ABSTRACT
The present study was aimed to prepare and evaluate the floating micro carriers of Cefixime, with the main objective is to prolong the gastric residence time. The multi particulate gastro retentive drug delivery system of Cefixime was prepared by the emulsion gelation method using sodium alginate and HPMCK5 in different concentrations and with constant concentration of calcium chloride and light liquid paraffin. The prepared Cefixime microcarriers were evaluated for their particle size, particle shape, FTIR, scanning electron microscopy, drug entrapment, in vitro buoyancy, in vitro drug release and its kinetics. The prepared Cefixime floating microcarriers exhibited prolonged drug release (12hrs) and remained buoyant for > 10 hrs. Based on the results obtained, formulation F5 showed maximum floating time and gave slow and controlled release of Cefixime. The drug release kinetics was best fitted for first order and the mechanism of drug release was by anomalous diffusion.

KEYWORDS: Cefixime, Sodium alginate, Light liquid paraffin, Floating microcarriers.

INTRODUCTION
Oral route remains the preferred route for the administration of therapeutic agents because of low cost therapy, ease of administration and patient compliance. The design of oral controlled drug delivery system should be primarily aimed to achieve more predictable and increased bioavailability of drug. An incomplete release of the drug and shorter residence time of the dosage form in the upper gastrointestinal tract (GIT), which is a prominent site for the absorption of many drugs, may lead to decreased bioavailability.1,2

One of the most feasible approaches for achieving a prolong and predictable drug delivery profiles in GIT is to control the gastric residence time using gastro retentive dosage forms that offer a new and better option for drug therapy. Several gastro retentive drug approaches being designed and developed.3,4,5 Among them, most commonly used approach to produce gastro retentive drug delivery system (GRDDS) is floating drug delivery system (FDDS) have a bulk density lower than gastric fluids and thus, remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, drug is released slowly at a predetermined rate.6 Cefixime, a third generation oral cephalosporin antibiotic used in the treatment of uncomplicated urinary tract infection, otitis media, pharyngitis, acute bronchitis, acute exacerbation of chronic bronchitis and uncomplicated gonorrhea. Cefixime is a weak acid (pka - 2.5) which remains unionized at acidic pH and thus increases its absorption in stomach and slowly incompletely absorbed from gastrointestinal tract, which results in poor bioavailability. It is primarily absorbed from stomach and upper part of the intestine.7-10 Based on the absorption characteristics and half life (3-4hrs), Cefixime was taken as a model drug for floating beads prepared by emulsion gelation method (non-effervescent method).
MATERIALS AND METHOD
Cefixime was received as gift sample from Aurobindo Laboratories Ltd, Hyderabad, India. Sodium alginate was purchased from Finar Chem Ltd., Ahmadabad, India. Light liquid paraffin and calcium chloride was purchased from S.D. Fine chemicals Ltd, Mumbai, India and Molychem Pvt. Ltd, Mumbai, India respectively. All other chemicals used were of analytical grade.

PREPARATION OF OIL ENTRAPPED CEFIXIME FLOATING MICROCARriers:
Formulation F1 to F7 was prepared by emulsion gelation technique. Sodium alginate and hydroxyl propyl methyl cellulose (HPMCK5) were taken in different concentrations as shown in the table no.1 and were dissolved in distilled water with agitation. Cefixime (100mg) and light liquid paraffin (2.5ml) were added to the solution and was homogenized for 10 min. This solution containing Cefixime and oil was extruded via a needle having a diameter of 18 mm from a distance of 5 cm into 5% calcium chloride solution with gentle agitation at room temperature. The emulsion gel beads were allowed to stand in the solution for 5 min before being separated and washed with 100ml of distilled water. The obtained beads were then filtered and air-dried at room temperature and were stored in a desicator11.

EVALUATION AND CHARACTERISATION OF MICROCARriers:

FTIR STUDIES:
IR spectroscopic studies were carried out for prepared beads to determine the integrity of the drug (Cefixime) in the formulation.

PHYSICAL APPEARANCE AND MORPHOLOGICAL ANALYSIS:
All the batches of Cefixime beads were studied for color and physical appearance. Surface and cross sectional morphologies of beads were examined with a scanning electron microscope (SEM).

MICROMERICITIC PROPERTIES:
The floating microcarriers were characterized for their micromeric properties such as angle of repose, Carr’s index and Hausner’s ratio12.

FLOATING BEHAVIOR:
The floating microcarriers samples (50mg) were placed in a beaker filled with 100ml of HCl solution (pH1.2) and the temperature was maintained at 37±0.5°C. The time between introduction of beads and its buoyancy on the gastric fluid (floating lag time) and the time during which beads remain buoyant (floating time) were measured13.

