Formulation and in vitro Evaluation of Floating Tablets of Dicloxacillin Sodium Using Different Polymers

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Abstract
Objectives: The purpose of the work was to develop gastro retentive floating tablets of dicloxacillin sodium using different ratios of HPMC K 100M, Xanthan gum, Guar gum. Sodium bicarbonate is used as a gas generating agent. Dicloxacillin sodium is used to treat a wide variety of bacterial infections and has a half-life of about 2 hr. Methods: Gastro retentive floating tablets containing 270 mg of dicloxacillin sodium were prepared by wet granulation method employing different ratios of polymers. Results: The formulated tablets were evaluated for precompression parameters and were in the acceptable limits. Post-compression parameters such as weight variation, hardness, friability, swelling index, floating lag time and total floating time were also evaluated. The formulation F3 with HPMC K 100M showed 98.87% of drug release at the end of 12 hr, maintained integrity of tablets and have an optimum floating lag time of 90±0.14 sec and total floating time of 12 hr. The optimized formulation F3 was fitted to various kinetic models and the results showed that F3 formulation followed Zero order kinetics with an R² value of 0.993. The mechanism of drug release from F3 formulation was non-fickian diffusion. Conclusion: The study concluded that, among all the developed formulations, F3 formulation floated up to 12 hr with maximum drug release and can be considered as promising formulation. Key words: Dicloxacillin sodium, Floating tablets, HPMC K 100M, Swelling index, Buoyancy.

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Introduction
Oral drug delivery is the most preferred route of drug delivery due to the ease of administration and patient compliance. Gastric emptying is a complex process that is highly variable and alters in vivo performance of drug delivery systems.1,2 Floating system is a low-density system that floats over the gastric content and tends to keep afloat in the stomach without affecting the gastric emptying rate for a prolonged period.3,4 While the system floating on the gastric content, drug is released slowly from the system at the desired rate, after the release of the drug, the system is emptied from the stomach. This results in increased GRT and better control of fluctuation of plasma drug concentration.5 Polymers are used in floating system so as to target the drug delivery at a specific region in the GI tract i.e. stomach. Both synthetic and natural polymers are used in floating drug delivery. Natural polymers used in the floating system are Guar gum, Chitosan, xanthan gum, Gellan gum, Sodium alginate. Synthetic polymers used for the floating drug delivery are HPMC, Eudragit, ethyl cellulose.6 Dicloxacillin sodium is used to treat a wide variety of bacterial infections. It is a penicillin-type antibiotic. It works by stopping the growth of bacteria. The half-life of the drug is 2 hr which requires frequent drug administration. Conventional tablets of Dicloxacillin sodium requires more dosing frequency. Hence an attempt was made to develop the floating tablets of Dicloxacillin sodium to decrease the dosing frequency, releasing the drug in a controlled manner for a prolonged period and to improve the bioavailability of the drug.7,8

Materials and Methods
Dicloxacillin sodium was received as a gift sample from DRL Hyderabad. HPMC K100 M, Xanthan gum, Guar gum, Sodium bicarbonate, Citric acid, Starch, Magnesium Stearate, MCC, Talc were procured from Yarrow Chem, Mumbai, India. All chemicals used were of analytical grade.

Preformulation studies

Compatibility studies by FTIR
Dicloxacillin sodium was analyzed by FTIR spectroscopy using potassium bromide pellet method. The powdered sample of the drug with different polymers was mixed thoroughly with previously dried potassium bromide. The powder mixture was transferred into hydraulic press and transparent pellet was formed.9 The samples were scanned in the range of 4000 to 400 cm⁻¹.

Analytical method development
100mg of dicloxacillin sodium pure drug was dissolved in 100ml of 0.1 N HCl (stock solution 1000µg/ml). From this 10ml of solution was taken and the volume was adjusted to 100ml with 0.1 N HCl (100µg/ml). From this 10ml of solution was taken and the volume adjusted to 100ml 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain a series of concentrations in the range of 1.0 to 6.0 µg/ml. The absorbance of the above concentrations was measured at 263nm by UV- Spectrophotometer using 0.1N HCl as the blank.10

Method of preparation
The floating tablets were prepared by wet granulation method, using different polymers HPMC K 100 M, Xanthan gum and Guar gum in differ-
ent ratios (Table 2). The ingredients were weighed accurately and mixed thoroughly. The granulation was done with the starch paste by passing through 10 mesh. The granules were dried in tray dryer at 45°C. The dried granules were sized through 22 mesh followed by lubricated with magnesium stearate and talc and then compressed using Rimex compression machine.\textsuperscript{11}

**Evaluation of Precompression parameters**

**Angle of repose**

Fixed funnel method was used to measure the flow properties where the granules were poured from funnel walls to form conical heap in which its lower tip is 2.5 cm away from the hard surface.\textsuperscript{12} The static angle of repose was measured by using the formula,

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

where \( h \) is the height of the heap, \( r \) is the radius of the heap.

