Enhancement of bioavailability and gastric residence time of cephalexin by hydrodynamically balanced system

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Abstract
Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation etc. From immediate release to site specific delivery, oral dosage forms have really progressed. More than 50% of the drug delivery systems available are to be administered through oral route. During the last decade, many studies have been performed concerning the sustained release dosage forms of the drug, which have aimed at the prolongation of gastric emptying time (GET). Oral sustained release gastro retentive dosage forms (GRDFs) offer many advantages for those acting locally in the stomach, improving the bioavailability of the medication. Floating Drug Delivery System is one amongst the GRDFs used to achieve prolonged gastric retention time. Cephalexin is in a group of antibiotics and is used to fight against gram positive infections in the body. In this present study to enhance the gastric retention of the Cephalexin, it is formulated as effervescent floating dosage form by direct compression method. The polymers like HPMC K4M, HPMC K15M, HPMC K100M and Sodium bicarbonate are used. From the results of dissolution profile it was conformed that the antimicrobial action of Cephalexin may be increased in the stomach due to increase retention time and absorption by using HPMC K100M (F9 formulation) than other formulations. Drug release of F9 was found to follow first order kinetic model and the mechanism of the drug release was found to be diffusion controlled process.

Key-Words: Cephalexin, Gastric Emptying Time (GET), Floating Drug Delivery System, HPMC K4M, HPMC K15M, HPMC K100M, First order

Introduction
Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation etc. From immediate release to site specific delivery, oral dosage forms have really progressed. More than 50% of the drug delivery systems available are to be administered through oral route. In oral delivery conventional oral dosage forms offer no control over drug delivery, leading to fluctuations in plasma drug level. And oral sustained drug delivery formulations show some limitations connected with the gastric emptying time. Variable and too rapid gastrointestinal transit could result in incomplete drug release from the device into the absorption window leading to diminished efficacy of the administered dose. It is evident from the recent research and patent literature that an increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time exists today.*

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During the last decade, many studies have been performed concerning the sustained release dosage forms of the drug, which have aimed at the prolongation of gastric emptying time (GET): swelling and expanding systems, alter dosage forms, low density or floating drug delivery systems, bioadhesive systems, high density non-floating drug delivery systems, modified shaped systems. Floating drug delivery system is also called as hydrodynamically balanced system. Depending on the mechanism of buoyancy, two distinctly different methods i.e. effervescent and non-effervescent system have been used in the development of floating drug delivery system. Cephalexin is in a group of drugs called cephalosporin antibiotics and is used to fight bacteria in the body. It works by interfering with the bacteria’s cell wall formation, causing it to rupture, and killing the bacteria. It’s have good absorption in GIT, low pKa, which remained unionized in the stomach for better absorption and it’s have half life 0.5-1-2 hours. Cephalexin is used to treat infections caused by bacteria, including upper respiratory infections, ear...
infections, skin infections, and urinary tract infections.\textsuperscript{9,10,11}

The aim of the present study was not only preparing a cephalixin floating system but also to release the drug in the controller manner, therefore the maximum drug release is maintained at desired site. The effect of different polymers and the effect of amount of polymers was investigated in the formulation to monitor the sustained release effect respectively.

### Material and Methods

#### Materials

Cephalexin was obtained as gift sample from orchid chemicals & pharmaceutics ltd., Chennai. HPMC all grades and other excipients are obtained from yarrow chem. Products.

#### Method of preparation

**Preparation of floating tablets of Cephalexin**\textsuperscript{12,13,14}

Floating effervescent tablets of cephalexin were prepared by direct compression method. The powder mixture contains drug, controlled release polymers as for the formulae and MCC was used as the diluent, sodium bicarbonate added as effervescent agent. The blend was lubricated with magnesium stearate for 3-5 mins and talc was added as glidant. Then the mixed blend was then compressed into tablets by direct compression method using 12.5 mm punches on a ten station rotary tablet punching machine.

#### Formulation Method\textsuperscript{15,16}

The composition of different formulations of cephalexin floating tablets is shown in the table no.1. Different tablet formulations were prepared by direct compression method. All the powders passed through 40/60 mesh sieve. The required quantity of drug, various polymers and other ingredients were mixed thoroughly. Talc and magnesium stearate were finally added as a glidant and lubricant respectively. The blend was compressed into tablets by direct compression method using 12 mm diameter punches on a 10 station rotary tablet punching machine.

#### Characterization of Cephalexin\textsuperscript{7,16,15,16}

**Description**

The pure drug cephalexin was analyzed for colour, odour and taste.

**Melting point**

The melting point of drug was determined by open capillary method.

**Standard curve**

Standard curve of cephalexin was estimated by UV spectrophotometric method.

