CALCIUM SILICATE BASED MICROSPHERES OF CEFPODOXIME PROXETIL FOR GASTRORETENTIVE FLOATING DRUG DELIVERY: PREPARATION AND IN VITRO CHARACTERIZATION

Ronak Dedania¹, Gali Vidhyasagar², Anil Bhandari¹, Zarna Dedania³

¹Department of Pharmaceutical Sciences, Jodhpur National University, Narnadi, Jhanwar Road, Jodhpur (Rajasthan), India.  
²Veerayatan Institute of Pharmacy, Jakhania, BhujMandvi road, Kutch-Gujarat, India.  
³Bhagwan Mahavir College of Pharmacy, Surat, Gujarat.

ABSTRACT
Oral sustained release gastroretentive dosage forms offer many advantages for drugs having absorption from upper gastrointestinal tract and improve the bioavailability of medications that are characterized by narrow absorption window. Microspheres were prepared by solvent evaporation technique consisting of Cefpodoxime proxetil (API), calcium silicate (FLR) as porous carrier and Ethyl Cellulose and HPMC K₄M as rate controlling polymer. Box Behnken statistical screening design was applied for optimization of formulation. The effect of various formulation and process variables on the particle morphology, entrapment efficiency, in vitro floating behaviour and in vitro drug release were studied. The percentage yield of all the formulation was found to be 71 - 85. The percentage entrapment efficiency was varied from 79 – 91%. The release rate was determined in simulated gastric fluids. The formulation demonstrated favourable in vitro floating and release characteristics. Multiple regression analysis was applied for study of the effect of independent variables on the dependent variables. Hence developed floating microspheres could be a promising delivery system for Cefpodoxime Proxetil with sustained release and improved bioavailability.

KEYWORDS: Cefpodoxime Proxetil, Floating Multiparticulate, Ethyl Cellulose and HPMC K₄M.

INTRODUCTION
To develop oral drug delivery systems, it is necessary to optimize both the residence time of the system within the gastrointestinal tract and the release rate of the drug from the system. Various attempts have been made to prolong the residence time of the dosage forms within the stomach. The prolongation of the gastric residence time (GRT) of delivery devices could be achieved by adhesion to the mucous membranes, by preventing their passage through the pylorus or by maintaining them in buoyant fashion ingastric juice. Various approaches have been used to retain the dosage forms in the stomach, as a way of increasing the gastric residence time (GRT) including floating, high density,
mucoadhesive[12], magnetic[13], unfoldable, extendible, swellable[14] and superporous hydrogel systems [15]. Both natural and synthetic polymers have been used to prepare floating microspheres.

The Gastro-retentive drug delivery system (GRDDS) is of special interest in improving the bioavailability of drugs that are poorly soluble or unstable at higher pH of the intestinal or colonic environment. In order to obtain local and sustained drug delivery in the stomach and proximal parts of the small intestine, it is desired to have prolonged gastric retention of the drug. This helps to have improved bioavailability and therapeutic efficacy which may also result in the reduction in dosing frequency of the dosage form. The diminished efficacy of the administered dose may be observed due to inter subject variability and short time of gastric emptying which may result because of incomplete drug release from the drug delivery system above the absorption zone (stomach, upper part of small intestine). Moreover, it has been reported that drug delivery system is one of the commercial system which is attributed to obtain the higher bioavailability than that of the non floating system. The GRDDS system is widely useful for the drugs which effectively act in the stomach and have absorption window in stomach. To formulate GRDDS the drug moiety should have good solubility at acidic pH and absorption window in upper GIT and short half life. To overcome the disadvantages of conventional dosage forms, such as the inter subject variability of GI transit time, due to their all or none effect of the multiple unit dosage form systems are developed. Multiple unit dosage form have proven the lower possibility of dose dumping as well as reduced inter and intra subject variability of the drug absorption [16].

Cefpodoxime proxetil (CP) is a prodrug of the third generation cephalosporins, which is broad-spectrum antibiotic and is administered orally. In human, the absolute bioavailability of cefpodoxime proxetil administered as a 130mg tablet (equivalent to 100mg of cefpodoxime) is about 50% [17]. Reported studies have pointed possible reasons for low bioavailability as: low solubility, typical gelation behaviour of CP particularly in acidic environments [18-20], and preabsorption of luminal metabolism into cefpodoxime acid by the action of digestive enzymes [21, 22]. It has been reported that the absorption of cefpodoxime proxetil is optimum at low pH [23].

The objective of the present work was to improve the bioavailability of cefpodoxime proxetil by formulating gastro-retentive microballoons (hollow microspheres) in order to sustain the drug release and provide protection from intestinal milieu. In this study the influence of various process variables on particle size, drug loading, incorporation efficiency and percentage yield, floating behaviour and in vitro drug release of microsphere formulation was investigated.
MATERIALS AND METHODS

Materials
Cefpodoximeproxetil (CP) was obtained as a gift sample from Que Pharmaceutical Ltd. (Surendranagar, India). Calcium silicate (FLR) was obtained as a gift sample from Tomita Pharmaceutical Co, Ltd. (Japan) Eudragit RL (ERL) and Eudragit RS (ERS) was supplied by Evonik Pharma (India). All solvents used were of analytical grades and were used as obtained.

