FORMULATION AND EVALUATION OF FLOATING MULTIPARTICULATE DRUG DELIVERY SYSTEM OF CEFPODOXIME PROXETIL

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ABSTRACT
The main aim of present study was to develop controlled release (CR) floating multiparticulate drug delivery system of Cefpodoxime proxetil. Microspheres were prepared by solvent evaporation technique consisting of Cefpodoxime proxetil (API) and Ethyl Cellulose and HPMC K\textsubscript{4}M as rate controlling polymer. Central composite statistical screening design was applied for optimization of formulation. The effect of various formulation and process variables on the particle morphology, entrapment efficiency, \textit{in vitro} floating behavior and \textit{in vitro} drug release were studied. The percentage yield for different formulation was varied from 63% to 84%. The drug entrapment efficiency of microsphere varied from 58% to 88%. The release rate was determined in simulated gastric fluids. The formulation demonstrated favorable \textit{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 K\textsubscript{4}M.

INTRODUCTION
Oral administration is the most convenient and preferred mean of drug delivery to the systemic circulation. Many attempts have been made to develop sustained-release preparations with extended clinical effects and reduced dosing frequency. In order to develop oral drug delivery systems, it is necessary to optimize both the release rate of the drug and the residence time of the system within the gastrointestinal tract. Various approaches have been used to retain the dosage forms in the stomach [1-3], as a way of increasing the gastric residence time (GRT) including floating [4-7], high density [3], mucoadhesive [8], magnetic [9], unfoldable, extendible, or swellable [10], and superporous hydrogel systems [11]. Both natural and synthetic polymers have been used to prepare floating microspheres.
Gastro-retentive floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. The increasing sophistication of delivery technology will ensure the development of increasing number of gastro-retentive drug delivery systems to optimize the delivery of molecules that exhibit low bioavailability and extensive first pass metabolism. A gastric floating drug delivery system can overcome at least some of these problems and is particularly useful for drugs that are primarily absorbed in the duodenum and upper-jejunum segments and it can prolong retention times of dosage forms in the GIT and thereby improve their oral bioavailability \[^{12, 20}\]. The control of gastro-intestinal transit could be the focus of the next decade and may result in new therapeutic possibilities with substantial benefits for patients.

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 130 mg tablet (equivalent to 100mg of cefpodoxime) is about 50% \[^{13}\]. Reported studies have pointed possible reasons for low bioavailability as: low solubility, typical gelation behavior of CP particularly in acidic environments \[^{14-16}\], and preabsorption of luminal metabolism into cefpodoxime acid by the action of digestive enzymes \[^{17, 18}\]. It has been reported that the absorption of cefpodoxime proxetil is optimum at low pH \[^{19}\]. 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 behavior and in vitro drug release of microsphere formulation was investigated.

**MATERIALS AND METHODS**

**Materials**

Cefpodoxime proxetil (CP) was obtained as a gift sample from Que Pharmaceutical Ltd. (Surendranagar, India). Ethyl cellulose and Hydroxypropylmethyl cellulose (HPMC K\(_4\)M) was supplied by Chemdyes Corporation (India). All solvents used were of analytical grades and were used as obtained.

**Factorial design**

Central composite statistical screening design was used to optimize and evaluate main effects, interaction effects and quadratic effects of the formulation ingredients on the \textit{in-vitro} release of the drug. A 2-factor, 3-level design used is suitable for exploring quadratic response surfaces and

\[ Y = \beta_0 + \beta_1A + \beta_2B + \beta_{12}AB + \beta_{11}A^2 + \beta_{22}B^2 \]

Where \( Y \) is the measured response associated with each factor level combination; \( \beta_0 \) is an intercept; \( \beta_1 \) to \( \beta_{22} \) are regression coefficients computed from the observed experimental values of \( Y \) from experimental runs; and \( A \) and \( B \) are the coded levels of independent variables. The terms \( AB, A^2 \) and \( B^2 \) represent the interaction and quadratic terms, respectively. The factors were selected based on preliminary study. Total amount of polymer (A) and % of Ethyl cellulose (B) were selected as independent variables. The T50%, T80% and value of \( n \) of peppas were selected as dependent variables.

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>% Ethyl Cellulose</td>
<td>B</td>
<td>20</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>% Ethyl cellulose (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>F2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>F3</td>
<td>-1</td>
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<tr>
<td>F4</td>
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<td>F6</td>
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<td>0</td>
</tr>
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<td>F7</td>
<td>0</td>
<td>0</td>
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<td>F8</td>
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<td>1</td>
</tr>
<tr>
<td>F9</td>
<td>1</td>
<td>-1</td>
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<tr>
<td>F10</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>F11</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Preparation of CP microspheres**

CP microspheres were prepared based on solvent evaporation technique. Different batches of CP microspheres were prepared by varying the concentration of ethyl cellulose and HPMC K4M...
polymer in the formulation as showed in Table 2. Weighed quantities of drug and polymers were dissolved in mixture of ethanol and dichloromethane (1:1 solvent ratio) at room temperature. This solution was poured into 250 mL 0.75% w/v polyvinyl alcohol. The resultant emulsion was stirred with a propeller type agitator at 500 rpm for 2 h to allow the volatile solvent to evaporate. The microspheres formed were filtered, washed with water and dried overnight at room temperature.

**Compatibility studies**

The pure drug and the mixtures of drug-ethyl cellulose and drug-HPMC K4M in the ratio of 1:1 were kept at room temperature for 30 days. Samples were subjected to FT-IR studies using KBr as a blank and the IR spectrum of pure drug and drug-excipient mixtures were compared to find any interaction between drug and excipients used for the formulation of microspheres.

