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ABSTRACT
The present study was carried out to develop the floating drug delivery with sustained release of Cefixime Trihydrate using, HPMC K100M and Carbopol P934, Ethyl cellulose polymers. FT-IR study was carried out which suggested that there was no significant drug interaction between Cefixime trihydrate with polymers and other excipients. Precompression parameter & post compression parameters are within pharmacopeial limits. In-vitro dissolution studies showed good percent yield, good buoyancy and release for more than 12hrs. Floating lag time of tablet found to be (15±0.87-37±0.08). And uniformity of content was found to be range (95.85±1.43to100.8±1.79). Stability studies at temperature 40°C/75% RH for 0,5,15,30,45,60 days on optimized batch showed no significant effect on physical properties, drug content, floating behavior and drug release.

Keywords: Cefixime Trihydrate, swelling index, Lag time, stability studies.

INTRODUCTION
Gastro-retention of drug delivery system in the stomach prolongs the overall gastrointestinal transit time, thereby resulting improved bioavailability. The floating dosage form has been used most commonly. GRDDs extend significantly the period of time over which the drug may be released. They only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form. Dosage forms that can be retained in the stomach are called gastro retentive drug delivery systems (GRDDS) 1-3. Gastro retention is essential for drugs that are absorbed from the stomach, drugs that are poorly soluble or degraded by the higher pH of intestine and drugs with an absorption which can be modified by changes in gastric emptying time 4-5. Gastro retentive drug system can remain in the gastric region for several hours and hence prolonged the gastric resistance time prolong the gastric retention improve bioavailability reduce drug waste and improve solubility of the drug that are less soluble in the high PH environment the need of gastro retentive dosages form has led to extensive effort both academic and industry to words the development of such drug delivery system.

Cefixime trihydrate is a third-generation cephalosporin antibiotics having bactericidal activity by inhibition of cell wall synthesis and used in the treatment of uncomplicated UI, otitis media, pharyngitis & tonsillitis. Its biological half life 3-4hrs. And bioavailability 40-50%. Cefixime trihydrate incompletely absorbed from the gastrointestinal tract because poor bioavailability. Improve the therapeutics effect of the drug by increasing its bioavailability.6-7

MATERIALS AND METHODS

Material
Cefixime trihydrate was obtained as kind gift sample from Covalent Pharma, Mumbai India. Xanthum gum purchased from Pure chem Laboratories Mumbai, India, Ethyl cellulose & Carbopol P-934 was purchased from Corel Pharma Chem, Mumbai India. All other materials used of analytical grades

Methods
Effervescent floating tablets containing Cefixime Trihydrate were prepared by direct compression technique using varying concentrations of different grades of polymers with Cefixime Trihydrate, HPMC K100M, ethyl cellulose, Carbopol P 934, sodium bicarbonate and citric acid. All the ingredients were accurately weighed. Different formulations were made in order to achieve desired friability, thickness, hardness and drug release. The tablets were formulated using drug, diluents, release rate retarding polymer, gas generating agent, and binder, lubricant and gradient. The direct compression method involves sifting of drug along with the polymer through sieve 40 and uniform mixing was carried out for 5 minutes in a polybag. Afterwards one by one all the ingredients were sifted and mixed in it accept the magnesium stearate. The blend was mixed thoroughly for 15 minutes. Finally, magnesium stearate was added and mixed for further 2-3 minutes. The weights of the tablets were kept constant for all formulation.
Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability using the following procedure. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre-weighed 6 tablets was placed in Roche friabilator which was then operated for 100 revolutions i.e., 4 minutes. The tablets were then dusted and reweighed. A loss of less than 1 % in weight in generally considered acceptable. Percent friability (% F) was calculated as follows

\[ \% F = \frac{\text{Initial weight} - \text{final weight}}{\text{initial weight}} \times 100 \]

Pre-compression Evaluation
The powder blend was evaluated for bulk density, tapped density, Carr’s index, Hausner’s ratio and angle of repose.6,9

Post-compression evaluation

Thickness
The thickness of the tablets was determined using a Vernier caliper. Five tablets from each type of formulation were used and average values were calculated. It is expressed in mm.

