Formulation and evaluation of Gastro retentive floating tablets of Cefixime

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Abstract
In the present research work, floating gastro retentive tablets of Cefixime were prepared to prolong the release of Cefixime. Floating tablets of Cefixime were prepared by employing lipid excipient Glyceryl benenate along with HPMC K 15M, Xanthan gum. The floating approach was achieved by the use of Sodium bicarbonate and citric acid system. The floating tablets were evaluated for physico-chemical characteristics, pre compression and post- compression parameters. FTIR studies of the pure drug, its physical mixture with polymer blend showed that no polymorphic changes occurred during manufacturing of tablets. The prepared tablets exhibited satisfactory physico-chemical characteristics and in vitro buoyancy. In vitro drug release data were fitted into zero order, first order, Higuchi’s model, Korsmeyer-Peppas and Hixon Crowell’s kinetic models. Increase in the HPMC K15M level was found to increase the floating time of the tablets. Optimized tablet formulation exhibited no significant change in physical appearance, drug content, total buoyancy time, or in vitro dissolution pattern after storage at 40°C/75% relative humidity for 3 months.

Key words: Cefixime, floating tablets, Glyceryl benenate, HPMC, Xanthan gum

Introduction
Cefixime is a third generation cephalosporin antibiotic having bactericidal activity and used in the treatment of uncomplicated UTI, otitis media, pharyngitis, acute bronchitis and acute exacerbation of chronic bronchitis, uncomplicated gonorrhea. Cefixime having pKa value of 2.5 is a weak acid which will remain unionized at acidic pH thus increases absorption in the stomach region. It is primarily absorbed from the stomach and upper part of intestine. In view of this absorption characteristic, the hypothesis of current investigation is that if the gastric residence time of Cefixime containing formulation is prolonged and allowed to float in the stomach for a long period, the oral bioavailability might be increased [1, 2]. Hence an attempt has been made for developing floating tablets of Cefixime using HPMC K15M, Glycerylbenenate and Xanthan gum. Gastro retentive systems can remain
in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment of small intestine [3]. The floating drug delivery system have a density less than gastric fluid and hence remain buoyant in the stomach without effecting gastric emptying rate for a prolonged period of time. These dosage forms increases gastric residence time and reduces fluctuations in plasma drug concentration [4].

Materials and Methods

Materials
Cefixime was obtained as a gift sample from Richar Pharmaceuticals, Hyderabad, India. Glycerylbenhenate, HPMC K 15M, Xanthan gum, Sodium bi carbonate, Citric acid, Micro Crystalline Cellulose and Magnesium stearate were procured from SD Fine chemicals, Mumbai, India. Double distilled water was used whenever necessary. All the reagents used were of AR grade. The drug samples were characterized by means of UV spectrophotometric method along with determination of solubility and pH for their authentication.

Preparation of Floating Tablets
Drug and excipients were passed through 40 # mesh separately and then transfer the Glyceryl benhenate into china dish and melt it and then add the drug and cool to room temperature. Molten mass is crushed in a mortar and pestle for getting uniform size particles. Add other polymers and transfer to polybag and mixed for 3 min. Add diluents and other excipients to the above mixture. Finally add the Glidant (Magnesium Stearate) to the above blend mix it for 2min. Compressed the above lubricated blend by using 10 mm round punches [5-8]. The detailed composition of each formulation was showed in Table 1.

Table 1. Composition of Cefixime Floating Tablets

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
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<tbody>
<tr>
<td>Cefixime</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
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<tr>
<td>Glycerylbenhenate</td>
<td>100</td>
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<td>-</td>
<td>-</td>
<td>200</td>
<td>200</td>
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<tr>
<td>HPMC K 15M</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>200</td>
<td>-</td>
<td>50</td>
<td>-</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>200</td>
<td>50</td>
<td>-</td>
<td>100</td>
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<tr>
<td>Sodium bi carbonate</td>
<td>40</td>
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<td>40</td>
<td>40</td>
<td>40</td>
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<td>Citric acid</td>
<td>5</td>
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<tr>
<td>Magnesium stearate</td>
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<td>600</td>
<td>600</td>
<td>600</td>
<td>600</td>
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Evaluation
Compatibility studies
Fourier Transform Infrared Spectroscopic (FTIR) analysis
The FTIR spectrums of Cefixime and Formulation (F6) blend were studied by using Fourier Transform Infrared (FTIR) spectrophotometer (Perkin Elmer, spectrum-100, Japan) using the KBr disk method (5.2012 mg sample in 300.0151 mg KBr). The scanning range was 500 to 4000 cm\(^{-1}\) and the resolution was 1 cm\(^{-1}\). This spectral analysis was employed to check the compatibility of drugs with the polymers used.

