Formulation Development of Floating Microspheres of Cefditoren Pivoxel by $3^2$ Factorial Design and in Vitro Characterization

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Abstract

Aim: The main objective of the present research work was to develop floating microspheres of cefditoren pivoxel (CP) to provide the delivery of the drug at a sustained rate. Materials and Methods: Floating microspheres of CP were prepared by solvent evaporation technique using hydroxypropyl methylcellulose (HPMC) K4M and ethyl cellulose as the rate controlling polymers. The optimization of formulation was carried out by $3^2$ factorial design using two factors; a total amount of polymer ($X_1$) and concentration of ethyl cellulose ($X_2$) as independent variables. The formulated floating microspheres were characterized by evaluating its yield, particle size, encapsulation efficiency, in vitro drug release, buoyancy, surface morphology (scanning electron microscopy analysis). Results and Discussion: The optimized formulation (F6) showed 91.5 ± 1.35% of drug release after 12 h and 75 ± 0.92% of entrapment efficiency. All the formulations have good buoyancy which was floated over 12 h in the dissolution medium. Conclusion: It can be concluded from the study that floating microspheres of CP can be prepared successfully using HPMC K4M and ethyl cellulose as the rate controlling polymers.

Key words: Cefditoren, entrapment efficiency, factorial design, floating, microspheres, pivoxel

INTRODUCTION

Oral drug delivery system has been known for decades as the most widely used route of administration among all the routes that have been explored for systemic delivery of drugs through various pharmaceutical products of different dosage forms.¹ Drugs that are easily absorbed from the gastrointestinal tract and having short half-life are quickly eliminated from the blood circulation. To avoid these problems oral controlled release formulations have been developed.²,³ These systems should be aimed at achieving more predictable and increased bioavailability of the drugs and it is necessary to optimize both the residence of the system within the gastrointestinal tract and the release rate of the drug from the system.⁴ However, there are several physiological difficulties such as inability to restrain and localize the drug delivery system within desired regions of the gastrointestinal tract and the highly variable nature of the gastric emptying process.⁵,⁶ To overcome these difficulties gastroretentive dosage forms which prolong the residence time of drug in the stomach and improve bioavailability have been developed.⁷ The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, floatation, sedimentation, and expansion/swelling. Among these approaches floating drug delivery is of particular interest due to its logical approach in the development of gastro retentive drug delivery system.⁸ A single unit floating dosage forms such as floating tablets are developed by utilizing matrices prepared by swellable polymers like methocel and natural polysaccharides and effervescent agents such as citric acid, tartaric acid, and sodium bicarbonate.⁹ Targeted drug

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Received: 16-12-2015
Revised: 25-01-2016
Accepted: 05-02-2016
delivery systems play a major role in delivering sufficient dose to the diseased lesions with the help of carriers. Nano and microparticulate carriers thus have important applications in the administration of therapeutic molecules. In the present study, an antibiotic drug CP is administered by encapsulating it in the microspheres.[10,33]

CP is an advanced-generation, broad spectrum cephalosporin antibiotic approved for the treatment of acute bacterial exacerbation of chronic bronchitis, group-A beta-hemolytic streptococcal pharyngotonsillitis and uncomplicated skin/skin structure infections in adult and adolescent patients.[24-27] CP has slightly bitter taste and has half-life of 1.6 h and has poor water solubility. It is absorbed in the upper part of gastrointestinal tract (GIT). Based on these properties CP has been selected to develop floating drug delivery system.[11] The objective of the present study was to develop multiunit floating drug delivery system of CP in order to provide the delivery of the drug at a sustained rate to improve bioavailability. Therefore, it was proposed to develop floating microspheres of CP by emulsion solvent evaporation method by optimizing formulation variables using hydroxypropyl methylcellulose (HPMC) K4M and ethyl cellulose as rate controlling polymers. From the literature, it has been found that no attempt has been reported yet to develop floating microspheres of CP to deliver the drug at a sustained rate in stomach and upper part of GIT, which is the absorption window of the drug, by optimizing formulation variables.

**MATERIALS AND METHODS**

CP was obtained as gift sample from Cadila Pharmaceuticals Limited (Ahmedabad). HPMC K4M and ethyl cellulose were purchased from Colorcon Pvt., Ltd., Hyderabad. All other reagents were of analytical grade and were used as received.

