Trikatu is a classical Ayurvedic formulation comprising of a 1:1:1 ratio of dried fruits of *Piper nigrum* Linn., *Piper longum* Linn., with dried rhizomes of *Zingiber officinale* Rosc, which is widely used for gastric and abdominal discomfort, to enhance the bioavailability of other formulations. Reported investigations about role of piperine, a major phytoconstituent obtained from Trikatu, which enhancing bioavailabilities of numerous formulations used for a wide range of disorders.2, 3 Trikatu is an Ayurvedic digestive stimulant consisting of three herbs in equal amounts, Black pepper (dried fruit of *Piper nigrum* Linn.), Long pepper (dried fruit of *Piper longum* Linn.) and Ginger (dried rhizome of *Zingiber officinale* Rosc.). In Ayurveda, the ingredients of Trikatu are important components of formulations used for a wide range of disorders.2-3 Trikatu is used internally in the treatment of gastric and abdominal disorders, asthma, bronchitis, coughs, dysentery, pyrexia, insomnia, colic, and intestinal infection.5 Several studies have demonstrated that Trikatu can significantly affect the bioavailability of other compounds, including herbal, nutrients and pharmaceutical drugs. The constituent responsible for bioavailability enhancing effect is piperine.6, 6 Enhanced bioavailability as a result of co-administration with either piperine, Black pepper or Long pepper, or Trikatu has been observed for several drugs including vasicine (from *Adhatoda vasica*), spartene (from *Spartium junceum* but also found in broom, *Cytisus scoparius*), phenytoin, propranolol, theophylline, pentobarbitone, sulfadiazine and tetracycline.2, 3, 6, 7

Rapid gastrointestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose. The gastro retentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydrodynamically balanced systems8, 9, swelling and expanding systems10, 11, polymeric bioadhesive systems12, modified-shape systems, high-density systems, and other delayed gastric emptying devices.13 The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.

The present investigation describes the development of floating matrix tablet of Trikatu to prolong gastric residence time resulting in prolonged drug delivery in gastrointestinal tract using HPMC K4M as sustain release polymers and to study process variables that ultimately affects the drug release.

**MATERIALS AND METHODS**

**MATERIALS**

Authenticated Black pepper (Dried fruit of *Piper nigrum* Linn.), Long pepper (Dried fruit of *Piper longum* Linn.) and Ginger (Dried rhizome of *Zingiber officinale* Rosc.) were procured from herbal drug supplier, Sanjivani Aushadhalay, Bhavnagar. They were powdered and passed through 60# mesh sieve. The Laboratory Trikatu was prepared by mixing the three powdered fruits in equal proportion according to Ayurvedic formulary.1
Piperine was purchased from Yucca Enterprise, Mumbai, India. Hydroxypropyl methylcellulose (HPMC K4 M) were received as gift samples from Colorcon Asia Pvt. Ltd, Goa. Sodium bicarbonate, Dibasic calcium phosphate, Lactose, Talc, Magnesium stearate were purchased from S.D. Fine-Chem Ltd, Ahmedabad, India.

METHODS

Preparation of Trikatu extract

Trikatu churna was extracted in 95% alcohol by soxhlet apparatus at the temperature 50 ± 5°C till sufficient extraction was done. The liquid extract was concentrated at reduced temperature (50 ± 5°C) on Rotary evaporator (Equitron rotevar, Medica instrument mfg. co.). Then semisolid extract was dried in desiccator. This dried extract was used for preparation for floating matrix tablets.

Estimation of piperine in Trikatu extract by UV spectrophotometer

Spectrophotometric measurement was carried out on Shimadzu 1601 UV/Vis double beam spectrophotometer. Absorbance was measured in a 1 cm cell at 342.5 nm. Piperine standard solution was prepared by weighing and diluting 10 mg of standard piperine up to 10 ml with ethanol. 1 ml of this solution was taken and diluted up to 10 ml with ethanol to bring the solution of 100 µg/ml (working standard solution). For preparation of sample solution, dissolve 0.5 g Trikatu extract in 50 ml ethanol. Filter the solution using whatman filter paper (stock solution). 1 ml of this solution was diluted with ethanol up to 10 ml volumetric flask. Again make a dilution, 1 ml of this solution was taken and diluted up to 10 ml with ethanol.