**Bulk and tapped density**

The blend was sieved to ensure free from agglomeration free and was introduced into a calibrated measuring cylinder. The initial volume was observed and then the cylinder was allowed to tap onto a hard surface from 2.5 cm height. The tapping was continued to get saturated volume. From the above values, both poured bulk density and tapped density were determined.\textsuperscript{13}

**Hausner’s ratio and compressibility index**

Hausner’s found that the ratio of tapped volume and poured volume was related to its interparticle friction and can be used as a direct tool for flow property evaluation. Compressibility index was determined by using the formula\textsuperscript{14}

\[
\text{Compressibility index} = \frac{\text{Tapped density}}{\text{Poured density}} \times 100
\]

\[
\text{Hausner Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}
\]

**Post Compression Parameters**

**Thickness and weight variation test**

Randomly selected 6 tablets were subjected for thickness measurements by using vernier calipers. To study the weight variation, 20 tablets of each formulation were weighed individually using an electronic balance, calculating the average weight and comparing the individual tablets weight to the average.\textsuperscript{15}

**Drug content**

To evaluate the drug content, 10 tablets of same weight were selected and crushed using mortar and pestle. Powder equivalent to the average weight of the tablet was weighed and dissolved in 0.1 M HCl and diluted suitably. The concentration of drug in the samples was detected using Ultraviolet (UV)-visible spectrophotometer.\textsuperscript{16}

**Hardness and friability**

Tablets from each formulation were subjected for crushing strength and friability by using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (electro lab, Mumbai, India), respectively.\textsuperscript{17}

**Swelling studies**

The swelling properties of tablets were determined by placing the tablet in the dissolution test apparatus containing 900 ml of 0.1 N HCl and maintained at 37±0.5°C. At periodic time intervals, the tablets were taken out of the medium and the weight gain in each tablet was checked using electronic weighing balance. The swelling characteristics were expressed in terms of the percentage of water uptake (WU %) according to the equation.\textsuperscript{18}

\[
\text{WU} = \frac{\text{weight of the swollen tablet} - \text{initial weight of the tablet}}{\text{initial weight of the tablet}} \times 100
\]

**In vitro buoyancy study**

The in vitro buoyancy was determined by observing the floating lag time and the total floating duration (floating capacity). Floating lag time was determined using 900 ml of 0.1 N HCl and three tablets were placed in it. The time required for the tablet to rise from the bottom to the surface of the media was recorded. The time was observed visually and recorded using a stopwatch. The total floating time was determined by placing three individual tablets from each formulation in a beaker containing 900 ml of 0.1N HCl. Then the time taken for each tablet to constantly float on the media was measured.\textsuperscript{19}

**In vitro dissolution Study**

The dissolution study was conducted using 900 ml of 0.1N HCl as dissolution medium employing USP apparatus-II (Paddle Method). The medium was allowed to equilibrate to the temperature of 37±0.5°C. Tablet was placed in the vessel and operated the apparatus for 12 hr at 50rpm. Samples were withdrawn at defined time intervals and replaced with fresh medium. Suitable dilutions were done with 0.1 N HCl and analyzed spectrophotometrically at 263 nm using UV-spectrophotometer.\textsuperscript{20}

**Kinetic modeling of drug release**

To analyze the drug release mechanism of the Dicloxacillin sodium floating tablets, the in vitro dissolution data of formulations were fitted to zero order, first order, Higuchi model and Korsmeyer Peppas model.\textsuperscript{21}

**Stability studies**

The accelerated stability studies were conducted employing screw-capped bottle to pack the optimized formulation and studies were carried out for 3 months, by maintaining at 40°C±2°C and 75%±5% RH. Samples were withdrawn at defined time intervals and investigated for changes in physical appearance, drug content, buoyancy and in vitro drug release as per ICH Q1A guidelines.\textsuperscript{22}

**RESULTS**

**Compatibility studies by FTIR**

All the characteristic IR peaks related to pure drug dicloxacillin sodium also appeared in the FTIR spectra of mixtures of drug with polymers. The FTIR spectra were illustrated in Figures 1-3.

**Analytical method development**

The standard graph of dicloxacillin sodium was constructed using 0.1N HCl and analyzed spectrophotometrically at 263 nm using UV-spectrophotometer.\textsuperscript{20}

**Evaluation of precompression parameters**

**Angle of repose**

The angle of repose of all formulations was carried out and results reported in Table 3, which ranges between 10.26ºC–14.64ºC. The optimized formulation F3 showed the angle of repose 25.58ºC.