**Preparation of floating microspheres**

The floating microspheres of CP were fabricated by emulsion solvent evaporation technique. First the polymer solution was prepared by dissolving hydroxyl propyl methyl cellulose (HPMC K4M) and ethyl cellulose in dichloromethane and ethanol mixture (40 ml) in the ratio of 1:1. Weighed amount of CP was added to the polymer solution (HPMC K4M:ethyl cellulose) at different ratios of 1:3, 1:4, and 1:5, respectively, at room temperature and kept for stirring on magnetic stirrer for 15 min for uniform distribution of the materials in the solvent system. The drug-polymer solution was then transferred to the processing medium, i.e., 1% polyvinyl alcohol (PVA) upon continuous stirring using 3 blade propeller. The agitation by propeller was continued for 6 h at 500 rpm, and the temperature was maintained at 40°C throughout the process. After the smell of dichloromethane disappears the solution was filtered, and the collected microspheres were washed with an excess amount of distilled water to remove any remnants of PVA. The microspheres were dried at room temperature.[12,30-32]

**Experimental design**

In the present research, work 3² factorial design was employed to develop the optimized formulation with the help of Design-Expert® 9 trial version software (Stat-Ease Inc., USA). A statistical model incorporating interactive and polynomial terms was used to evaluate the response (Equation 1):

\[ Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2 \]  

(1)

Where Y is the dependent variable, \( b_0 \) is the arithmetic mean response of the nine runs, and \( b_i \) is the estimated coefficient for the factor \( X_i \). The main effect (\( X_1 \) and \( X_2 \)) represents the average result of changing one factor at a time from its low medium to a high value. The interaction terms \( X_1^2 \), \( X_2^2 \) shows how the response changes when two factors are changed simultaneously.[13]

The independent and dependent variables selected were as follows:

**Independent variables**

a. Total amount of polymer (\( X_1 \))

b. Concentration of ethyl cellulose (\( X_2 \))

dependent variables

a. Percentage yield (\( Y_1 \))

b. Particle size (\( Y_2 \))

c. Entrapment efficiency (EE) (\( Y_3 \))

d. Dissolution efficiency (DE) (\( Y_4 \))

The various levels of independent variables used in experimental trials are shown in Table 1 and the composition of floating microspheres is shown in Table 2.

**In vitro evaluation of floating microspheres**

**Percentage yield**

The prepared microspheres of all batches were accurately weighed. The weighed quantity of prepared microspheres was divided by the total amount of all the excipients and drug used in the fabrication of microspheres, which gave the total percentage yield of floating microspheres.[14,15] The above experiment was done in triplicate, and the mean value of %

<table>
<thead>
<tr>
<th>Table 1: Independent variables and their levels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Levels</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>−1</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>+1</td>
</tr>
</tbody>
</table>
yield was taken into consideration. It was calculated using the following formula:

Percentage yield = \( \frac{\text{Actual yield of product}}{\text{Total weight of excipients and drug}} \times 100 \)

### Particle size measurement

The particle size of prepared microspheres was measured using an optical microscope and the mean particle size was calculated by measuring 100 particles with the help of a calibrated eye piece micrometer. The average particle size was taken into consideration.

### EE

The EE was determined based on the total drug content and the unentrapped drug of the floating microspheres. The unentrapped drug was determined by taking one dose equivalent of floating microspheres and washed with 0.1 N HCl to remove the surface associated drug. The absorbance of the filtrate was taken at 272 nm to estimate the surface drug content. The drug content of CP floating microspheres was determined by dispersing 50 mg of formulation (accurately weighed) in 10 ml of 0.1 N HCl, followed by agitation on magnetic stirrer for 12 h to extract the total drug. The drug concentration of both the solutions of unentrapped drug and the total drug was determined spectrophotometrically at 272 nm by making desired dilution with 0.1 N HCl.

Devi & Sengupta: The EE was calculated based on the results of in vitro drug release. It is determined by the following equation:

\[
\text{Dissolution efficiency} = \int_0^t \frac{Y(t)}{Y_{t0}} \times 100
\]

### In vitro buoyancy

The floating ability of the prepared microspheres was determined using USP dissolution apparatus type II (paddle). Floating microspheres were spread over the surface of dissolution medium which contains 900 ml of 0.1 N HCl and was agitated by a paddle rotated at 50 rpm for 12 h. After agitation for 12 h, the microspheres remained on the surface were collected with the help of pipette and then the microspheres settled at the bottom were collected. After drying of each fraction of microspheres, percentage buoyancy was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.

\[
\% \text{ Buoyancy} = \frac{Q_f}{Q_f + Q_s}
\]

Where \( Q_f \) and \( Q_s \) are the weight of the floating and the settled microspheres, respectively.