Preparation of floating matrix tablets of Trikatu

Floating matrix tablets of Trikatu extract were prepared by direct compression technique. All the powders were passed through 80 mesh sieve. Required quantity of drug, HPMC K4M as polymer, sodium bicarbonate as gas generating agent, DCP in each formulation were mixed thoroughly. Talc and magnesium stearate were finally added as glidant and lubricant respectively. The blend was compressed (12 mm diameter, flat punches) using multipunch tablet compression machine. Each tablet (500 mg) contained 50 mg of Trikatu extract. The Compression force was adjusted to obtain tablets with hardness in range of 3 to 4 kg/cm². The formulations of the preliminary trial batches A1 to A5 and B1 to B4 are shown in Table 1.

Floating behavior of the tablets (In Vitro buoyancy studies)

The in vitro buoyancy was determined by floating lag time method described by Rosa et al. The tablets were placed in 100 ml beaker containing 0.1 N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time. The time the tablets constantly float on the water surface was determined as duration of floating.

Determination of swelling index

The swelling index of tablets was determined in 0.1 N HCl at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

\[
\text{Swelling index} = \frac{(W_f - W_o) \times 100}{W_o}
\]

Where, \(W_o\) is the initial weight of tablet, and \(W_f\) is the weight of the tablet at time \(t\).

In vitro drug release

The drug release study was carried out using USP XXIV dissolution testing apparatus II (paddle method) at 37 ± 0.5°C and 100 rpm using 900 ml of 0.1 N HCl containing 10% alcohol as a dissolution medium. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hours, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 m membrane filter and diluted to a suitable concentration with 0.1 N HCl containing 10% alcohol. Absorbance of these solutions was measured at 342.5 nm using a Shimadzu UV-1601 UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

Factorial Design

A statistical model incorporating interactive and polynomial terms was used to evaluate the responses:

\[
Y = b_0 + b_1X_1 + b_2X_2 + b_3X_1X_2 + b_4X_1^2 + b_5X_2^2,
\]

where, \(Y\) is the dependent variable, \(b_0\) is the arithmetic mean response of the 9 runs, and \(b_i\) is the estimated coefficient for the factor \(X_i\). The main effects (\(X_1\) and \(X_2\)) represent the average result of changing one factor at a time from its low to high value. The interaction terms (\(X_1X_2\)) show how the response changes when 2 factors are simultaneously changed. The polynomial terms (\(X_1^2\) and \(X_2^2\)) are included to investigate non-linearity. On the basis of the preliminary trials in the present study a 3² full factorial design was employed to study the effect of independent variables, i.e. amount of polymer (\(X_1\)) and amount of sodium bicarbonate (\(X_2\)) on dependent variables floating lag time, duration and swelling index. During preparation of floating matrix tablets, Trikatu extract (50 mg) and DCP (200 mg) remain constant in all batches.

RESULT AND DISCUSSION

Estimation of piperine

The calibration curve was created for the entire range from 1 to 8 µg/ml. The readings were taken in the triplicate manner to reduce the error. The concentration of piperine in Trikatu extract was 20.02 ± 0.15 % w/w.

Preliminary trials

The floating matrix tablets of Trikatu were prepared by direct compression technique. HPMC K4M was selected as a matrixing agent considering its widespread applicability and excellent gelling activity in sustained release formulations. Sodium bicarbonate was used as a gas generating agent.
Table 1: Formulation of Trikatu floating matrix tablets with different amount of polymer & with different amount of NaHCO3

<table>
<thead>
<tr>
<th>Batchcode</th>
<th>Ingredients (mg)</th>
<th>NaHCO3</th>
<th>DCP</th>
<th>Lactose</th>
<th>Mg. stearate</th>
<th>Talc</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Drug HPMC K4M</td>
<td>50</td>
<td>100</td>
<td>200</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>A2</td>
<td>50</td>
<td>100</td>
<td>200</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>A3</td>
<td>50</td>
<td>200</td>
<td>100</td>
<td>-</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>A4</td>
<td>50</td>
<td>200</td>
<td>100</td>
<td>-</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>A5</td>
<td>50</td>
<td>200</td>
<td>100</td>
<td>-</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>B1</td>
<td>50</td>
<td>150</td>
<td>50</td>
<td>200</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>B2</td>
<td>50</td>
<td>150</td>
<td>75</td>
<td>200</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>B3</td>
<td>50</td>
<td>150</td>
<td>100</td>
<td>-</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>B4</td>
<td>50</td>
<td>150</td>
<td>100</td>
<td>-</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 2: Evaluation parameters for batch A1-A5