**In vitro buoyancy and in vitro dissolution parameter**

**Compression study**

The compression study was employed to evaluate the flow properties, compressibility, and friability. The Hausner’s ratio of all the formulations was determined and the results were reported in Table 4, which ranges between 11.64%–14.64%. The optimized formulation F3 showed compression index of 12.11%.
Hausner’s ratio
Hausner ratio for all the formulations was found to be in the range of 1.10–1.17. The optimized formulation F3 showed hausner’s ratio of 1.12.

Evaluation of post compression parameters

Thickness and Weight variation
The thickness of all tested tablets was within the range of 4.48–4.81 mm. All the formulations passed weight variation test as the % weight variation was within the standard pharmacopeia limits of ± 5% of the weight.

Drug content
In order to estimate the amount of drug in each tablet for the therapeutic activity of Dicloxacillin sodium, the prepared tablets were evaluated for drug content and the drug content of all the formulations were found to be in the range from 98.33%–100%.

Hardness and friability
The hardness of tablets of each tested batch was in the range of 6.8–7.8 kg / cm². This ensures good handling characteristics for all formulations. The Percentage friability was less than 0.5% in all the formulations ensuring that all tablets were mechanically stable.

Swelling studies
The swelling index of all formulations was found to be in the range of 76.65% - 92.65%. The optimized formulation showed the swelling index of 92.65% at the end of 8 h and tabulated in Table 5.

In vitro buoyancy study
The floating ability of prepared formulations was evaluated in 0.1N HCl. The time took for formulations to emerge (Buoyancy lag time) and the time for which formulations floated continuously on the medium (duration of buoyancy) were evaluated. F1, F2, F3 formulations floated in 58,86,90 secs and total floating time of 8,10,12 h. F4, F5, F6 formulations floated in 65, 78, 80 secs and total floating time of 9, 11, 12. F7, F8, F9 formulations floated in 68, 75, 125 secs and total floating time of 9, 10, 12 h. Respectively and tabulated in Table 4.

In vitro Dissolution Study
In vitro drug release of formulations F1, F2, F3 were found to be 78.53% in 8 hr, 92.36% in 10 hr, 98.87% in 12 hrs. The drug release of F4, F5, F6 was found to be 98% in 9 hr, 88.69% in 11 h, 93% in 12 hrs. In vitro drug release of F7, F8, F9 were found to be 94% in 9 hrs. 98.04% in 10 h, 93.76% in 12 hr and the results were depicted in Figure 5.

Kinetic modeling of drug release
Zero order, First order, Higuchi and Korsmeyer-peppas plots were plotted for the optimized formulation F3 and the results were shown in the Figures 6-9. Regression coefficients of these plots were shown in Table 6. R² values of Zero order of formulation F3 was found to be 0.993.

DISCUSSION
The drug excipients interactions study was carried out using FTIR. The spectral data obtained showed that Dicloxacillin sodium was compatible with all the excipients used in the formulations. From FTIR studies, it was shown that there is no significant change in the nature and position of the characteristic band of drug and excipients used in the formulations, hence it can be concluded that there is no chemical interaction between drug and excipients as illustrated in Figure 1-3. The Standard graph of dicloxacillin sodium was plotted and it showed R² value of 0.9991. The powder blend of drug and other excipients used for the formulation of Dicloxacillin floating tablets were evaluated for flow properties. The results of optimized formulation F3 indicates that all the flow properties were good and in the acceptable range. Tablets prepared were round with creamy white color and smooth texture. The thickness of all tested tablets was within the range of 4.48 – 4.81 mm. The hardness of tablets