### In vitro drug release study

The drug release study was carried out using USP dissolution apparatus type II (paddle) at 37 ± 0.5°C and at 50 rpm using 900 ml of 0.1 N HCl (pH 1.2) as a dissolution medium. 5 ml of sample solution was withdrawn at predetermined time intervals (1, 2, 4, 6, 8, 10, and 12 h) and simultaneously equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. The samples were diluted suitably and analyzed spectrophotometrically with UV-visible spectrophotometer at a wavelength of 272 nm. The dissolution studies were performed in triplicate, and the average percentage drug release was taken into consideration.

### DE

DE was calculated based on the results of in vitro drug release. It is determined by the following equation:

\[
\text{DE} = \int_0^t \frac{Y(t)}{Y_{t0}} \times 100
\]
The equation of DE can also be represented in the simple terms as follows:\(^{[24,28,29]}\)

\[
\text{Dissolution efficiency} = \frac{\text{AUC}}{\text{Total area}} \times 100
\]

**Morphological studies**

The surface morphology and surface characteristics of the best formulation were examined by scanning electron microscope (SEM). Microspheres were scanned and examined under electron microscope connected with fine coat, ion sputter. The sample was loaded on the copper sample holder and sputter coated with followed by gold.\(^{[15]}\) The surface morphology of microspheres explains about their floating ability and the mechanism of drug release.

**RESULTS AND DISCUSSION**

**Formulation development of floating microspheres of CP**

Floating microspheres of CP were successfully fabricated by solvent evaporation technique by applying \(^3^2\) factorial design. All the nine possible experimental trials were successfully carried out according to the design layout and were further evaluated.

**In vitro evaluation of floating microspheres of CP**

**Percentage yield**

The floating microspheres were prepared, and percentage yield was calculated for all the formulations. The results of % yield are shown in Table 3. The percentage yield was in the range of 60-80% for all the formulations. The recovery of microspheres was high as there is an increase in the concentration of the polymers which are used in the formulation for controlling the release rate.

**Table 3: Observations of in vitro evaluation parameters of floating microspheres of cefditoren pivoxil**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>% Yield*</th>
<th>Particle size** (μm)</th>
<th>Entrapment efficiency*</th>
<th>% Buoyancy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>58.2±1.7</td>
<td>53.2±1.8</td>
<td>68.3±1.3</td>
<td>88±2.1</td>
</tr>
<tr>
<td>F2</td>
<td>63.6±1.55</td>
<td>59.8±2.2</td>
<td>63.4±1.2</td>
<td>90±1.5</td>
</tr>
<tr>
<td>F3</td>
<td>65.5±1.82</td>
<td>69.1±2.5</td>
<td>59±0.9</td>
<td>91.2±1.9</td>
</tr>
<tr>
<td>F4</td>
<td>61±1.2</td>
<td>66.5±1.77</td>
<td>76±1.3</td>
<td>85.7±2.48</td>
</tr>
<tr>
<td>F5</td>
<td>67.2±1.62</td>
<td>71.8±0.94</td>
<td>73±1.1</td>
<td>90±2.23</td>
</tr>
<tr>
<td>F6</td>
<td>70±1.09</td>
<td>79.8±1.1</td>
<td>75±0.85</td>
<td>92±1.88</td>
</tr>
<tr>
<td>F7</td>
<td>66.7±1.23</td>
<td>63.8±1.92</td>
<td>80±1.6</td>
<td>85±1.42</td>
</tr>
<tr>
<td>F8</td>
<td>71.3±1.3</td>
<td>82.4±1.2</td>
<td>77.2±2.3</td>
<td>78.6±2.7</td>
</tr>
<tr>
<td>F9</td>
<td>72.1±1.46</td>
<td>83.7±1.6</td>
<td>72±1.5</td>
<td>76±2.31</td>
</tr>
</tbody>
</table>

*All values represent mean±SD; n=3, **All values represent mean±SD; n=100. SD: Standard deviation

**Particle size measurement**

The particle size was measured using calibrated optical microscope, and the average particle size of floating microspheres was found to be in the range of 50-85 μm as shown in Table 3. As the concentration of polymer increases, the particle size also increases. This is because of the viscosity of the polymers used in the formulation. The higher the concentration of the polymer solution, the lower is the stirring efficiency. Due to this nature, the polymer rapidly precipitates and leads to hardening which in turn avoids further reduction in the particle size during solvent evaporation.