<table>
<thead>
<tr>
<th>Evaluation parameters</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
<th>A4</th>
<th>A5</th>
</tr>
</thead>
<tbody>
<tr>
<td>t80(min)</td>
<td>434</td>
<td>512</td>
<td>575</td>
<td>540</td>
<td>696</td>
</tr>
<tr>
<td>Swelling index</td>
<td>1.45</td>
<td>1.76</td>
<td>2.09</td>
<td>2.35</td>
<td>2.55</td>
</tr>
<tr>
<td>Floating lag time (sec)</td>
<td>51</td>
<td>55</td>
<td>45</td>
<td>42</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 3: A 3² full factorial design for Trikatu floating matrix tablets and evaluation parameters

<table>
<thead>
<tr>
<th>Batch code</th>
<th>X₁*</th>
<th>X₂*</th>
<th>Drug content (%)</th>
<th>Floating lag time (sec)</th>
<th>Duration of floating (hr)</th>
<th>Swelling index</th>
<th>t80</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>125</td>
<td>125</td>
<td>96.73 ± 1.5</td>
<td>120</td>
<td>&gt;12</td>
<td>1.35 ± 0.02</td>
<td>528</td>
</tr>
<tr>
<td>F2</td>
<td>125</td>
<td>150</td>
<td>96.23 ± 0.25</td>
<td>55</td>
<td>&gt;12</td>
<td>1.80 ± 0.12</td>
<td>512</td>
</tr>
<tr>
<td>F3</td>
<td>125</td>
<td>175</td>
<td>93.7 ± 0.89</td>
<td>35</td>
<td>&gt;12</td>
<td>1.71 ± 0.08</td>
<td>486</td>
</tr>
<tr>
<td>F4</td>
<td>150</td>
<td>125</td>
<td>98.4 ± 0.64</td>
<td>100</td>
<td>&gt;12</td>
<td>1.98 ± 0.21</td>
<td>576</td>
</tr>
<tr>
<td>F5</td>
<td>150</td>
<td>150</td>
<td>96.73 ± 0.21</td>
<td>45</td>
<td>&gt;12</td>
<td>2.25 ± 0.02</td>
<td>560</td>
</tr>
<tr>
<td>F6</td>
<td>150</td>
<td>175</td>
<td>95.85 ± 0.1</td>
<td>30</td>
<td>&gt;12</td>
<td>2.13 ± 0.23</td>
<td>540</td>
</tr>
<tr>
<td>F7</td>
<td>175</td>
<td>125</td>
<td>96.7 ± 0.18</td>
<td>105</td>
<td>&gt;12</td>
<td>2.35 ± 0.37</td>
<td>616</td>
</tr>
<tr>
<td>F8</td>
<td>175</td>
<td>150</td>
<td>97.5 ± 0.20</td>
<td>40</td>
<td>&gt;12</td>
<td>2.5 ± 0.16</td>
<td>588</td>
</tr>
<tr>
<td>F9</td>
<td>175</td>
<td>175</td>
<td>95.6 ± 0.47</td>
<td>20</td>
<td>&gt;12</td>
<td>2.39 ± 0.27</td>
<td>575</td>
</tr>
</tbody>
</table>

*All quantity in mg, * Mean ± SD (n=3)

X₁ – amount of polymer,
X₂ – amount of sodium bicarbonate

Figure 1: In vitro drug release for A1-A5

Figure 2: In vitro buoyancy study
Floating behavior of the tablets (In Vitro buoyancy studies)

The pictorial results of in vitro buoyancy study of the best batch is shown in Figure 2, which clearly depicts the floating lag time, stable and persistent buoyancy and swelling characteristic of tablet. Sodium bicarbonate was used as a gas-generating agent in order to float the tablet. The sodium bicarbonate induces CO₂ generation in the presence of dissolution medium (0.1 N HCl). The gas generated is trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of the tablet below 1 gm/ml, and the tablet becomes buoyant. As concentration of NAHCO₃ increased floating lag time was reduced. Duration of floating for all batches was greater than 12 hr.