Hardness
The resistance of tablets to shipping, breakage, under conditions of storage, transportation and handling before usage depends on its hardness. For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm². Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted

Friability

| Table 1: Combination Batches F1 to F8 |
|-------------------------------------|
| **Ingredients** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** |
| Cefixime trihydrate | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| HPMCK100M | 35 | 45 | 55 | 65 | 75 | 85 | 95 | 105 |
| Xanthum gum | 105 | 95 | 85 | 75 | 65 | 55 | 45 | 35 |
| Ethyl cellulose | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Carbopol P934 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Sodium bicarbonate | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |
| Citric acid | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Magnesium stearate | 2.6 | 3.6 | 4.6 | 5.6 | 6.6 | 7.6 | 8.6 | 9.6 |
| TOTAL | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |

Weight Variation Test
To find out weight variation, 20 tablets of each type of formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight.10

Matrix Integrity
The prepared tablets were visually checked for matrix integrity and uniformness. The tablets were checked for matrix integrity during dissolution.

Floating Behavior

The in-vitro buoyancy was determined by floating lag time and floating time. The tablets were placed in dissolution vessel containing 900 ml of 0.1N HCl. The time required for the tablet to rise to the surface and afloat was determined as floating lag time. The duration for which the tablet remains afloat on surface of solution is known as floating time.11-12

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 37°C. The time required for the tablet to rise to the surface and float was determined as floating lag time.13-14

Uniformity of drug content
Five tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 100 mg of cefixime trihydrate was weighed and dissolved in 100 ml of 0.1N HCl (pH 1.2). This was the stock solution from which 0.2 ml sample was withdrawn and diluted to 10 ml with 0.1N HCl. The absorbance was measured at wavelength 287 nm using double beam UV-Visible spectrophotometer.15

\[ \% \text{ Purity} = 10 \frac{C}{(\text{Au} / \text{As})} \]

Where, \( C \) - Concentration,
Au and As - Absorances obtained from unknown preparation and standard preparation, respectively.

**In-vitro dissolution studies**

The in-vitro dissolution study was performed using Dissolution test apparatus: USP (Type II) at 100 RPM. Aliquot (10 ml) of the solution was collected from the dissolution apparatus (from a zone midway between the surface of dissolution medium and the top of rotating paddle not less than 1 cm apart from the vessel wall) at the time interval of one hour and was replaced with fresh dissolution medium. The withdrawn samples were analyzed by an UV spectrophotometer at 287 nm using 0.1 N HCl as a blank. Drug content in dissolution sample was determined using calibration curve.

**Accelerated Stability Testing**

Since, the period of stability testing can be as long as two years, it is time consuming and expensive. Therefore, it is essential to devise a method that will help rapid prediction of long-term stability of dosage form. Stability testing of formulation batch was carried out to determine the stability of drug and carrier and also to determine the physical stability of formulation under accelerated storage condition at 45°C/70%RH. The prepared tablets were placed in borosilicate screw capped glass containers. The samples were kept at condition of 45°C/70% RH and were analyzed at 7th, 14th, 21st and 28th days for drug content, hardness and in-vitro dissolution study.16

**Fourier Transform Infrared Spectrophotometric (FT-IR) Study**

The IR spectra of previously dried samples were recorded by potassium bromide dispersion technique. 2-3 mg of sample of drug, polymers and their physical mixtures was mixed with previously dried potassium bromide and kept in sample cell, the cell was then fitted on sample holder and spectrums were recorded. (Shimadzu, Japan).17-19

**RESULT AND DISCUSSION**

**Infrared Spectroscopy studies**

The IR spectrum did not show presence of any additional peaks for new functional groups indicating no chemical interaction between cefixime trihydrate & the used polymers. The observed peaks along with assignment of functional groups to the peak are given below:

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### Table 3: Physical parameters of powder blend Final Batches

| Parameter                  | Formulation | Bulk Density (g/ml) ±SD | Tapped Density (g/ml) ±SD | Angle of Repose (°) ±SD | Carr’s Index (%) ±SD | Hausner’s Ratio ±SD |
|----------------------------|-------------|-------------------------|--------------------------|------------------------|----------------------|----------------------|
| F1                        | 0.394±0.096 | 0.412±0.019             | 23.54±12                 | 16±0.51                | 1.1±0.063            |
| F2                        | 0.375±0.052 | 0.434±0.056             | 25.61±24                 | 19±0.04                | 1.04±0.034           |
| F3                        | 0.410±0.086 | 0.409±0.043             | 23.45±02                 | 21±0.42                | 1.12±0.022           |
| F4                        | 0.383±0.096 | 0.442±0.081             | 26.05±19                 | 22±0.68                | 1.08±0.045           |
| F5                        | 0.405±0.076 | 0.482±0.053             | 24.68±09                 | 18±0.04                | 1.21±0.055           |
| F6                        | 0.397±0.070 | 0.502±0.025             | 23.91±23                 | 23±0.79                | 1.15±0.061           |
| F7                        | 0.382±0.086 | 0.417±0.023             | 24.86±31                 | 20.10±56               | 1.09±0.039           |
| F8                        | 0.416±0.082 | 0.399±0.033             | 26.10±28                 | 22±0.54                | 1.11±0.06            |

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**Figure 1: FT-IR spectrum of Cefixime trihydrate.**

**Figure 2: FT-IR spectrum of Physical mixture.**

**Pre-compression Evaluation**

The bulk density obtained for all the formulations in the range of 0.394 to 0.416 (g/ml) and the tapped density in the range of 0.412 to 0.399 (g/ml). The Angle of repose of the powder blend of all the formulations was found in the range of 23.54° to 26.10° which is in the good or in the acceptable range means showing the good flowability necessary for proper flow of powder blend into the die cavity. The Carr’s index of the powder blend of all the formulations was found in the range of 16 to 22.63 which is good or in the acceptable range means showing the good flowability in compression evaluation.

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Evaluation of Floating Tablets

The floating tablets were evaluated for hardness, thickness, % friability and weight variation. The results of all the formulations are given in Table 22. The results obtained indicated that the physical parameters were within pharmacopoeial limit. The hardness of tablets was found to be 4.01 to 4.66 kg/cm². Thicknesses of all tablets were found to be in the range of 3.148-3.526 mm. All the tablets shows % friability in the range of 0.4044-0.7745% which is within the limit. All the formulations pass the weight variation test as all tablets within the range limit for weight variation. It is included in reading in table no 4.

Table 4: Physical parameters of tablets Final Batches (F1 to F8)

| Formulation | Hardness (kg/cm² ± SD) | Thickness (mm ± SD) | % Friability (± SD) | Wt. Variation (± SD) |
|-------------|------------------------|---------------------|---------------------|----------------------|
| F1          | 4.36±0.16              | 3.33±0.12           | 0.79±0.13           | 247±0.95             |
| F2          | 4.50±0.09              | 3.28±0.21           | 0.90±0.10           | 251±0.86             |
| F3          | 3.99±0.35              | 3.24±0.13           | 0.88±0.09           | 249±1.1              |
| F4          | 4.25±0.12              | 3.36±0.25           | 0.83±0.18           | 251±0.92             |
| F5          | 4.41±0.17              | 3.35±0.16           | 0.77±0.25           | 247±0.78             |
| F6          | 4.36±0.24              | 3.30±0.18           | 0.87±0.15           | 245±0.98             |
| F7          | 4.48±0.10              | 3.42±0.12           | 0.92±0.21           | 248±1.12             |
| F8          | 3.95±0.18              | 3.37±0.20           | 0.91±0.19           | 248±0.94             |

Matrix integrity

All the tablets were observed visually in dissolution medium for the matrix integrity. All the tablets showed good matrix integrity in dissolution medium. Tablets remained intact for more than 18 hrs.