**Fourier Transform Infrared Spectroscopy (FTIR)**

FTIR studies were performed on drug, excipient and the optimized formulation using FTIR. The sample were analysed between wave numbers 4000 and 400 cm\(^{-1}\).

#### Evaluation\textsuperscript{9,10,17,18,19,20}

**Evaluation of granules**

**Angle of repose**

Angle of repose were determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (q) was calculated using the formula.

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

**Bulk density**

Apparent bulk density (p\textsubscript{b}) were determined by pouring the blend in to a graduated cylinder. The bulk volume (V\textsubscript{b}) and weight of the powder (M) was calculated using the formula.

\[
p_{b} = \frac{M}{V_{b}}
\]

**Tapped density**

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V\textsubscript{t}) occupied in the cylinder and the weight (M) of the blend were measured. The tapped density (p\textsubscript{t}) was calculated using formula.

\[
p_{t} = \frac{M}{V_{t}}
\]

**Compressibility index**

The simplest way for measuring of free flow of powder was compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I) was calculated as follows.

\[
I = \frac{V_0 - V_t}{V_0} \times 100
\]

Where, V\textsubscript{0} is the bulk volume and V\textsubscript{t} is tapped volume.

**Hausner’s ratio**

Hausner’s ratio was an indirect index of ease of powder flow. It was calculated by the following method

\[
Hausner ratio = \frac{\rho_{t}}{\rho_{d}}
\]

Where, \(\rho_{t}\) tapped density and \(\rho_{d}\) bulk density lower hausner ratio.

**Evaluation Of Tablets**

**Characterization of tablets for physiochemical parameters**

The prepared Cephalexin floating tablets were evaluated for their physicochemical parameters like weight variation, hardness, friability and drug content.

**In vitro floating lag time**

The in vitro buoyancy was determined by floating lag time. The tablets were placed in a 100 ml beaker containing 0.1N HCl. The media was kept in stagnant condition and the temperature was maintained at
The floating capacity of the tablets was determined using USP Dissolution apparatus II containing 900ml of simulated gastric fluid. The time interval between introduction of the tablet in to the dissolution medium and its buoyancy to the dissolution medium was taken as buoyancy lag time and for which time the tablet constantly floats on the surface of the medium was observed visually and taken as floating lag time.

**In vitro floating duration time**
The floating capacity of the tablets was determined using USP Dissolution apparatus II containing 900ml of simulated gastric fluid. The time interval between introduction of the tablet in to the dissolution medium and its buoyancy to the dissolution medium was taken as buoyancy lag time and for which time the tablet constantly floats on the surface of the medium was observed visually and taken as floating duration.

**In vitro drug release**
The release of Cephalexin from floating tablets was determined by using Dissolution type II test apparatus. The dissolution test was performed using 900 ml 0.1N HCl solution at 37 ± 0.5°C temperature and at 50 rpm. At specified time intervals, samples of 5 ml were withdrawn from the dissolution medium and that amount was replaced with fresh medium to maintain the volume constant. The samples were filtered and diluted to a suitable concentration with 0.1 N HCl. The absorbance value of the diluted sample was measured at 257nm for Cephalexin by using UV-Visible double beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from standard curve.

**Characterization of drug in Floating tablets**
FTIR studies were conducted for characterization of drug in tablets. The floating tablets were compressed and powdered. The pelletized powder along with KBr was used for FTIR studies. The IR spectra were recorded using Fourier Transform Infrared spectrophotometer. The IR spectra of pure Cephalexin and pelletized powder of tablets were taken, interpreted and compared with each other.

**Results and Discussion**
The sample of drug Cephalexin was off white or almost, white, crystalline powder and have characteristicodour. The melting point value was found to be 257 nm when scanned between 200 to 400 nm in 0.1 N HCl by the UV-Visible spectrophotometer. FTIR spectra revealed that there was no interaction between the drug and the polymers.

The Preformulation studies were performed and the results were shown in the following table 2. Bulk density was found in the range of 0.64-0.66 g/cm³ and the tapped density between 0.77-0.80 g/cm³. Using these two density data compressibility index was calculated. The compressibility index was found between 15.38 and 22.02 and the compressibility-flowability correlation data indicated a fairly good flowability of the blend. The good flowability of blend was also evidenced with angle of repose (range of 21.05° – 29.62°), which is below 40° indicating good flowability.

The mean thickness values were found in the range from 2.72±0.06 to 2.86±0.12 mm, the hardness of formulated tablets was found to be 4.52 to 5.80 kg/cm². The loss in friability was ranged from 0.28±0.06 to 0.41±0.03. These values were represented in Table 3. The disintegration time was ranged from 22.8 to 39.2 sec. All the formulations showed good floating buoyancy time i.e. >12 hrs so the formulations remained in the stomach for long time thus the bioavailability of the dosage form was increased.

