2-88.45), drug entrapment efficiency (27.5%-48.5%), % yield (50.5-70.1) and *in vitro* drug release was studied for 12 h. The floating microspheres showed better result and it may be use full for prolong the drug release in stomach and improve the bioavailability.

Key words: Floating microspheres, cefpodoxime proxetil, hydroxyl propyl methyl cellulose, ethyl cellulose, *in vitro* release studies, bioavailability.

Introduction

The present study to improve the bioavailability of Cefpodoxime Proxetil is a prodrug; which is orally absorbed cephalosporin with only 50% absolute bio availability. The in vitro, in situ and ex vivo studies showed interesting results, where metabolism of Cefpodoxime Proxetil into Cefpodoxime acid (CA) inside the intestinal epithelial cell and preferential efflux of into Cefpodoxime acid lumen was identified as primary reason for low oral bioavailability of Cefpodoxime Proxetil (Vasu et al. 2006). By developing controlled drug delivery system, especially the floating microspheres can be improve the bioavailability of Cefpodoxime Proxetil because of the low bioavailability of Cefpodoxime Proxetil due to intestinal lumen hydrolysis may be to some extent prevented. Moreover the absorption of the Cefpodoxime Proxetil in the upper G.I.T. is more (Sylvie et al. 1998).

Cefpodoxime Proxetil has good activity against enterobacteriaceae, *Hemophilus* spp. and *Moraxella* spp. and it has also active against Gram positive bacteria, especially against strepto cocci. It is the one of the first third generation Cefpodoxime Proxitil available in oral form. It has been used most widely in the treatment of respiratory and urinary tract infection.

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In multicenter study the *in vitro* activity of Cefpodoxime was compared with that of cefixime, Cefuroxime, Cefaclor, cefadroxil and Clarithromycin against 5556 recent clinical isolates Cefpodoxime demonstrated potent activity against members of Enterobacteriacea (Sader et al. 1993). Floating drug delivery is be able to prolong the gastric retention of microspheres, thereby improving oral bioavailability of Cefpodoxime Proxetil. Some studies have been contented to evaluate the suitability of various excipient to achieve floating dosage forms (Gerogianis et al. 1993).

Materials and Methods

Cefpodoxime Proxetil (CP) was obtained as a gift sample from Orchid pharma and HPMC K4M, are provided by Coloron Asia Private Limited; Goa. and ethyl cellulose was obtained from Signet chemicals and all polymers and solvents used were of pharmaceutical or analytical grade.

Preparation of floating microspheres: Microspheres containing Cefpodoxime Proxetil drug as a core material were prepared by a Non-aqueous Solvent Evaporation method. Drug and HPMC K4M and EC were mixed in the mixture dichloromethane and ethanol at 1:1 ratio. The slurry was slowly introduced into 30 ml of liquid paraffin containing 0.01%. Tween 80 while being stirred at 1200 rpm using mechanical stirrer equipped with three bladed propellers at room temperature. The solution was stirred for 2 h and allowed the solvent to evaporate completely and filtered by using filter paper. The microspheres obtained were washed repeatedly with petroleum ether (40°-60°C) until free from oil. The collected microspheres were dried at room temperature and subsequently stored in desiccators. Same procedure was repeated for all the three batches (Srivastava et al. 2005).

Buoyancy percentage: The microspheres weighed about (0.3 g) were spread over the surface of USP XXIV. Dissolution apparatus (Type II) filled with 900 ml of 0.1 mol L^{-1} HCl containing 0.02% of Tween80. The medium was agitated with a paddle rotating at 100 rpm for 12h. 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 total mass of the microspheres (Asha et al. 2006).

Drug entrapment efficiency: Microspheres equivalent to 50 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance was measured at 263 nm against appropriate blank. The amount of drug entrapped in the microspheres was calculated by the following formula:

$$DEE = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

Yield of microspheres: The prepared microspheres with a size range of 251-μm were collected and weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

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

In vitro drug release study: In vitro drug release studies were carried out for all products by using USP type I (38) dissolution test apparatus. 100mg of pure drug was used for the dissolution studies and microspheres equivalent to 273mg of the pure drug were used. Two ml of the aliquot was withdrawn at

predetermined intervals a filtered. The required dilutions were made with 0.1N HCl and the solution was analyzed for the drug content spectrophotometrically at 263 nm against suitable blank. Equal volume of the dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. Three trials were carried out for all formulations. From this percentage drug release was calculated and plotted against function of time to study the pattern of drug release.