DRUG LOADING ANG ENTRAPMENT EFFICIENCY:
50mg of floating microcarriers were weighed and ground to fine powder in a mortar and the fine powder was dissolved in 25ml of 0.1N HCl. Volume of this solution was made up to 50ml with washings of mortar. The solution was kept for 24 hrs, and then it was filtered. The filtrate was assayed spectrophotometrically at 288nm14. The drug loading (%) and entrapment efficiency (%) was calculated according to the following relationship:
% Drug loading = Actual drug content/Weight of powdered microcarriersx100…… (1)
%Drug entrapment efficiency = Actual drug content/ Theoretical drug content x100………… (2)

IN-VITRO DRUG RELEASE STUDIES:
The in vitro release studies were carried out using USP Type II dissolution apparatus containing 900ml of HCl solution (pH1.2) maintained at 37±0.5°C and stirred at 50 rpm. Aliquots of 5ml were withdrawn at different time intervals up to 12hrs and replaced with 5ml of fresh dissolution medium. Drug content of the beads was determined by UV-Visible spectroscopy at 288 nm and the cumulative percentage release was calculated over sampling time15.

RELEASE KINETICS:
The results of in vitro release profile obtained for all the formulations were fitted to zero order, first order, Higuchi and Korsmeyer- Peppa’s equation to assess the kinetic modeling of drug release. A Zero order release would be predicted by the following equation.

A = A - Kt ……………… (3)
Where,
A - Drug release at Time ‘t’,
A0 - Initial drug concentration, K0 - Zero-order rate constant (hr\(^{-1}\)).

First - order release would be predicted by the following equation:-

\log C = \log C_0 - Kt/2.303. ……… (4)
Where,
C =Amount of drug remained at time ‘t’, C\(_0\) - Initial amount of drug,
K = First order rate constant (hr\(^{-1}\)).

Drug release from the matrix devices by diffusion has been described by following Higuchi’s classical diffusion equation.
Q = [Dε/τ(2A-εCs)Cst]½ ...(5)

Where,
Q - Amount of drug released at time ‘t’.
D - Diffusion coefficient of the drug in the matrix,
A - Total amount of drug in unit volume of matrix, Cs - the solubility of the drug in the matrix.
ε - Porosity of the matrix,
τ - Tortuosity,
t - Time (hrs) at which ‘q’ amount of the drug is released.

Above equation may be simplified if one assumes that ‘D’, ‘Cs’, and ‘A’, are constant. Then the equation becomes,

Q=Kt½ .................... (6)

To study the mechanism of drug release from the sustained release matrix tablets of Cefixime, the release data were also fitted to the well-known exponential Korsmeyer-Peppa’s law equation, which is often used to describe the drug release behavior of polymeric systems.

Mt/M∞ = Ktⁿ ............ (7)

Where,
Mₜ/ Mα - the fraction of drug released at time‘t’.
K - Constant incorporating the structural and geometrical characteristics of the drug / polymer system.
n - Diffusion exponent related to the mechanism of the release.

The above equation can be simplified by applying the log of both sides, and we get:

Log Mt / Mα = Log K + n Log t ...... (8)

For Fickian release ‘n’ = 0.5
while for anomalous (non -Fickian) transport ‘n’ ranges between 0.5 and 1.0

RESULTS AND DISCUSSION

The shape of the microcarriers was found to be spherical and creamy white in color. FTIR results suggesting that the drug and excipients used in the formulation were compatible with each other. The SEM photographs of the optimized formulation were shown in the fig. 1 & 2. The surface smoothness of the Cefixime microcarriers was increased by increasing the polymer concentration and rough, wrinkled surface of microcarriers were obtained at lower polymer concentration. The results of angle of repose, Carr’s index and Hausner’s ratio of all formulations confirm the better flow properties and the values were reported in the table no.2. A gradual increase in the size of microcarriers was observed upon increasing concentration of polymer in the formulation. All the formulations (F1-F7) remained buoyant for more than 10 hrs and the floating lag time was between 15-18 min as shown in the table no.3. The drug entrapment efficiency was found to be in range of 71.55%-96.24% and the results were shown in the table no.4. Formulation, F5 (96.24%) had having highest % drug entrapment and the formulation, F1 (71.5%) had lowest entrapment efficiency of Cefixime. Upon increasing the concentration of HPMCK5 from 100 to 300mg, the entrapment efficiency also increased from 71.5 to 96.24% but on further increase in the concentration up to 400mg, the entrapment decreased to 73.6% due to increased viscosity of the polymer. In vitro drug release studies were conducted in simulated gastric fluid HCl solution (pH1.2). In vitro release profiles of all the formulations were shown in the fig.3. All the formulations were found to release Cefixime in a controlled manner for a period of 12hrs. With decreasing concentrations of sodium alginate from 900 to 700mg and increasing concentrations of HPMCK5 from 100 to 300mg, the drug release increased for the formulations F1 to F5 i.e. from 76.4% to 99.24% but on further increase in the concentration of sodium alginate (650mg, 600mg), the drug release for the formulations F6 and F7 was 98.2% at the end of 10hr and 99.1% at the end of 9 hr respectively. The constant concentration of calcium chloride (5%) and light liquid paraffin (2.5ml) had no effect on the release of Cefixime. The in vitro release data were fitted into various kinetic models which suggest that the highest correlation (r²) was best fitted for first order kinetics and the best fit model was found to be Korsmeyer Peppas model. The ‘n’ value was found to be 0.69, indicating that the drug release followed anomalous (non-fickian) diffusion model. Based on the drug entrapment efficiency, floating behavior, in vitro release studies formulation F5, was selected as an optimized formulation for gastro retentive floating drug delivery system (GRFDDS) of Cefixime.