Compatibility studies
Interaction between drug–polymer was studied by infrared spectroscopy using FTIR spectrometer. Sample preparation involved potassium bromide (KBr) pallet technique. The spectrum was scanned over a frequency range 4000-400 cm$^{-1}$.

Method of Preparation of Floating Microspheres

Preparation of drug adsorbed FLR
FLR was dispersed in 10 mL methanolic solution of drug to prepare slurry. The slurry was ultrasonicated in an ice bath using a bath sonicator to entrap the drug solution inside the pores of porous carrier and then dried at room temperature for 1 h.

Preparation of floating microspheres
Microspheres were prepared using emulsion solvent diffusion technique. The drug adsorbed FLR was added into the polymer solution of Eudragit RL (ERL) and Eudragit RS (ERS) in methanol and dichloromethane (1:1) and sonicated using sonicator. The resulting suspension was slowly poured into the dispersion medium consisting of liquid paraffin containing 1.5% span 80. The system was stirred using propeller type agitator at a speed of 900 rpm at 40 °C over a period of 2-3 h, to ensure complete evaporation of the solvent. The microspheres were separated by filtration through a whatman filter paper, washed twice with petroleum ether and air dried.

Factorial design
Box Behnken statistical screening design was used to optimize and evaluate main effects, interaction effects and quadratic effects of the formulation ingredients on the in-vitro release of the drug.

The factors were selected based on preliminary study. Total amount of polymer (A), % of ERL (B) and amount of FLR (C) were selected as independent variables. The Q6, Q10 and K of Zero order were selected as dependent variables.

$$Y_i = b_0 + b_1A + b_2B + b_3C + b_{12}AB + b_{13}AC + b_{23}BC + b_{123}ABC$$
Table 1: Coded values for amount of polymers

<table>
<thead>
<tr>
<th>Name of the Factor</th>
<th>Coded values</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-1</td>
</tr>
<tr>
<td>Total amount of polymer</td>
<td>A</td>
<td>200</td>
</tr>
<tr>
<td>% of ERL</td>
<td>B</td>
<td>20</td>
</tr>
<tr>
<td>Amount of FLR</td>
<td>C</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2: Different batches with their respective composition

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Total amount of polymer (A)</th>
<th>% of ERL (B)</th>
<th>Amount of FLR (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>-1</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>F2</td>
<td>1</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>F3</td>
<td>-1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>F4</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>F5</td>
<td>-1</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>F6</td>
<td>1</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>F7</td>
<td>-1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>F8</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>F9</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>F10</td>
<td>0</td>
<td>1</td>
<td>-1</td>
</tr>
<tr>
<td>F11</td>
<td>0</td>
<td>-1</td>
<td>1</td>
</tr>
<tr>
<td>F12</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>F13-T1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>F13-T2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>F13-T3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Particle size analysis

Microsphere size was determined by using optical microscopic method with the help of ocular and stage micrometer. The sizes of around 100 particles were measured and their average particle size was determined.

% Yield of Microspheres

The prepared microspheres 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.
% Yield = \[ \frac{\text{Actual weight of product}}{\text{Total weight of excipient and drug}} \times 100 \]

**Entrapment Efficiency**

Microspheres weighing 50 mg were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting the drug using 50 mL SGF (pH 1.2). The solution was filtered and take one mL extract in to 50 mL volumetric flask, dilute up to 50 mL using SGF (pH 1.2). The absorbance was measured at 260 nm against SGF (pH 1.2) as blank.

\[
\% \text{ Entrapment efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100
\]

**In vitro Buoyancy**

Microspheres (100 mg) were spread over the surface of a dissolution apparatus type I filled with 900 mL of hydrochloric acid buffer pH 1.2 containing 0.02% tween 80. The contents were stirred at 50 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.

\[
\% \text{ Buoyancy} = \frac{W_f}{(W_f + W_s)} \times 100
\]

Where, \( W_f \) and \( W_s \) are the weight of the floating and settled microspheres respectively.

**In vitro drug release studies**

*In vitro* release characteristics from floating microspheres were evaluated employing dissolution testing type I apparatus. The dissolution test was performed using 900 ml of SGF buffer as dissolution medium maintained at 37±0.5 °C. The contents were stirred at 50 rpm. A 5 mL aliquot of the solution was withdrawn at predetermined time intervals for 12 h and fresh 5 mL dissolution media was replaced to maintain sink condition. The sample aliquots were analysed spectrophotometrically at a wavelength of 263 nm.