Swelling index

Swelling index of all floating matrix tablets are as shown in Table 3. As concentration of polymer increased, swelling index increased. Tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water, this gel layer governs the drug release. Kinetics of swelling is important because the gel barrier is formed with water penetration. Swelling is also vital factor to ensure floating. To obtain floating, the balance between swelling and water acceptance must be restored.¹⁶ ¹⁷

3² full factorial design

Factorial equation for floating lag time

\[ y = 43.89 - 7.5X_1 - 40X_2 + 4.17 X_1^2 + 21.7 X_2^2 \]

The floating lag time of the floating matrix tablet of Trikatu varied from 20 to 120 sec (Table 3) and show good correlation coefficient (0.992). Results of the equation indicate that the effect of \( X_1 \) is more significant than \( X_2 \). But the effect of \( X_1 \) is negative, so as the amount of bicarbonate increases the floating lag time decreases. Wherever, the amount of polymer not directly affects the floating time but as the amount of polymer increases the floating lag time also decreases.

Factorial equation for swelling index

\[ y = 2.25 + 0.398X_1 + 0.09X_2 - 0.077X_1X_2 - 0.105X_1^2 - 0.2X_2^2 \]

The swelling index varied from 1.35 to 2.5 (Table 3) and showed good correlation coefficient (0.9932). The amount of polymer directly affected the solvent transfer rate; thus, as amount of the polymer \( X_1 \) increased the swelling index also increased. In addition of sodium bicarbonate \( X_2 \) modifies the matrix hydration volume, increasing at the beginning, reaching a maximum, and then declining. Thus, we can conclude that the amount of polymer directly affects swelling index.

Factorial equation for \( t_{sw} \)

\[ y = 558.56 + 42.17X_1 - 19.83X_2 + 0.25X_1X_2 - 7.83X_1^2 + 0.17 X_2^2 \]

The \( t_{sw} \) varied from 486 to 616 min (Table 3) and show good correlation coefficient (0.9891). In vitro drug release profiles for F1 to F9 Batch are shown in Figure 3. Results of the equation indicate that the effect of \( X_1 \) is more significant than \( X_2 \). The effect of \( X_1 \) was found significant than effect of \( X_2 \). As the amount of polymer in-

As the amount of HPMC K4M was increased from 20% to 45%, the \( F_{lag} \) was increased indicating that high amount of HPMC K4M is undesirable to achieve low \( F_{lag} \). Below 25%, HPMC K4M might not give sufficient strength to the matrix to prolong drug release up to 12 h. Hence, HPMC K4M concentration was decided by preliminary trials. Batches A1 to A5 (Table 1) were prepared to study the effect of HPMC K4M on the drug release. In all these batch sodium bicarbonate concentration remains constant. The results of preliminary trial batches A1-A5 as shown in Table 2. In vitro drug release profile was shown in Figure 1. As the amount of HPMC K4M was increased from 100 to 200 mg. HPMC K4M (100mg) not give sufficient strength to the matrix to prolong drug release up to 12 h. If concentration of polymer was 200 mg, then \( t_{lag} \) increased and drug released more then 12 hr. Hence, it was decided to optimize HPMC K4M in between 125 and 175mg.

It is well known that higher percentage of sodium bicarbonate decreases the \( F_{lag} \). So it was decided to optimize sodium bicarbonate concentration range (50, 75, 100, 125 mg) to keep the \( F_{lag} \) below 3 min. Batches B1-B4 was prepared to check floating lag time. Floating lag time for batch B1, B2, B3, B4 was 600, 130, 55, 38 sec respectively. If concentration of sodium bicarbonate was 50 mg, then floating lag time 10 min. It is not desirable. Further increase in concentration of sodium bicarbonate does not show any significant effect on floating behavior. Moreover, the increased amount of sodium bicarbonate caused a large amount of effervescence, which in turn resulted in pore formation, which led to rapid hydration of the polymer matrix and thereby to rapid drug release. If tablet contain 75, 100, 125 mg sodium bicarbonate, floating lag time was reduced below 2.5 min. Hence, it was decided to optimize sodium bicarbonate in between 75 and 125 mg.
creases the dissolution time for release of drug to 80% ($t_{80}$) increases. Up to some extent, a minor effect of bicarbonate was seen from the data that it decreases $t_{80}$ but not as significant as $X$, which increases the drug release time.

CONCLUSION

The effervescent-based floating drug delivery is a promising approach to achieve in vitro buoyancy by using gel-forming polymer HPMC K4M and gas-generating agent sodium bicarbonate. A systematic study using a $3^2$ full factorial design revealed that the amount of polymer and sodium bicarbonate had an effect on floating lag time, swelling index, $t_{80}$. Thus, by selecting a suitable composition of polymer and sodium bicarbonate, the desired in vitro buoyancy and drug dissolution profile can be achieved.

REFERENCES


Source of support: Nil, Conflict of interest: None Declared