The FTIR spectrum of formulated blend showed characteristic peaks of drug which indicated that the compatibility of the drug with the excipients used. The spectrum was shown in Figure 1. The release of Cephalexin from floating tablets was determined by using Dissolution type II test apparatus. And the dissolution profile was represented in the below figures 2-4.

From the results of % drug release of the tablet dosage form it was observed that all the formulations show a compatibility of the drug with the excipients used. Parameter such as % drug release and dissolution rate was compared to formulations with lower HPMC viscosity grades. By observing the dissolution profile of the formulation it can be concluded that the anti
microbial activity of the Cephalexin may be increased in the stomach due to increase in the retention time and absorption by using HPMC K100M than the other polymers. Drug release of F9 was found to follow first order kinetic model and the mechanism of the drug release was found to be diffusion controlled process.

References
7. Good man and Gilman’s The pharmacological basis of therapeutics. 11th edition. Medical publication division. 1095-154
9. URL: http://www.drugbank.com/generic/view

Table 1: Composition of 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>
</tr>
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<tbody>
<tr>
<td>Drug</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
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<td>250</td>
<td>250</td>
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<tr>
<td>HPMC K 4M</td>
<td>80</td>
<td>140</td>
<td>190</td>
<td>-</td>
<td>-</td>
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<td>HPMC K 15M</td>
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<td>-</td>
<td>80</td>
<td>140</td>
<td>190</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>HPMC K 100M</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>110</td>
<td>165</td>
<td>220</td>
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<td>NaHCO₃</td>
<td>55</td>
<td>55</td>
<td>55</td>
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<td>55</td>
<td>55</td>
<td>55</td>
<td>55</td>
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<td>MCC</td>
<td>140</td>
<td>80</td>
<td>30</td>
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<td>80</td>
<td>30</td>
<td>140</td>
<td>80</td>
<td>30</td>
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<tr>
<td>Talc</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Mg. stearate</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
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<tr>
<td>Total weight</td>
<td>550</td>
<td>550</td>
<td>550</td>
<td>550</td>
<td>550</td>
<td>550</td>
<td>550</td>
<td>550</td>
<td>550</td>
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</tbody>
</table>

Note: All ingredients are mentioned above table is in mg/tab

Table 2: Flow properties of Cephalexin powder blend:

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Angle of repose</th>
<th>Bulk density</th>
<th>Tapped density</th>
<th>Carr’s index</th>
<th>Hausner’s ratio</th>
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</thead>
<tbody>
<tr>
<td>F1</td>
<td>29.13 ± 0.04</td>
<td>0.64 ± 0.02</td>
<td>0.80±0.02</td>
<td>20.02 ±0.04</td>
<td>1.25 ± 0.02</td>
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<tr>
<td>F2</td>
<td>27.31 ± 0.03</td>
<td>0.65 ± 0.02</td>
<td>0.78±0.03</td>
<td>16.66 ±0.02</td>
<td>1.20 ± 0.01</td>
</tr>
<tr>
<td>F3</td>
<td>28.26 ± 0.01</td>
<td>0.64 ± 0.01</td>
<td>0.78±0.02</td>
<td>17.94 ±0.04</td>
<td>1.21 ± 0.04</td>
</tr>
<tr>
<td>F4</td>
<td>28.46 ± 0.02</td>
<td>0.65 ± 0.04</td>
<td>0.78±0.04</td>
<td>16.58 ±0.03</td>
<td>1.20 ± 0.02</td>
</tr>
<tr>
<td>F5</td>
<td>29.62 ± 0.04</td>
<td>0.65 ± 0.02</td>
<td>0.79±0.01</td>
<td>17.72 ±0.01</td>
<td>1.21 ± 0.05</td>
</tr>
<tr>
<td>F6</td>
<td>28.14 ± 0.03</td>
<td>0.66 ± 0.03</td>
<td>0.78±0.01</td>
<td>15.38 ±0.02</td>
<td>1.18 ± 0.01</td>
</tr>
<tr>
<td>F7</td>
<td>28.22 ± 0.03</td>
<td>0.65 ± 0.01</td>
<td>0.77±0.04</td>
<td>15.58 ±0.01</td>
<td>1.18 ± 0.04</td>
</tr>
<tr>
<td>F8</td>
<td>27.15 ± 0.02</td>
<td>0.64 ± 0.04</td>
<td>0.78±0.01</td>
<td>17.64 ±0.04</td>
<td>1.21 ± 0.08</td>
</tr>
<tr>
<td>F9</td>
<td>27.18 ± 0.01</td>
<td>0.64 ± 0.03</td>
<td>0.77±0.02</td>
<td>17.56 ±0.02</td>
<td>1.20 ± 0.03</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± SD, n=3
### Table 3: Evaluation of physical parameters of Cephalexin floating tablets

