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Development of a new single dose extended release formulation of cefpodoxime proxetil

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ABSTRACT

Objective: To develop floating microspheres of cefpodoxime proxetil (CP) in order to achieve an extended retention in the upper GIT for 12 hour. **Methods:** 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 & 1:1:6), in the mixture of dichloromethane and ethanol at ratio of (1:1),with tween80 as the surfactant. **Results:** The floating microspheres was extended over 10-12 hours and were characterized by particle size analysis (75-600 μ m), buoyancy percentage (68.1%-85.4%), drug entrapment efficiency (67.5%-88.8%), % yield (50.50%-77.31%) and *in vitro* drug release was studied for 12 hours. **Conclusions:** The floating microspheres show better result and it may be use full for prolong the drug release in stomach and improve the bioavailability.

1. Introduction

The extended drug delivery systems are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of orally administrated form, however this period is measured in hours and critically depends on the residence time of the dosage form in the gastrointestinal tract. The term controlled release has become associated with those systems form which therapeutics agents may be automatically delivered at predetermined rates over a long period of time[1].

Many concepts have been proposed in the recent years to provide a dosage form with a longer transit time and therefore a maximum efficient absorption. The concept of floating microspheres is one of them to increase gastric retention of drug[2].

Cefpodoxime proxetil is a prodrug; which is orally absorbed cephalosporin with only 50% absolute bioavailabity. By developing controlled drug delivery system, especially the floating microspheres can improve the bioavailability of cefpodoxime proxetil because the cause of intestinal lumen hydrolysis may be to some extent prevented; and the absorption of the cefpodoxime proxetil in the upper GIT can be increased[3, 4].

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. In multicenter study the *in vitro* activity of cefpodoxime was compared with that of cefixime, cefuroxime, cefaclor, cefadroxil and clarithromycin against 5 556 recent clinical isolates cefpodoxime demonstrated potent activity against members of enterobacteriacea[5].

Floating drug delivery is able to prolong the gastric retention of microspheres, thereby improve oral bioavailability of cefpodoxime proxetil. Some studies have been contented to evaluate the suitability of various excipient to achieve floating dosage forms[6].

The objective of this study is to formulate and evaluate extended release floating microsphere of cefpodoxime proxetil that can be capsulated and reduce the frequency of the dosing by formulating as single dose and thus increase patient compliance.

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2. Materials and methods

2.1. Materials

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

2.2. Preparation of floating microspheres

Non-aqueous solvent evaporation method was used for preparation of cefpodoxime proxetil microspheres. cefpodoxime proxetil, 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 1 200 rpm using mechanical stirrer equipped with three bladed propellers at room temperature. The solution was stirred for 2 hours and allowed the solvent to evaporate completely and filtered by using filter paper. The microspheres obtained were washed repeatedly with petroleum ether (40- 60 ℃) until free from oil. The collected microspheres were dried at room temperature and subsequently stored in desiccator. Same procedure was repeated for all the three batches [7].

2.3. 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 HCl containing 0.02% of Tween80. The medium was agitated with a paddle rotating at 100 rpm for 12 h. 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 [8].

2.4. Drug entrapment efficiency (DEE)

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:

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

2.5. Yield of microspheres

The prepared microspheres with a size range of 251 mico meters 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.

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

2.6. Compatibility study

FTIR spectra of pure drug, polymer (HPMC and CE), and various ratios of microspheres were obtained in KBr pellets at moderate scanning speed between 4 000-200 cm^{-1} in a Perkin-Elmer FTIR spectroscope. Compatibility studies were performed using IR spectrophotomer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied.

2.7. 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. 100 mg of pure drug was used for the dissolution studies and microspheres equivalent to 273 mg 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.

2.8. Drug release kinetics

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models: zero order (Equation 1) as cumulative amount of drug released vs time, first order (Equation 2) as log cumulative percentage of drug remaining vs time, and Higuchi´s model (Equation 3) as cumulative percentage of drug released vs square root of time [9,10].

$$C = K_0 t \quad (1)$$

Where K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

$$\text{Log}C = \text{Log}C_0 - Kt / 2.303 \quad (2)$$

Where C_0 is the initial concentration of drug, k is the first order constant, and t is the time.

$$Q = K t_{1/2} \quad (3)$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release

rate is proportional to the reciprocal of the square root of time.