Floating lag time (Flag) and floating time

As dissolution medium was imbibed into the matrix, the interaction of acidic fluid with sodium bicarbonate resulted in the formation and entrapment of carbon dioxide gas within the swollen gel thus, causing floatation as the matrix volume expanded and its density decreased. Therefore, effervescent system was chosen to compromise the matrix integrity with the possible shortest lag time and floating duration more than 12 h. It was observed that all the tablets floated within 4-5 min after immersion into 900 ml 0.1 N HCl at 37 ± 0.5 °C in the dissolution vessels and the systems remain buoyant over the entire dissolution period in each case the floating lag time. Tablets from each batch showed uniformity of content in the range 95.85% to 103.33% which is within pharmacopeial specifications. All the formulations complies the test for uniformity of content as it found to be within the limit of 90-110%. Show result in Table no.5.

Table 5: Floating behavior of prepared batches

| Formulations | Flag (second) ± SD | Floating Time (hr) ± SD | Uniformity of Content ± SD (%) |
|--------------|-------------------|-------------------------|--------------------------------|
| F1           | 28±0.02           | >12                     | 97.36±3.04                     |
| F2           | 30±0.10           | >12                     | 100.8±3.79                     |
| F3           | 37±0.08           | >12                     | 97.81±4.06                     |
| F4           | 29±0.35           | >12                     | 103.3±4.06                     |
| F5           | 35±0.67           | >12                     | 101.96±1.82                    |
| F6           | 26±0.23           | >12                     | 103.08±4.67                    |
| F7           | 20±0.76           | >12                     | 102.5±3.46                     |
| F8           | 15±0.87           | >12                     | 95.85±2.34                     |

n=3

Swelling behavior

Hydrophilic matrices when immersed in water get swells and eventually dissolve. When they are placed in water, swelling starts and the tablet thickness increases. Initially, water diffuses through the polymeric matrix. As the polymer chains become more hydrated and the gel becomes more diluted, the disentanglement concentration may be reached that is the critical polymer concentration below which the polymer chains disentangle and detach from the jellified matrix. Thus, there is a slow diminution of the matrix thickness due to polymer dissolution. The polymer in the matrix undergoes simultaneous swelling, dissolution and diffusion into the bulk medium resulting in erosion of the polymer.
The matrices %WU increases at the beginning attains a maximum and then declines as can be seen in Fig 23. The matrices behavior can be ascribed to a natural hydration process. Hydrophilic matrices in contact with water swell and increase their volume and weight due to water diffusion through the matrix. The polymer chains continue the hydration process and the matrix gain more dissolution medium. The increasing water content dilutes the matrix until a disentanglement concentration is attained. At this point, the polymer molecules are released from the matrix and diffused to the bulk of the dissolution medium. Hence, the matrix volume decreases slowly because of polymer dissolution. Polymeric matrices experience simultaneously swelling, polymer dissolution and diffusion.

In-Vitro drug release study

Besides the satisfactory buoyancy, the Floating tablets are required to release cefixime tri hydrate gradually over prolonged period. Hence, they were tested for release kinetics by conducting in-vitro dissolution test. Floating tablet showed sustained release of the drug in acidic condition (pH 1.2) and the drug release was found to be approximately linear. Approximately 12-15% of the drug was released initially. Furthermore, drug release from the floating matrix tablet was controlled by the polymer. As the polymer content was increased and the drug loading was decreased, the release of drug was decreased significantly.

The effect of Carbopol, (drug release retardant) concentration on the drug release rate was also studied. In the present floating tablet formulation Carbopol was used to decrease the release of drug. The release of drug was decrease significantly when the concentration of Carbopol was in the range of 3-4 %. In order to increase the release rate of drug, the ratio of polymer was decreased and plasticizer was increased. Formulation F4 showed best appropriate balance between buoyancy and drug release rate. Results of cumulative % release have been shown table no 5.