**RESULT AND DISCUSSION**

The results revealed no considerable changes in the FT-IR peaks of CP in the physical mixture when compared to pure drug, indicating the absence of any interaction.
The floating microspheres were prepared by emulsion solvent evaporation technique. Size of microspheres was in ranged 325 µm to 663 µm. The size of microspheres formed may be a
function of many factors such as stirring speed, viscosity of the dispersed phase and dispersion medium, temperature, concentration of polymer, amount and size of porous carrier. Therefore, it is possible to prepare microspheres of desired size by varying some of these parameters. The percentage yield of all the formulation was found to be 71 - 85%. It can be due to minimum involvement of process parameters and smaller amount of drug and polymer loss during manufacturing. Percentage yield of microsphere was observed to increase with increase in both the quantity of FLR and polymer. The percentage entrapment efficiency was varied from 79 – 91%. Drug entrapment was attributed to the permeation characteristics of polymers used, that could facilitate the diffusion of part of entrapped drug to the surrounding medium. When the loading was high the proportion of large particle form was also high. The floating ability test was carried out to investigate the floatability of the prepared microspheres. The microspheres were spread over the surface of a simulated gastric fluid and the fraction of microspheres settled down as a function of time was quantitated. In vitro % buoyancy of the microspheres were in the range of 87.81 to 96.22% at the end of 12 h. This characteristic may be attributed to the low tapped density of the microspheres as a result of the entrapment of low density FLR within the system. Microsphere formulation F12 showed the best floating ability 96.22% in SGF (pH 1.2) as compared with other formulations because it contained highest amount of FLR and ERL.

It was found that with increase in concentration of FLR, ERL and ERS the drug release decreased as shown in figure 3. The drug release of the developed formulation was varied from 78 to 100%. The increased density of the polymer matrix at higher concentration results in an increased diffusion path length. This may decrease the drug release from the polymer matrix. All the formulation did not show initial burst effect. It was found that the greater the content of ERL, the greater is the rate of drug release. ES 100 polymer is of low permeability and insoluble in acid medium. It is an anionic copolymer of methacrylic acid and methyl methacrylate containing free carboxylic and ester groups. Its very low permeability results from high intermolecular attraction between its molecules. Hydrogen bonding between the hydroxyl groups of the carboxylic moiety and the carbonyl oxygen of ester groups increases the degree of compactness of the polymer and decreases its porosity and permeability. On the other hand, ERL is a copolymer of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. The ammonium groups present as salts give rise to permeability and after their dissolution as channelling agents for the entrance of the dissolution medium through the floating microparticle wall causing its swelling. This gives an opportunity for the dissolved drug to diffuse out to the bulk medium.
Figure 3: *In vitro* drug release profile of developed formulation

Figure 4: 3D surface plot of Q10 for various formulations
Y1 (Q10) for all developed formulation was varied from 61.02 – 99.38. Y2 (Q6) was varied from 36.60 – 70.51 and Y3 (K of zero order) was varied from 6.25 - 10.85.
Y1 = 121.82 – 0.17354 * A + 0.01192 * B + 0.017752 * C + 0.0001313 * AB + 0.000082 * AC
Y2 = 85.63 – 0.162 * A + 0.030 * B + 0.0302 * C + 0.000678 * A^2 + 0.000043 * C^2
Y3 = 14.04 – 0.033 * A + 0.005 * B + 0.011 * C - 0.0000086 * AC + 0.000029 * A^2 - 0.000043 * C^2

Only statistically significant (p < 0.05) coefficients are included in the equations. A positive value represents an effect that favours the optimization, while a negative value indicates an inverse relationship between the factor and the response. Three-dimensional response surface plots are presented in Figures. 4 - 6, which are very useful to study the interaction effects of the factors on the responses. These types of plots show the effects of two factors on the response at a time. In all the presented figures, it was concluded that as the total amount of polymer (A) decrease and % of ERL (B) in polymer mixture increase, the Q10 increased as shown in figure 4. The total amount of polymer (A) decrease and % of ERL (B) in polymer mixture increase, the Q6 increased as shown in figure 5. The total amount of polymer (A) decrease and amount of FLR (C) increase, the value of K of zero order is also increased as shown in figure 6.

The selection of optimized formulation was done by following way. The criteria for selection of suitable feasible region were Q10 was targeted to 83.33 %, Q6 was targeted to 50% and K of zero order was targeted to 8.33. By considering the desired criteria the overlay plot was obtained. It indicated desirability region by overlaying the plots of all responses. It shows that any point in this region gives desired responses. Formulation F10 was fulfilling all above criteria, so it was selected as a most satisfactory formulation in this study.

**CONCLUSION**

Incorporation of FLR in the microspheres proved to be an effective method to achieve the desired release behaviour and buoyancy. The microspheres so prepared will remain buoyant on surface of gastric fluid releasing CP in sustained fashion. Inferences drawn from *In vitro* studies suggest that microspheres may prove as potential delivery system for cefpodoxime proxetil by improving bioavailability in comparison to conventional dosage forms.

**REFERENCES**


For Correspondence
Ronak Dedania
Email: dedaniaronak229@yahoo.co.in