3. Results

Floating microspheres were prepared by non-aqueous solvent evaporation method with HPMC K4M 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 of different batches of formulations. The parameters which were evaluated for microspheres are given in the Figure 1. Drug release profiles of different batches of formulations are shown in the Figure 2. The best formulation selected among them was FB_2 and drug release kinetic studies were done by using various kinetic models such as Higuchi´s model zero order as cumulative amount of drug released vs. time, first order, are given in Figure.3,4,5 respectively. IR spectrum of pure drug and physical mixture of drug and polymer were studied. The floating microspheres was extended over 10-12 hours and were characterized by particle size analysis (75-600 μm), buoyancy percentage (68.1%-85.4%), drug entrapment efficiency (67.5%-88.8%), % yield (50.5%-72.1%) and *in vitro* drug release was studied for 12 hours.

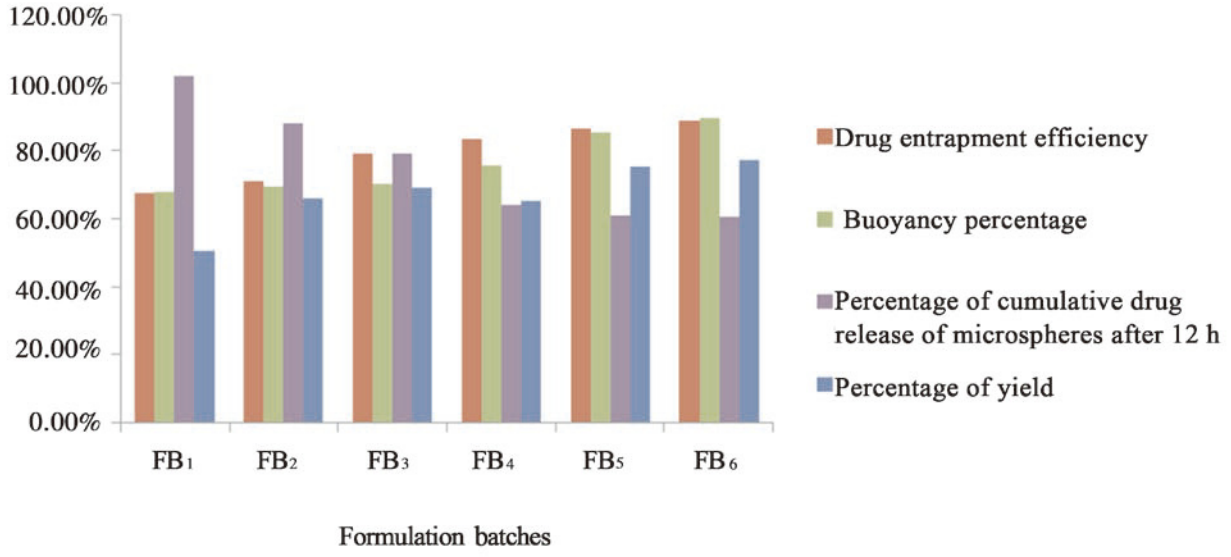

Figure 1. Evaluation parameters of cefpodoxime proxetil floating microspheres.

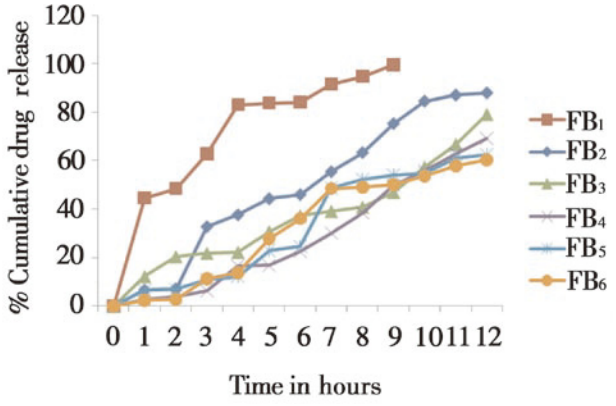

Figure 2. Drug release profiles of cefpodoxime proxetil from floating microspheres with different ratios of HPMC K4M.