Pre-compression parameters
Angle of repose
Angle of repose was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height (h), was obtained. Diameter of heap, (D), was measured. The angle of repose (\(\Theta\)) was calculated by the following equations [9-11],

\[ \Theta = \tan^{-1} \left( \frac{h}{r} \right) \]

Where, \(\Theta\) is the angle of repose, \(h\) is the height in cm and \(r\) is the radius.

Bulk Density
Apparent bulk density was determined by pouring pre sieved drug excipient blend into a graduated cylinder and measuring the volume and weight “as it is”. It is expressed in g/ml and is given by the following equation [9-11].
\[
\text{Db} = \frac{M}{V_0}
\]

Where,
- \( M \) is the mass of powder and \( V_0 \) is the Bulk volume of the powder

**Tapped density**

It was determined by placing a graduated cylinder, containing a known mass of drug-excipient blend, on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by the following equation [9-11].

\[
\text{Dt} = \frac{M}{V_t}
\]

Where,
- \( M \) is the mass of powder and \( V_t \) is the tapped volume of the powder.

**Carr’s Index (I_C):** It is expressed in percentage and is expressed by the following equation [9-11].

\[
I_C = \frac{\text{Dt} - \text{Db}}{\text{Dt}}
\]

Where,
- \( \text{Dt} \) is the tapped density of the powder and \( \text{Db} \) is the bulk density of the powder.

**Hausner’s ratio (H_R)**

It is expressed in percentage and is expressed by the following equation [9-11].

\[
H_R = \frac{\text{Dt}}{\text{Db}}
\]

Where,
- \( \text{Dt} \) is the tapped density of the powder and \( \text{Db} \) is the bulk density of the powder.

**Evaluation of Tablets**

**Post compression parameters**

The prepared floating tablets were evaluated for uniformity of weight using 20 tablets, hardness (Pfizer tester) and friability using 10 tablets (Roche type friabilator). Each test was evaluated for 5 times to get accurate and precise values [12].

**In vitro buoyancy studies**

The formulated tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid of pH 1.2. The time taken for the tablet to rise to the surface and float was taken as floating lag time. The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time [13-17].

**Drug Content Estimation**

10 tablets were weighed and pulverized to a fine powder, and a quantity of powder Equivalent to 100 mg of Cefixime was dissolved in 100 ml of methanol and the liquid was filtered using whatman filler paper and diluted up to 50µg/ml. The Cefixime content was determined by measuring the absorbance at 288 nm using UV spectrophotometer (UV-1601, Shimadzu, Japan), after appropriate dilution with methanol.

**In-vitro drug release studies:**

The drug release from the Cefixime tablets was investigated in a USP-II (paddle) apparatus, 900 ml of 0.1N HCl (50 rpm, 37±0.5°C). At predetermined time intervals, 5-ml samples were withdrawn and take 1ml sample and diluted to 10 ml and then analyzed with UV spectrophotometry at \( \lambda \) max of 288nm.

**In vitro drug release kinetic studies**

The exact mechanism by which Cefixime releasing from dosage form was determined by analyzing the data to various kinetic models viz., zero order, first order, Korsmeyer- Peppas, Higuchi and square root models [18-21]. The data were processed for regression analysis using MS EXCEL-2013 statistical function.

**Accelerated Stability studies**

The promising formulation (F6) was tested for a period of 3 months at different temperature of 40°C with 75% RH, for their drug content [22].