**Particle size analysis**

The size was measured using an optical microscope and the mean particle size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer.

**% 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.

\[
\text{% Yield} = \left( \frac{\text{Actual weight of product}}{\text{Total weight of excipient and drug}} \right) \times 100
\]

**Floating ability**

Floating behavior of hollow microspheres was studied in a USP dissolution test apparatus by spreading the microspheres (100 mg) on a 0.1 M HCl containing 0.02% Tween 80 as a surfactant. The medium was agitated with a paddle rotating at 100 rpm and maintained at 37 ± 0.5 °C. After 12 h, both the floating and the settled portions of microspheres were collected 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**

The release rate of CP from microspheres was determined using USP dissolution testing apparatus II(Paddle type). The dissolution test was performed using 900 mL of 0.1N HCl, at 37 ±
0.5 °C and 100 rpm. Microspheres equivalent to 200 mg of CP were used for the test. A 5 mL sample solution was withdrawn from the dissolution apparatus every 1 h up to 12 h. Samples were replaced by its equivalent volume of dissolution medium. The samples were filtered through Whatmann filter paper and solutions after appropriate dilution were analyzed at 263 nm by UV Spectrophotometer (Shimadzu-1800).

RESULTS 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.

Figure 1: FT-IR spectra of Cefpodoxime Proxetil

Figure 2: FT-IR spectra of physical mixture of drug and polymers
The floating microspheres were prepared by emulsion solvent evaporation technique. A solution of drug with polymer in ethanol and dichloromethane was poured into an agitated aqueous solution of polyvinyl alcohol. The ethanol rapidly partition into the external aqueous phase and the polymer precipitated around dichloromethane droplets. The subsequent evaporation of the entrapped dichloromethane droplets lead to the formation of internal cavity within micro-particle. The microspheres were observed with microscope and were found to be irregularly spherical shape and exhibited range size from 220 to 640 µm. However average particle size increase and wall thickness also increase as the amount of polymer increase. The viscosity of medium increase at higher polymer concentration resulting in enhance interfacial tension, shearing efficiency is also diminished at higher viscosities, this result in formation of large particle. The optimum rotation speed for this experimental system was 500 rpm, as judge from the result of particle size distribution and drug content. The size of the microspheres formed may however be a function of many factors such as stirring speed, viscosity of the dispersed phase and dispersion medium, temperature, amount and size of porous carrier, etc. Therefore, it is possible to prepare microspheres of desired size by varying some of these parameters.

The percentage yield for different formulation was varied from 63% to 84%. In general yield was satisfactory. The drug entrapment efficiency of microsphere varied from 58% to 88%. The high entrapment efficiency of drug is believed to be its poor aqueous solubility. Result demonstrated increase in concentration of polymer increase the entrapment of drug. 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. The buoyancy percentage for all batches was almost above 70%, which was studied for 12 h. The highest percentage was obtained with formulation F11. Average buoyancy in percentage was found to be 71% to 83%. 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 gel forming polymer HPMC K4M which caused swelling because of increased amount of the polymers present. It was also observed that the microspheres of larger size, showed the longer floating time. It was obvious from results that most of the prepared microspheres remained floating for longer than 12 h thereby releasing the drug in dissolution media in sustained manner.

It was found that formulations F1 to F11 showed 80 to 99 % of release at 12 h (Figure 3). It was observed that as the concentration of ethyl cellulose was increased the % cumulative drug release
and initial burst release decreased. The increased ethyl cellulose concentration leads to increased density of polymer matrix in to the microspheres which results in an increased diffusional path length and consequent retardation in drug release. In case of controlled or sustained release formulations, diffusion, swelling and erosion are the three most important rate controlling mechanisms. Formulations containing swelling polymers showed swelling as well as diffusion mechanism, because in addition to diffusion, processes includes relaxation of polymer chains, imbibitions of water causing polymer to swell and changing them from initial glassy to rubbery state. Korsmeyer-Peppas was best fit model with formulation showing an n value from 0.47 to 0.87 which indicate the release mechanism following anomalous transport.

Figure 3: *In vitro* drug release profile of developed formulation
Figure 4: 3D surface plot of T50% for various formulations

Figure 5: 3D surface plot of T80% for various formulations
A central composite statistical experimental design as the response surface method requires 11 experiments. The independent variables and the responses for all 11 experimental runs are given in Table-1. Y1 (T50%) for all developed formulation was varied from 1.95 – 6.39. Y2 (T80%) was varied from 4.78 to 13.33 and Y3 (n of pappas) was varied from 0.47 - 0.83.

\[
Y1 = -0.11137 + 0.004605 * A + 0.05622 * B - 0.00001566 * AB \\
Y2 = -3.72674 + 0.026956 * A + 0.18117 * B + 0.000398 * AB \\
Y3 = 0.30251 + 0.00024 * A + 0.0054 * B
\]

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. It is evident that the total amount of polymers (A) and % of ethyl cellulose (B) have positive effects on the responses T50% (Y1), T80% (Y2) and n of pappas (Y3). 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) and % of ethyl cellulose (B)
cellulose (B) in polymer mixture increase, the T50% increased as shown in figure 4. The total amount of polymer (A) and % of ethyl cellulose (B) in polymer mixture increase, the T80% increased as shown in figure 5. The total amount of polymer (A) and % of ethyl cellulose (B) in polymer mixture increase, the value of n of peppas 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 T50% was targeted at 6 h, T80% was targeted at 9.6 h and n of peppas value was in ranged from 0.47 - 0.87. 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

It was satisfactory attempt to prepare a floating and controlled release preparation using HPMC K4M and EC in suitable proportions. 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:


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