Table 5: % of drug release of formulation Final Batches F1-F8

| Time | F1     | F2     | F3     | F4     | F5     | F6     | F7     | F8     |
|------|--------|--------|--------|--------|--------|--------|--------|--------|
| 0    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      |
| 1    | 1.29±0.2 | 2.26±0.10 | 5.21±0.11 | 2.14±0.16 | 1.25±0.2 | 2.89±0.13 | 3.56±0.20 | 5.56±0.22 |
| 2    | 2.26±0.1 | 5.18±0.11 | 10.36±0.19 | 5.61±0.12 | 10.35±0.12 | 9.36±0.22 | 11.36±0.20 | 11.24±0.30 |
| 3    | 19.78±0.7 | 10.69±0.17 | 21.25±0.15 | 12.35±0.22 | 25.36±0.20 | 16.35±0.45 | 19.36±0.25 | 19.36±0.33 |
| 4    | 24.31±0.17 | 19.24±0.8 | 36.17±0.36 | 19.25±0.30 | 32.7±0.25 | 25.45±0.34 | 28.65±0.35 | 27.76±0.34 |
| 5    | 32.41±0.34 | 22.21±0.56 | 42.12±0.78 | 29.35±0.78 | 49.23±0.98 | 39.24±0.45 | 39.46±0.56 | 36.15±0.35 |
| 6    | 36.92±0.25 | 29.35±0.23 | 59.1±0.26 | 39.15±0.65 | 55.36±0.65 | 46.89±0.58 | 46.78±0.94 | 49.58±0.65 |
| 7    | 42.15±0.30 | 37.15±0.45 | 61.29±0.45 | 51.24±0.76 | 61.21±0.56 | 59.36±0.34 | 52.46±0.65 | 57.16±0.36 |
| 8    | 47.13±0.34 | 46.87±0.78 | 69.47±0.45 | 62.45±0.47 | 69.75±0.69 | 65.45±0.54 | 59.41±0.67 | 69.46±0.56 |
| 9    | 51.32±0.37 | 56.72±0.34 | 75.14±0.56 | 69.38±0.67 | 75.48±0.78 | 69.36±0.56 | 62.27±0.46 | 76.48±0.67 |
| 10   | 60.89±0.40 | 62.35±0.56 | 82.13±0.34 | 76.41±0.36 | 82.16±0.68 | 72.16±0.56 | 69.45±0.67 | 80.26±0.89 |
| 11   | 65.78±0.42 | 65.25±0.89 | 86.1±0.56 | 79.32±0.56 | 89.15±0.67 | 79.16±0.67 | 77.89±0.46 | 86.95±0.87 |
| 12   | 69.12±0.45 | 72.89±0.78 | 90.34±0.65 | 82.25±0.56 | 94.26±0.56 | 86.92±0.65 | 89.13±0.53 | 90.15±0.78 |
Accelerated Stability Study

Accelerated stability studies (AST) were carried for optimized formulation F5 by exposing it to 40°C/75% RH for one month and analyzed the sample at the interval of 7,14,21,28 days. The sample was analyzed for drug content, hardness and cumulative percentage drug release.

| Parameters                  | Days |
|-----------------------------|------|
|                             | 0    | 15  | 30  | 45  | 60  |
| Hardness                    | 4.41±0.12 | 4.25±0.12 | 4.05±0.1 | 4.1±0.13 | 4.2±0.10 |
| Drug content (%)            | 98.96±1.82 | 96.78±1.79 | 98.52±13.34 | 97.76±1.89 | 94.69±2.41 |
| In-vitro dissolution study  | 94.26±1.56 | 82.33±0.62 | 82.00±0.62 | 81.93±0.42 | 81.96±0.39 |
| Hardness                    | 4.41±0.17 | 4.25±0.13 | 4.05±0.1 | 4.1±0.13 | 4.2±0.10 |

The stability of formulation F5 was also confirmed by IR spectroscopic study as shown in Fig. No.4

**CONCLUSION**

The present study was carried out to develop the floating drug delivery with sustained release of Cefixime Trihydrate using, HPMC K100M and Carbopol P934, Ethyl cellulose polymers. *In-vitro* dissolution studies showed good percent yield, good buoyancy and release for more than 12hrs, followed by the non- Fickian transport. Thus, results of the current study clearly indicate, a promising potential of the Cefixime Trihydrate floating system as an alternative to the conventional dosage form. However, further clinical studies are needed to assess the utility of this system.

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