**Results and Discussion**

**Drug excipients compatibility studies**

**Fourier transform infra-red (FTIR) studies**

FTIR spectrum (Fig.1) of Cefixime (in KBr) displays a characteristic –NH\(_2\) absorption peak at 3544.32 cm\(^{-1}\), which is a normal range of absorption of primary amines. It exhibits a strong band for C=O stretching of the non-conjugated carboxylic acid at 1764.75 cm\(^{-1}\) whereas the second band which is expected to shift to lower frequency (owing to conjugation) appears as a overlapping band. The carbonyl of cyclic as well as acyclic amide appears at.
1664.45 cm\(^{-1}\). FTIR spectrum of formulation (Fig. 2) does not show any appreciable change in the position of assigned bands. It can be inferred that drug and the polymer do not exhibit significant chemical interaction and therefore, are compatible with each other.

**Pre compression parameters:**
The angles of repose (\(\theta\)) for the blend of various formulations F1 to F9 was ranged from 21.81±0.41 to 29.39±0.36, indicating that the studied blends have excellent flow property. The values of loose bulk density and tapped bulk densities were required to calculate Compressibility Index and Hausner’s ratio. The Carr’s Index was ranged from 4.76±0.21 to 26.19±0.02 and Hausner’s ratio was ranged from 1.04±0.01 to 1.15±0.01, which indicates the good flow ability of the powder formulation. The results of the flow properties were shown in Table 2.

**Post compression parameters**
The weight of the tablet varied between 0.59±0.004 to 0.60±0.004 g. The variation in weight was within the range and complying with pharmacopoeial specifications. The thickness of tablets was ranged from 5.3±0.4 to 5.6±0.4 mm. The hardness for different formulations was found to be between 6.9±0.9 to 8.9±1.4 kg/cm\(^2\). The friability was
ranged from 0.21±0.4 to 0.26±0.23 %, indicates the formulated tablets have good mechanical strength. The drug content was ranged from 99.68±0.2 to 99.91±0.2 %. The buoyancy floating time was ranged from 34±1.5 to 51±1.5 sec (Fig.3). All these values were represented in Table 3. The drug release from floating tablets was shown in Fig.4. This dissolution was treated with kinetic modeling viz., First order, Korsmeyer-Peppas, Higuchi and Hixon Crowell’s modeling. The graphs were represented in Fig 5 to 8. The optimized formulation was subjected to accelerated stability studies as per ICH guidelines. The formulated tablets did not show any changes in all the characters before and after stability studies and these values were represented in table 4 and fig.9.

Table 2. Pre compression parameters of formulation blends

<table>
<thead>
<tr>
<th>Parameter</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle of repose</td>
<td>27.55±0. 52</td>
<td>29.39±0. 36</td>
<td>23.31±0. 16</td>
<td>28.81±0. 55</td>
<td>28.65±0. 54</td>
<td>26.74±0. 65</td>
<td>28.39±0. 65</td>
<td>21.81±0. 41</td>
<td>24.81±0. 25</td>
</tr>
<tr>
<td>Carr’s Index</td>
<td>4.76±0.2 01</td>
<td>14.54±0. 01</td>
<td>5.88±0.0 5</td>
<td>10.63±0. 01</td>
<td>6.66±0.0 2</td>
<td>10.52±0. 01</td>
<td>10.86±0. 01</td>
<td>26.19±0. 02</td>
<td>13.11±0. 01</td>
</tr>
<tr>
<td>Hausner’s ratio</td>
<td>1.04±0.0 1</td>
<td>1.14±0.0 1</td>
<td>1.05±0.0 0 1</td>
<td>1.10±0.0 0 1</td>
<td>1.06±0.0 0 1</td>
<td>1.10±0.0 0 1</td>
<td>1.15±0.0 0 1</td>
<td>1.13±0.0 1</td>
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</table>