Table 1. Drug polymer ratios specifications for each batch of microspheres preparation.

Formulation Code	Polymer ratio (EC/HPMCK4M)	Solvent ratio (dichloromethane/ethanol)
FB1	1:1	1:1
FB2	1:2	1:1
FB3	1:3	1:1
FB4	1:4	1:1
FB5	1:5	1:1
FB6	1:6	1:1

Results and Discussion

Floating Microspheres were prepared by non-aqueous solvent evaporation method with HPMCK4M in various proportions on fixed proportion of ethyl cellulose. Six batches for each of three formulations of 270 mg of drug and various ratios of polymer. 1:1 to 1:6 were selected for the preparation f different batches of formulations. The parameters which were evaluated for microspheres are given in the Table 2. Percentage yield for different batches of namely FB_1-FB_6, were determined, it was found 50.5-70.1%. In general with batch c percentage of yield was satisfied. The encapsulation efficiency was found to be 27.5%-48.5%. However the entrapment efficiency somewhat poor it may be attributed to mixing technique used, physical compatibility with polymer used and viscosity of media and particle size may also play a part in the entrapment of drug.

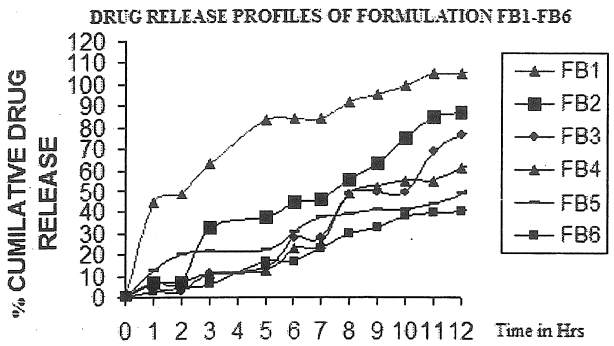
Table 2. Evaluation parameters of Cefpodoxime Proxetil floating microspheres.

Formulation batch	Percentage of yield	Drug entrapment efficiency	buoyancy percentage	Percentage of cumulative drug release of microspheres after 12 h
FB1	50.5%	27.5%	68.1%	108.01%
FB2	65.9%	33.12%	69.3%	87.82%
FB3	69.1%	39.11%	70.4%	78.99%
FB4	65.3%	45.5%	75.55%	64.17%
FB5	75.1%	48.4%	85.42%	61.05%

The buoyancy percentage for all batches almost was above 50% which was studied for 12 hours. The highest percentage was obtained with the batch B6. Average buoyancy in percentage was found to be 68.1% - 85.42%.In general with increase in the amount of polymers there was an increase in the buoyancy percentage. The increase in the buoyancy percentage may be attributed to air which caused swelling because of increased amount of the polymers present. Microspheres were subjected to *in vitro* release using USP dissolution apparatus Type I

in 900 ml of simulated gastric pH medium (0.01M HCl). With all the formulation there was initial intermittent burst release. But the release seems to be somewhat sustained with increased in the amount of polymer. Drug release profiles of different batches of formulations are shown in the Figure 1. The release rate was found to be decreased in accordance with the increase in ratio of polymer used. The best release was found to be with lower drug polymer ratio (1:2).

Figure 1. Drug release profiles of Cefpodoxime Proxetil from floating microspheres with different ratios of HPMC K4M.



Conclusion

In the present study floating microspheres of Cefpdoxime Proxetil showed encouraging results. It was observed that the increase in polymer concentration, the entrapment efficiency as well as percentage yield increases. The *in vitro* release studies showed that the better release profile with the formulation FB2, therefore 1:2 ratio of Cefpdoxime Proxetil and HPMC K4M can be considered as best formulation while compared with other batches. This can be concluded that by formulating Cefopdoxime Proxetil as floating microspheres can improve the low oral bioavailability Cefpodoxime Proxetil by expended drug release in the upper part of stomach.

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Received: 26.03.2009
Accepted: 27.05.2009