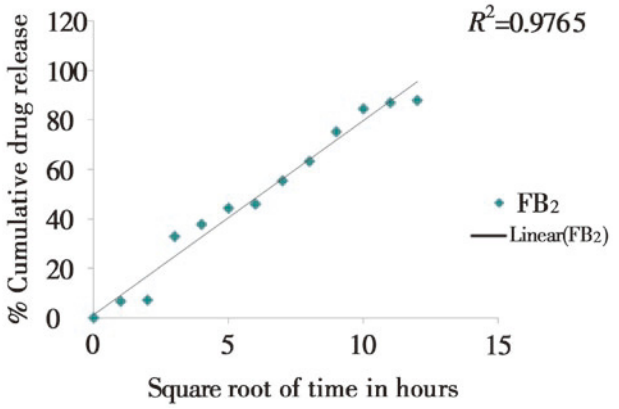

Figure 3. Higuchi kinetics of formulation FB_2.

4. Discussion

Percentage yield for different batches of namely FB_1-FB_6, were determined, it was found to be 50.5% to77.31% .In general with batch c percentage of yield was satisfied. The encapsulation efficiency was found to be 67.5% to 88.8%. However, the entrapment efficiency was better.

The Buoyancy percentage for all batches almost was above 60% which was studied for 12 hours.The highest percentage was obtained with the batch FB_6. Average buoyancy in percentage was found to be 68.1% and 85.4%. In general with increase in the amount of polymers there was an increase in the buoyancy percentage. The increase in the buoyancy

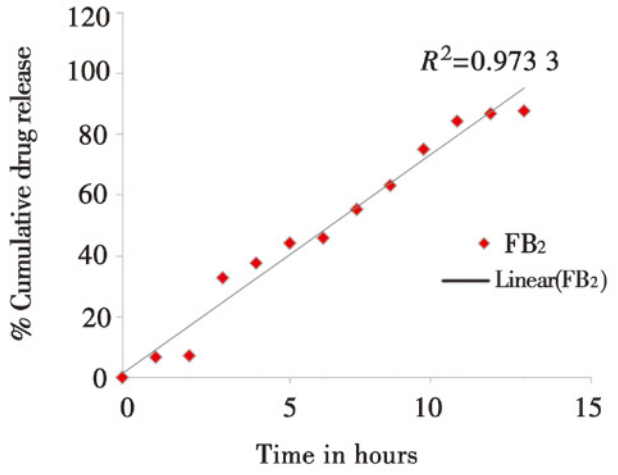

Figure 4. Zero order plot of drug release profile of FB_2 with linearity plot.

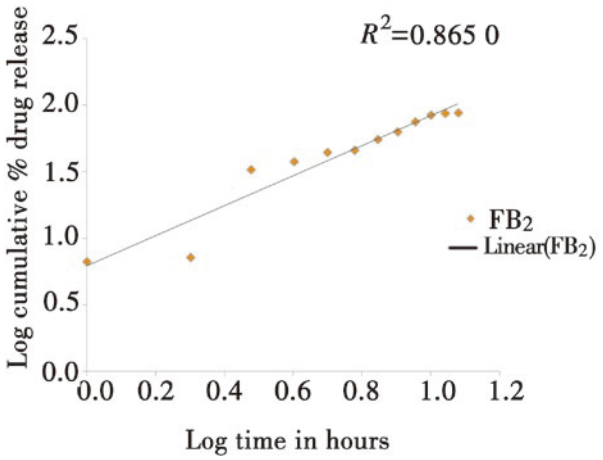

Figure 5. Log % cumulative drug release vs log time.

percentage may be attributed to air which caused swelling because of increased amount of the polymers present.

The characteristics absorption peaks of cefpodoxime proxetil were obtained at wave number 3 442 cm^{-1}, 2 936 cm^{-1}, 1 760 cm^{-1} and 1 273 cm^{-1}. The peaks obtained in the spectra of each formulation correlates with the peaks of spectrum. This indicates that the drug is compatible with the formulation components.

Microspheres were subjected to *in vitro* release using USP dissolution apparatus Type I in 900 mL of simulated gastric pH medium (0.1N 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.

From the release profile better formulation were selected on basis of the microspheres ware designed to expend the drug release of drug for 12 hours. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models and Drug release kinetics indicated that drug release was best explained by Higuchi´s equation, as these plots showed the highest linearity (r^2=0.976 5). However, drug release was also found to be very close to zero-order kinetics, indicating that the concentration was nearly independent of drug release, but a close relationship was also noted with zero-order kinetics (r^2= 0.973 3).

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 all increased. The *in vitro* release studies showed that the better release profile with the formulation FB_2, there for 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.

Conflict of interest statement

We declare that we have no conflict of interest.

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