CONCLUSION

The gastro retentive floating microcarriers of Cefixime were successfully prepared by emulsion gelation technique. Cefixime microcarriers were spherical in shape and the entrapment efficiency was found to be between 71.55- 96.24%. The buoyancy results suggested that beads were able to restrict the drug release in stomach. From all the batches, the formulation, F5 showed better results in terms of percentage yield, entrapment and drug release. The drug release kinetics was best fitted for first order and the drug release mechanism followed Korsmeyer Peppas anomalous (non-fickian) diffusion model.
### Table 1
Formulations of floating microcarriers of Cefixime

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Amount of Cefixime (mg)</th>
<th>Amount of sodium alginate (mg)</th>
<th>Amount of HPMCK5 (mg)</th>
<th>Concentration of calcium chloride (%)</th>
<th>Amount of light liquid paraffin (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>100</td>
<td>900</td>
<td>100</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>F2</td>
<td>100</td>
<td>850</td>
<td>150</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>F3</td>
<td>100</td>
<td>800</td>
<td>200</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>F4</td>
<td>100</td>
<td>750</td>
<td>250</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>F5</td>
<td>100</td>
<td>700</td>
<td>300</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>F6</td>
<td>100</td>
<td>650</td>
<td>350</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>F7</td>
<td>100</td>
<td>600</td>
<td>400</td>
<td>5</td>
<td>2.5</td>
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### Table 2
Flow characteristics of Cefixime microcarriers

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Angle of repose</th>
<th>Hausner’s ratio</th>
<th>Carr’s index</th>
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<tbody>
<tr>
<td>F1</td>
<td>24.5±0.84</td>
<td>1.17±0.02</td>
<td>15.0±0.91</td>
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<td>F2</td>
<td>25.6±1.24</td>
<td>1.20±0.01</td>
<td>17.1±0.29</td>
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<tr>
<td>F3</td>
<td>22.4±1.02</td>
<td>1.22±0.06</td>
<td>18.6±0.35</td>
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<tr>
<td>F4</td>
<td>26.0±0.97</td>
<td>1.15±0.02</td>
<td>13.5±0.28</td>
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<tr>
<td>F5</td>
<td>22.8±0.77</td>
<td>1.21±0.06</td>
<td>17.7±0.97</td>
</tr>
<tr>
<td>F6</td>
<td>26.4±0.72</td>
<td>1.22±0.07</td>
<td>18.3±0.82</td>
</tr>
<tr>
<td>F7</td>
<td>28.6±0.92</td>
<td>1.19±0.09</td>
<td>16.1±0.35</td>
</tr>
</tbody>
</table>

### Table 3
Floating lag time and buoyancy duration of Cefixime microcarriers

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Floating lag time (min)</th>
<th>Buoyancy duration (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>15</td>
<td>&gt;10</td>
</tr>
<tr>
<td>F2</td>
<td>18</td>
<td>&gt;10</td>
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<tr>
<td>F3</td>
<td>16</td>
<td>&gt;10</td>
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<td>&gt;10</td>
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<tr>
<td>F6</td>
<td>15</td>
<td>&gt;10</td>
</tr>
<tr>
<td>F7</td>
<td>16</td>
<td>&gt;10</td>
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### Table 4
Drug loading and Entrapment efficiency of Cefixime microcarriers

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Drug loading (%)</th>
<th>Entrapment efficiency (%)</th>
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</thead>
<tbody>
<tr>
<td>F1</td>
<td>78.6</td>
<td>71.5</td>
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<tr>
<td>F2</td>
<td>82.3</td>
<td>77.7</td>
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<tr>
<td>F3</td>
<td>86.2</td>
<td>83.9</td>
</tr>
<tr>
<td>F4</td>
<td>92.4</td>
<td>93.6</td>
</tr>
<tr>
<td>F5</td>
<td>94.2</td>
<td>96.2</td>
</tr>
<tr>
<td>F6</td>
<td>90.3</td>
<td>84.7</td>
</tr>
<tr>
<td>F7</td>
<td>89.7</td>
<td>73.6</td>
</tr>
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Fig. 1
SEM photograph of optimized formulation (F5)

Fig. 2
SEM photograph of optimized formulation (F5)
REFERENCES