<table>
<thead>
<tr>
<th>Ingredients</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>
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<td>270</td>
<td>270</td>
<td>270</td>
<td>270</td>
<td>270</td>
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<tr>
<td>Xanthan gum</td>
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<td>...</td>
<td>...</td>
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<td>240</td>
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</tr>
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<td>116</td>
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<td>136</td>
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<td>96</td>
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<tr>
<td>Talc</td>
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<td>7</td>
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<td>7</td>
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<td>7</td>
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<td>Total weight</td>
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<td>700</td>
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Table 3: Precompression parameters for formulations F1-F9.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Angle of Repose(θ) ± SD*</th>
<th>Bulk Density (g/ml) ±SD*</th>
<th>Tapped Density (g/ml) ±SD*</th>
<th>Carr’s Index (%) ±SD*</th>
<th>Hausner Ratio± SD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>25.58 ±0.14</td>
<td>0.49 ± 0.12</td>
<td>0.54 ±0.12</td>
<td>10.26±0.12</td>
<td>1.10±0.12</td>
</tr>
<tr>
<td>F2</td>
<td>26.15 ±0.15</td>
<td>0.51 ±0.15</td>
<td>0.58 ±0.14</td>
<td>12.05±0.15</td>
<td>1.13±0.21</td>
</tr>
<tr>
<td>F3</td>
<td>25.58 ±0.14</td>
<td>0.47 ±0.16</td>
<td>0.54±0.13</td>
<td>12.11±0.16</td>
<td>1.12±0.19</td>
</tr>
<tr>
<td>F4</td>
<td>28.65 ±0.12</td>
<td>0.50 ±0.17</td>
<td>0.57 ±0.19</td>
<td>12.05±0.17</td>
<td>1.11±0.20</td>
</tr>
<tr>
<td>F5</td>
<td>27.43 ±0.20</td>
<td>0.45 ±0.12</td>
<td>0.52±0.12</td>
<td>14.64±0.12</td>
<td>1.17±0.19</td>
</tr>
<tr>
<td>F6</td>
<td>26.96 ±0.15</td>
<td>0.51 ±0.14</td>
<td>0.57 ±0.12</td>
<td>10.53±0.14</td>
<td>1.12±0.13</td>
</tr>
<tr>
<td>F7</td>
<td>27.10 ±0.21</td>
<td>0.48 ±0.15</td>
<td>0.55±0.12</td>
<td>13.78±0.14</td>
<td>1.16±0.18</td>
</tr>
<tr>
<td>F8</td>
<td>26.01 ±0.077</td>
<td>0.56 ±0.12</td>
<td>0.64±0.003</td>
<td>12.98±0.19</td>
<td>1.14±0.19</td>
</tr>
<tr>
<td>F9</td>
<td>28.63 ±0.11</td>
<td>0.53 ±0.12</td>
<td>0.60±0.01</td>
<td>10.26±0.99</td>
<td>1.11±0.15</td>
</tr>
</tbody>
</table>

* n=3 All values are expressed as mean ± SD

Table 4: Evaluation of post compression parameters.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Average Weight(mg) ± SD* (n=20)</th>
<th>Thickness (mm) ±SD* (n=3)</th>
<th>Friability (w/w) ±SD* (n=3)</th>
<th>Content Uniformity (%±SD* (n=10)</th>
<th>Hardness (kg/cm²) ± SD* (n=6)</th>
<th>Floating Lag time SD* (sec) (n=3)</th>
<th>Total floating Time SD* (h) (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>700.2±0.15</td>
<td>4.52±0.13</td>
<td>0.45±0.13</td>
<td>98.33±0.18</td>
<td>7.8 ±0.21</td>
<td>58±0.21</td>
<td>8±0.12</td>
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<tr>
<td>F2</td>
<td>699.2±0.14</td>
<td>4.61±0.14</td>
<td>0.28±0.13</td>
<td>99±0.18</td>
<td>7.4±0.14</td>
<td>86±0.12</td>
<td>10±0.15</td>
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<tr>
<td>F3</td>
<td>700.3±0.13</td>
<td>4.68±0.12</td>
<td>0.41±0.15</td>
<td>99.67±0.15</td>
<td>7.2±0.15</td>
<td>90±0.14</td>
<td>12±0.12</td>
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<tr>
<td>F4</td>
<td>699.9±0.17</td>
<td>4.81±0.13</td>
<td>0.38±0.12</td>
<td>100±0.13</td>
<td>7.4±0.14</td>
<td>65±0.16</td>
<td>9±0.12</td>
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<tr>
<td>F5</td>
<td>699.9±0.18</td>
<td>4.72±0.12</td>
<td>0.36±0.17</td>
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<td>11±0.15</td>
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<tr>
<td>F6</td>
<td>699.9±0.21</td>
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<tr>
<td>F7</td>
<td>699.9±0.15</td>
<td>4.48±0.15</td>
<td>0.46±0.12</td>
<td>99.67±0.21</td>
<td>7.4±0.16</td>
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<tr>
<td>F8</td>
<td>700.7±0.19</td>
<td>4.52±0.15</td>
<td>0.38±0.14</td>
<td>99±0.19</td>
<td>7.8±0.18</td>
<td>75±0.13</td>
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<tr>
<td>F9</td>
<td>699.7±0.20</td>
<td>4.51±0.20</td>
<td>0.36±0.13</td>
<td>98.33±0.15</td>
<td>7.5±0.19</td>
<td>125±0.19</td>
<td>12±0.14</td>
</tr>
</tbody>
</table>

Table 5: Swelling Index (%) of formulations F1- F9.