**EE**

The EE of floating microspheres of CP was calculated, and the results are depicted in Table 3. The EE was high at lower concentrations of the water-insoluble polymer ethyl cellulose. The EE was found to be in the range of 60-80% for all the formulations.

**In vitro buoyancy**

The percentage buoyancy was calculated for all the formulations and it was found that all the formulations were able to float on the dissolution medium (0.1 N HCl) over a period of 12-h. Even after 12 h of agitation of the dissolution medium, the microspheres continued to float without any apparent gelation. The high buoyancy of the microspheres is mainly due to the presence of pores and cavities which were formed during solvent evaporation. The percentage buoyancy was slightly decreased as the concentration of the polymers increased. This is because of the high viscosity of the polymer solution which in turn is the reason for the less formation of pores and cavities in microspheres during solvent evaporation. The results of in vitro buoyancy studies are shown in Table 3.

**In vitro drug release study**

Dissolution studies of all the nine formulations were carried out using USP dissolution apparatus type II (paddle).
The dissolution profiles were compared among different formulations. The results obtained in the *in vitro* drug release studies were plotted in five models of data treatment as follows:[24]

- The amount of drug remained to be released versus time (h) – Zero order kinetics.
- Log amount of drug remained to be released versus time (h) – First order kinetics
- Higuchi’s classical equation (Higuchi’s matrix) in which cumulative amount of drug release was plotted against square root time.
- Hixson-Crowell equation, in which cube root of cumulative percentage drug retained was plotted against time (h).
- Korsmeyer–Peppas model, in which a graph was plotted by taking log time on X axis and log Mt/M (log fraction dissolved) on Y axis and it gives a straight line.

The cumulative percentage drug release was decreased with increase in the polymer concentration. Based on the results of in vitro drug release studies, it was found that F6 has shown sustained drug release for 12 h. The results of the in vitro drug release studies are shown in Table 4 and the dissolution profile in Figure 1. The in vitro release kinetics revealed that the optimized formulation (F6) release the drug in first order manner with non-Fickian diffusion mechanism based on the regression values of first order, Higuchi and Korsmeyer–Peppas model, respectively. Observed $R^2$ values, $n$ values and the relative plots of the optimized formulation are shown in Table 5.

### Experimental design

Floating microspheres of CP were successfully fabricated by solvent evaporation technique. 3 level 2 factor experimental design was applied to know the effect of formulation variables on prepared floating microspheres of CP. In the present investigation, the effect of total amount of polymer and the concentration of ethyl cellulose on % yield, particle size, EE and DE revealed wide variation as shown in Table 6. The data clearly indicates that the dependent variables are dependent on the independent variables. The fitted equation relating the response % yield, particle size, % EE and DE to the transformed factor are shown in the equations 2, 3, 4, and 5, respectively. The value of correlation coefficient indicates a good fit as shown in Table 7. The polynomial equation can be used to draw a conclusion after considering the magnitude of the coefficient and the mathematical sign it carries (+/−). To demonstrate the effect of the independent variables on the prepared floating microspheres, the response surface plots and contour plots were generated for the dependent variables using Design-Expert® 9 trial version software (Stat-Ease Inc., USA).

### Effect of formulation variables on the dependent variables

#### Effect of formulation variables on % yield

The results of multiple linear regression analysis reveal that, on increasing the total amount of polymer ($X_1$), concentration of ethyl cellulose ($X_2$), an increase in the percentage yield was observed. In the equation $b_1$ and $b_2$ bears positive sign that

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**Table 4: In vitro drug release profile of floating microspheres of cefditoren pivoxil**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Cumulative percentage of drug release*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>F1</td>
<td>53.6±1.56</td>
</tr>
<tr>
<td>F2</td>
<td>46.9±2.21</td>
</tr>
<tr>
<td>F3</td>
<td>42.7±1.27</td>
</tr>
<tr>
<td>F4</td>
<td>32±1.86</td>
</tr>
<tr>
<td>F5</td>
<td>36.7±1.34</td>
</tr>
<tr>
<td>F6</td>
<td>34.2±1.5</td>
</tr>
<tr>
<td>F7</td>
<td>38.3±2.18</td>
</tr>
<tr>
<td>F8</td>
<td>29.7±1.23</td>
</tr>
<tr>
<td>F9</td>
<td>32.1±0.44</td>
</tr>
</tbody>
</table>