Table 3. Post compression parameters of formulations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight variation</td>
<td>0.60±0.0 04</td>
<td>0.59±0.0 05</td>
<td>0.59±0.0 04</td>
<td>0.60±0.0 05</td>
<td>0.60±0.0 04</td>
<td>0.59±0.0 04</td>
<td>0.59±0.0 04</td>
<td>0.60±0.0 04</td>
<td>0.60±0.0 04</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>5.5±0.4</td>
<td>5.6±0.4</td>
<td>5.3±0.4</td>
<td>5.6±0.4</td>
<td>5.5±0.4</td>
<td>5.5±0.3</td>
<td>5.5±0.4</td>
<td>5.5±0.1</td>
<td>5.5±0.2</td>
</tr>
<tr>
<td>Hardness (kg/cm²)</td>
<td>8.9±1.4</td>
<td>7.4±1.2</td>
<td>8.2±1.2</td>
<td>6.9±0.9</td>
<td>8.4±1.9</td>
<td>8.1±0.7</td>
<td>8.2±1.5</td>
<td>8.3±1.6</td>
<td>8.2±1.4</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.22±0.2 3</td>
<td>0.26±0.2 3</td>
<td>0.25±0.1 9</td>
<td>0.25±0.2 6</td>
<td>0.25±0.2 2</td>
<td>0.22±0.0 1</td>
<td>0.21±0.4</td>
<td>0.21±0.5</td>
<td>0.21±0.7</td>
</tr>
<tr>
<td>Assay (%)</td>
<td>99.91±0. 2</td>
<td>99.84±0. 4</td>
<td>99.87±0. 3</td>
<td>98.88±0. 2</td>
<td>99.88±0. 3</td>
<td>99.89±0. 2</td>
<td>99.88±0. 2</td>
<td>99.68±0. 2</td>
<td>99.88±0. 2</td>
</tr>
<tr>
<td>Floating lag time (sec)</td>
<td>41±1.5</td>
<td>42±1.0</td>
<td>43±1.5</td>
<td>51±1.5</td>
<td>42±1.5</td>
<td>34±1.5</td>
<td>36±2.0</td>
<td>39±1.5</td>
<td>41±2.0</td>
</tr>
</tbody>
</table>

All values mentioned as mean ±S.D; Number of trials (n)=5

Fig.3. Buoyancy floating of formulated floating tablets
Fig. 4. Zero Order Plot for Optimized Formulation (F6)

Zero Order Plot

\[ y = -0.124x + 2.156 \]

\[ R^2 = 0.891 \]

Fig. 5. First Order Plot for Optimized Formulation (F6)

First Order Plot

\[ \log \% \text{ Drug Retained} = -0.124x + 2.156 \]

\[ R^2 = 0.933 \]

Fig. 6. Higuchi Plot for Optimized Formulation (F6)

Higuchi Plot

\[ y = 24.16x - 0.139 \]

\[ R^2 = 0.933 \]
Table 4. Results of stability studies of optimized formulation (F6)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Parameters</th>
<th>Initial</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Month</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Month</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; Month</th>
<th>Limits as per Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>F6</td>
<td>25°C/60%RH % Release</td>
<td>99.85</td>
<td>99.84</td>
<td>99.84</td>
<td>99.83</td>
<td>Not less than 85 %</td>
</tr>
<tr>
<td></td>
<td>30°C/75% RH % Release</td>
<td>99.85</td>
<td>99.84</td>
<td>99.84</td>
<td>99.83</td>
<td>Not less than 85 %</td>
</tr>
<tr>
<td></td>
<td>40°C/75% RH % Release</td>
<td>99.85</td>
<td>99.84</td>
<td>99.84</td>
<td>99.83</td>
<td>Not less than 85 %</td>
</tr>
<tr>
<td></td>
<td>25°C/60% RH Assay Value</td>
<td>99.91</td>
<td>99.89</td>
<td>99.89</td>
<td>99.89</td>
<td>Not less than 90 %</td>
</tr>
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<td>99.89</td>
<td>99.89</td>
<td>Not less than 90 %</td>
</tr>
<tr>
<td></td>
<td>40°C/75% RH Assay Value</td>
<td>99.92</td>
<td>99.89</td>
<td>99.89</td>
<td>99.89</td>
<td>Not less than 90 %</td>
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</table>
The effervescent based floating drug delivery was a promising approach to achieve buoyancy. The addition of lipophilic ingredient (Glycerylbenhenate), gel forming polymer Hydroxy Propyl Methyl Cellulose (K15M) and gas generating agent sodium bicarbonate along with citric acid was essential to achieve buoyancy. By this technique Cefixime floating tablets can be made.

References

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