<table>
<thead>
<tr>
<th>TIME (hr)</th>
<th>Swelling index (%) ±SD*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>1</td>
<td>10.31±0.12</td>
</tr>
<tr>
<td>2</td>
<td>21.42±0.15</td>
</tr>
<tr>
<td>3</td>
<td>28.15±0.14</td>
</tr>
<tr>
<td>4</td>
<td>39.63±0.13</td>
</tr>
<tr>
<td>5</td>
<td>48.05±0.20</td>
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<tr>
<td>6</td>
<td>57.63±0.16</td>
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<td>7</td>
<td>69.67±0.19</td>
</tr>
<tr>
<td>8</td>
<td>76.65±0.18</td>
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</table>
of each tested batch ranged between 6.8 – 7.8 kg / cm² and values were tabulated in Table 4. This ensures good handling characteristics for all formulations. The Percentage friability was less than 0.5% in all the formulations ensuring that all tablets were mechanically stable. The weights of all the tablets were found to be uniform. Floating lag time and total floating time was evaluated for all the formulations. The floating ability of prepared formulations was evaluated in 0.1N HCl. Formulations F1, F4, F7 shown less floating lag time and the total floating time was less than 10 h. An increase in the polymer ratio in the formulations F2, F5, F8 and F3, F6, F9 increased the floating lag time and the total floating time. F3, F6 and F9 formulations floated within 90, 80 and 125secs and have good buoyancy for 12, 12, 12 respectively. Thus, from the results it was observed that an increase in the concentration of polymers increased the total floating time of the tablets. An increase in the polymer concentration in the formulations F2, F5, F8 able to release the drug for a period of 10-11 hr and shown the drug release of 92.36%, 88.69%, 98.04% respectively. Formulations F3, F6, F9 can able to release the drug upto 12 hr. When compared with the formulations F6 and F9 containing Xanthan gum and guar gum, formulation F3 containing HPMC K 100 M of drug :Polymer ratio of 1:0.96 shown the drug release.

The swelling index was performed for all the formulations. The swelling index was increased with an increase in the polymer concentration. The F3 formulation containing HPMC K100 M shown the maximum swelling index of 92.65%, this could be due to the hydrophilic nature of the polymer. In vitro drug release studies were conducted in the dissolution medium of 0.1N HCl. Formulations F1, F4, F7 containing different polymers having drug: polymer ratio of 1:0.81 could not able to release the drug for 12h and shown the drug release of 78.53%, 98%, 94.09% in 8, 9, 9 hr respectively. An increase in the polymer concentration in the formulations F2, F5, F8 able to release the drug for a period of 10-11 hr and shown the drug release of 92.36%, 88.69%, 98.04% respectively. Formulations F3, F6, F9 containing Xanthan gum and guar gum, formulation F3 containing HPMC K 100 M of drug :Polymer ratio of 1:0.96 shown the drug release.
of 98.87% at the end of 12 hr. This clearly suggests that an increase in the concentration of the polymer retarded the drug release up to 12 hr.\textsuperscript{25} Zero order, First order, Higuchi and Korsmeyer-peppas plots were plotted for the optimized formulation F3 and were shown in the Figures 6-9. Regression coefficients of these plots were shown in Table 6. $R^2$ values of Zero order (0.993) for optimized formulation (F3) were greater than $R^2$ values of First order (0.813). Hence the drug release follows Zero order kinetics. The $n$ value of koresmeyer peppas plot for F3 formulation was found to be 0.862. This suggests that it follows non fickian mechanism. The 3 months accelerated stability data indicates that the formulation F3 is stable in terms of physical appearance, drug content, dissolution and buoyancy as represented in Table 7.

**CONCLUSION**

Gastroretentive floating tablets of Dicloxacillin sodium were successfully prepared by using wet granulation method employing HPMC K 100 M, xanthan gum, guar gum in different ratios. Among all the formulations, F3 has shown 98.87% controlled drug release at the end of 12 hr. The floating lag time of optimized formulation F3 was 90±0.15 sec. Stability studies of the F3 formulation was performed according to ICH guidelines for 3 months and no major changes were observed indicated that the F3 formulation was stable and can be considered as the promising formulation.
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CONFLICT OF INTEREST
The authors declare no conflict of interest.

ABBREVIATIONS
HPMC: Hydroxypropyl methylcellulose; GRT: Gastric residence time; MCC: Microcrystalline cellulose; FTIR: Fourier-transform infrared spectroscopy; USP: United states of pharmacopoeia.

REFERENCES