*All values represent mean±SD; (n=3). SD: Standard deviation
Table 5: Drug release kinetics of cefditoren pivoxil floating microspheres

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Zero order release ($R^2$)</th>
<th>First order release ($R^2$)</th>
<th>Higuchi ($R^2$)</th>
<th>Hixson-Crowell ($R^2$)</th>
<th>Korsmeyer–Peppas (n value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.517</td>
<td>0.342</td>
<td>0.759</td>
<td>0.449</td>
<td>0.205</td>
</tr>
<tr>
<td>F2</td>
<td>0.660</td>
<td>0.626</td>
<td>0.863</td>
<td>0.676</td>
<td>0.265</td>
</tr>
<tr>
<td>F3</td>
<td>0.738</td>
<td>0.734</td>
<td>0.915</td>
<td>0.649</td>
<td>0.310</td>
</tr>
<tr>
<td>F4</td>
<td>0.741</td>
<td>0.774</td>
<td>0.921</td>
<td>0.802</td>
<td>0.413</td>
</tr>
<tr>
<td>F5</td>
<td>0.770</td>
<td>0.851</td>
<td>0.945</td>
<td>0.858</td>
<td>0.356</td>
</tr>
<tr>
<td>F6</td>
<td>0.888</td>
<td>0.986</td>
<td>0.992</td>
<td>0.978</td>
<td>0.469</td>
</tr>
<tr>
<td>F7</td>
<td>0.804</td>
<td>0.945</td>
<td>0.981</td>
<td>0.913</td>
<td>0.356</td>
</tr>
<tr>
<td>F8</td>
<td>0.853</td>
<td>0.959</td>
<td>0.965</td>
<td>0.934</td>
<td>0.360</td>
</tr>
<tr>
<td>F9</td>
<td>0.807</td>
<td>0.907</td>
<td>0.956</td>
<td>0.880</td>
<td>0.323</td>
</tr>
</tbody>
</table>

Table 6: Observed responses from 3<sup>2</sup> factorial design

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Independent variables</th>
<th>Dependent variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$X_1$</td>
<td>$X_2$</td>
</tr>
<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>
<td>1</td>
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<tr>
<td>F4</td>
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<td>–1</td>
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<td>F5</td>
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<td>1</td>
<td>–1</td>
</tr>
<tr>
<td>F8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>F9</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

$X_1=$Total amount of polymer; $X_2=$Concentration of ethyl cellulose; $Y_1=$% yield; $Y_2=$Particle size; $Y_3=$% Entrapment efficiency; $Y_4=$Dissolution efficiency

Effect of formulation variables on EE

The results of multiple linear regression analysis reveal that, on increasing the total amount of polymer ($X_1$), an increase in the EE ($Y_4$) was observed. In the equation, $b_1$ bears positive sign that indicates when increasing the amount of polymer there is an increase in the EE. In the equation, $b_2$ bears negative sign that indicates when increasing the amount of polymer and polymer blend ratio there is an increase in the particle size observed and is pictorially represented by the response surface plots (A) and contour plots (B) in Figure 2. This suggests that as the concentration of polymer increases there is an increase in the viscosity which will play a major role in preventing the loss of hydrophilic polymers into the processing medium (PVA).

$$Y_2 = 74.03 + 7.99X_1 + 8.20X_2 + 1.00X_3 - 4.00X_4 - 1.98X_5X_6$$

Effect of formulation variables on DE

The results of multiple linear regression analysis reveal that, on increasing the total amount of polymer and the concentration of ethyl cellulose, a decrease in the DE was found. In the equation, $b_1$ and $b_2$ bears negative sign that indicates when increasing the amount of polymer ($X_1$) and increasing the concentration of ethyl cellulose ($X_2$) decrease in the DE was found and is pictorially represented by the response surface plots (A) and contour plots (B) in Figure 5.