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Thickness (mm)</th>
<th>Hardness (kg/cm²)</th>
<th>Average weight (mg)</th>
<th>Friability (%)</th>
<th>Drug content (%)</th>
<th>Floating lag time (sec)</th>
<th>Total floating time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>2.86 ± 0.12</td>
<td>4.52</td>
<td>552</td>
<td>0.41 ± 0.05</td>
<td>99.81 ± 1.4</td>
<td>18</td>
<td>&gt; 24</td>
</tr>
<tr>
<td>F2</td>
<td>2.82 ± 0.16</td>
<td>5.20</td>
<td>550</td>
<td>0.31 ± 0.08</td>
<td>99.67 ± 1.7</td>
<td>13</td>
<td>&gt; 24</td>
</tr>
<tr>
<td>F3</td>
<td>2.85 ± 0.14</td>
<td>4.55</td>
<td>549</td>
<td>0.36 ± 0.03</td>
<td>98.75 ± 0.5</td>
<td>20</td>
<td>&gt; 24</td>
</tr>
<tr>
<td>F4</td>
<td>2.81 ± 0.08</td>
<td>4.95</td>
<td>553</td>
<td>0.37 ± 0.01</td>
<td>99.47 ± 1.3</td>
<td>21</td>
<td>&gt; 24</td>
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<tr>
<td>F5</td>
<td>2.79 ± 0.12</td>
<td>5.25</td>
<td>554</td>
<td>0.36 ± 0.08</td>
<td>100.07 ± 0.4</td>
<td>24</td>
<td>&gt; 24</td>
</tr>
<tr>
<td>F6</td>
<td>2.79 ± 0.10</td>
<td>5.30</td>
<td>551</td>
<td>0.28 ± 0.06</td>
<td>100.38 ± 0.6</td>
<td>17</td>
<td>&gt; 24</td>
</tr>
<tr>
<td>F7</td>
<td>2.75 ± 0.12</td>
<td>5.45</td>
<td>548</td>
<td>0.41 ± 0.03</td>
<td>100.01 ± 1.5</td>
<td>36</td>
<td>&gt; 24</td>
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<tr>
<td>F8</td>
<td>2.72 ± 0.06</td>
<td>5.80</td>
<td>552</td>
<td>0.36 ± 0.12</td>
<td>98.24 ± 0.6</td>
<td>32</td>
<td>&gt; 24</td>
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<tr>
<td>F9</td>
<td>2.73 ± 0.14</td>
<td>5.68</td>
<td>554</td>
<td>0.34 ± 0.10</td>
<td>99.39 ± 0.2</td>
<td>38</td>
<td>&gt; 24</td>
</tr>
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</table>

### Table 4: Regression coefficient fits to different drug release kinetics models

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi’s model</th>
<th>Korsmeyer Peppas</th>
<th>n</th>
<th>Best fit model</th>
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<tbody>
<tr>
<td>F1</td>
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<td>0.9803</td>
<td>0.9991</td>
<td>0.7073</td>
<td>Peppas</td>
</tr>
<tr>
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<td>0.9021</td>
<td>0.9935</td>
<td>0.9975</td>
<td>0.5782</td>
<td>Peppas</td>
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<tr>
<td>F3</td>
<td>0.935</td>
<td>0.9783</td>
<td>0.9892</td>
<td>0.9892</td>
<td>0.5413</td>
<td>Peppas</td>
</tr>
<tr>
<td>F4</td>
<td>0.9423</td>
<td>0.9451</td>
<td>0.9868</td>
<td>0.9929</td>
<td>0.6140</td>
<td>Peppas</td>
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<tr>
<td>F5</td>
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<td>0.9951</td>
<td>0.9958</td>
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<td>0.9915</td>
<td>0.9905</td>
<td>0.9942</td>
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<tr>
<td>F7</td>
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<tr>
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<td>0.9953</td>
<td>0.7248</td>
<td>1st order</td>
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</table>
Fig. 1: FTIR Spectra of Cephalexin by Polymers

Fig. 2: Dissolution profile of Cephalexin with HPMC K4 M
Fig. 3: Dissolution profile of Cephalexin with HPMC K15 M

Figure 4: Dissolution profile of Cephalexin with HPMC K100

Fig. 5: Graphical representation of in vitro drug release kinetics for F9