$$Y_3 = 75.06 + 6.47X_1 - 3.38X_2 + 0.32X_3 - 4.63X_4 - 0.58X_5X_6$$

Effect of formulation variables on particle size

The results of multiple linear regression analysis reveal that, on increasing the total amount of polymer ($X_1$), concentration of ethyl cellulose ($X_2$), an increase in the particle size was observed. In the equation, $b_1$ and $b_2$ bears positive sign that indicates when increasing the amount of polymer and polymer blend ratio there is an increase in the particle size was observed and is pictorially represented by the response surface plots (A) and contour plots (B) in Figure 3.

$$Y_1 = 67.25 + 3.81X_1 - 3.61X_2 - 0.49X_3 + 0.18X_4 - 1.77X_5X_6$$

Morphological studies

The surface morphology of the floating microspheres was studied using SEM. The surface morphology of optimized formulation (F6) was studied; it was revealed that the microspheres were spherical in shape with a rough surface and porous in nature as shown in Figure 6.
Table 7: Regression coefficients for the responses

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Coefficients of regression parameters</th>
<th>( b_0 )</th>
<th>( b_1 )</th>
<th>( b_2 )</th>
<th>( b_{12} )</th>
<th>( b_{11} )</th>
<th>( b_{22} )</th>
<th>( R^2 ) value</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Yield</td>
<td></td>
<td>+67.25</td>
<td>+3.81</td>
<td>+3.61</td>
<td>−0.49</td>
<td>+0.18</td>
<td>−1.77</td>
<td>0.9863</td>
<td>0.0054</td>
</tr>
<tr>
<td>Particle size</td>
<td></td>
<td>+74.03</td>
<td>+7.99</td>
<td>+8.20</td>
<td>+1.00</td>
<td>−4.00</td>
<td>−1.98</td>
<td>0.9414</td>
<td>0.0456</td>
</tr>
<tr>
<td>% Entrapment efficiency</td>
<td></td>
<td>+75.06</td>
<td>+6.47</td>
<td>−3.38</td>
<td>+0.32</td>
<td>−4.63</td>
<td>−0.58</td>
<td>0.9689</td>
<td>0.0181</td>
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<tr>
<td>Dissolution efficiency</td>
<td></td>
<td>+57.1</td>
<td>−6.55</td>
<td>−4.68</td>
<td>−1.50</td>
<td>−4.22</td>
<td>+2.68</td>
<td>0.9732</td>
<td>0.0146</td>
</tr>
</tbody>
</table>

Figure 2: Response surface plots (A) and contour plots (B) showing effect of the total amount of polymer (X1) and concentration of ethyl cellulose (X2) on % yield (Y1)

Figure 3: Response surface plots (A) and contour plots (B) showing effect of the total amount of polymer (X1) and concentration of ethyl cellulose (X2) on particle size (Y2)

Figure 4: Response surface plots (A) and contour plots (B) showing effect of the total amount of polymer (X1) and concentration of ethyl cellulose (X2) on % entrapment efficiency (Y3)

Figure 5: Response surface plots (A) and contour plots (B) showing effect of the total amount of polymer (X1) and concentration of ethyl cellulose (X2) on dissolution efficiency (Y4)
CONCLUSION

Floating microspheres of CP were successfully prepared by solvent evaporation method using different ratios of HPMC K4M and ethyl cellulose as rate controlling polymers, by applying $3^2$ factorial design. The prepared formulations were further evaluated and based on the results of in vitro evaluation studies F6 was chosen as the best formulation. To determine the effect of independent variables, response surface plots and contour plots were plotted, and the results of multiple linear regression analysis revealed that as the concentration of total amount of polymer and concentration of ethyl cellulose is increased, % yield, particle size and EE were increased and DE was decreased. The release kinetics revealed that the drug release from the floating microspheres of CP followed first order non-Fickian diffusion. Hence, the objective of the current research work has been achieved.

ACKNOWLEDGMENTS

The satisfaction that accomplished the successful completion of any task would be incomplete without the mention of the people who made it possible and whose constant guidance and encouragement crown all the effects with success. We would like to acknowledge Cadila Pharmaceuticals Limited, Ahmedabad for providing the gift sample of CP. We are grateful to Colorcon Pvt Ltd., for providing the gift sample of HPMC K4M, Ethyl Cellulose used in the study. We would also like to acknowledge the support of management of Janagao Institute of Pharmaceutical Sciences for providing the required facilities for successful completion of the project.

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Source of Support: Nil. Conflict of Interest: None declared.