Optimization of floating bilayered tablets of Ketorolac Tromethamine

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ABSTRACT

Objective: The aim of the present study was to formulate the floating bilayer tablets of Ketorolac tromethamine, first immediate release layer and second sustained release floating layer which would provide initial loading dose of drug and remain in stomach and upper part of GIT for prolonged period of time in a view to maximize solubility of drug which is necessary for its absorption.

Methods: The floating bilayered tablets of Ketorolac tromethamine were prepared by using 3² factorial designs by direct compression method. For this, polymers like sodium starch glycolate and polyox WSR 303 were used in various concentrations. Sodium bicarbonate was used as a floating effervescent agent. The formulations were evaluated for hardness, friability, weight variation, swelling index, floating lag time, floating time, % CDR etc

Results: From the result obtained, S3 having 23% Polyox WSR 303 and 12% sodium bicarbonate showed better results.

Conclusions: The results showed that Polyox WSR is promising tool to designing of sustained release formulation.

Keywords: Ketorolac tromethamine, Bilayered, Sodium starch glycolate, Polyox WSR 303

Introduction

Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain avoidance, versatility and most importantly patient compliance.1,2 Floating drug delivery systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.3,4 While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force is also required to keep the dosage form reliably buoyant on the surface of the meal.5-7 Ketorolac tromethamine - 5-benzoyl -2,3-dihydro -1H -pyrrolizine-1-carboxylic acid with 2 – amino – 2 -

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(hydroxymethyl)-1,3-propanediol is an non selective cyclooxygenase (COX) inhibitor. Ketorolac tromethamine (KT) is a well-known non-steroidal anti-inflammatory drug with potent analgesic activity.

**Materials and Methods**

Ketorolac tromethamine was obtained as gift sample from Intas Pharmaceuticals, Ahmedabad. All other chemicals were used of analytical standard.

**Formulation**

Development of bilayer tablets of Ketorolac tromethamine were performed by $3^2$ factorial design carried out in three stages. Two layers such as immediate release (IR) layer and sustained release (SR) layer were formulated separately using different concentration of polymers in different ratios. After optimization of individual layers by *in-vitro* studies, bilayer tablets were prepared using optimized formula. Bilayer tablets were prepared on rotary tablet compression machine. First the extended release layer was pre-compressed on compression machine manually and the immediate release layer was loaded on top of pre-compressed layer and punched.

**Evaluation parameters**

**Pre compression parameters**

All the flow properties were studied such as bulk density, tapped density, Carr’s index, Hausner’s ratio and angle of repose.

**Post compression parameters**

Bilayered floating tablets were evaluated for hardness, weight variation, friability and content uniformity. Sustained release floating layer was also evaluated for.

**Lag time**

The *in vitro* buoyancy was determined by the lag time. The tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for a

**Table 1: Composition of bilayered floating tablet of Ketorolac Tromethamine.**

<table>
<thead>
<tr>
<th>Materials (mg)</th>
<th>S1</th>
<th>S2</th>
<th>S3</th>
<th>S4</th>
<th>S5</th>
<th>S6</th>
<th>S7</th>
<th>S8</th>
<th>S9</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immediate release layer (IR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketorolac tromethamine</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
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<tr>
<td>Sodium starch glycolate</td>
<td>5</td>
<td>5</td>
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<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
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<tr>
<td>Dicalcium phosphate</td>
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<td>82</td>
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<td>82</td>
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<td>1</td>
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<td>1</td>
<td>1</td>
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</tr>
<tr>
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<td>2</td>
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<td>2</td>
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<td>2</td>
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<tr>
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<td>15</td>
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<tr>
<td><strong>Polyox WSR 303 (%)</strong></td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>28</td>
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<td>Sodium bicarbonate (%)</td>
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<td>10</td>
<td>15</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>5</td>
<td>10</td>
<td>15</td>
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<td>PVP (%)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
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<td>5</td>
<td>5</td>
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</tr>
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<td>Citric acid (%)</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Magnesium stearate (%)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Dicalcium phosphate (%)</td>
<td>54.5</td>
<td>49.5</td>
<td>44.5</td>
<td>51.5</td>
<td>46.5</td>
<td>41.5</td>
<td>48.5</td>
<td>43.5</td>
<td>38.5</td>
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<tr>
<td>Talc (%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tablet weight(mg)</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
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</tbody>
</table>
The tablets were placed in a 100 ml glass beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface for floating was determined as the lag time.\textsuperscript{18,19} Floating time The tablets were placed in a 100 ml glass beaker containing 0.1 N HCl. The time required for which the tablet remained floating on the surface of medium was determined as floating time.

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. Determinations were made in triplicate.\textsuperscript{20}

\[
\text{% Swelling index} = \frac{W_t - W_0}{W_t}
\]

Where, $W_0$ is the initial weight of tablet, $W_t$ is the weight of the tablet at time.

**In-vitro drug release study**

The test was performed on the prepared Ketorolac tromethamine tablets using the USP dissolution apparatus II. Six individual tablets from each formula were tested. Test was performed in 900 ml of 0.1 N HCl. In all studies, the temperature of the dissolution medium was maintained at $37\pm 0.5^\circ C$. The Aliquots of 5 ml were withdrawn at regular intervals, filtered and analysed spectrophotometrically at 322 nm.

**Results and Discussion**

**Precompression parameters**

The results of pre compression were showed that all the formulations were exhibit good flow characteristics.

**Post compression parameters**

All the formulations were evaluated for their post compression parameters and results were in their acceptance range

**Swelling index**

The S3 batch was showed the highest % swelling index among all batches.

**In-vitro dissolution Study**

As seen from the, contour plot of the lag time revealed that there was corresponding increase in lag time with increase in the concentration of Polyox WSR 303(A). Moreover it was revealed that increase in concentration of sodium bicarbonate (B) also led to decrease in lag time by generating more CO$_2$. Thus combination of both in suitable concentration might decrease the lag time of the floating tablets.
Figure 4: % Drug release of bilayered tablets S7-S9.

As seen from the figure contour plot of %CDR at 12th hour revealed that there was corresponding decrease in %CDR at 12th hour with increase in the concentration of polyox WSR 303 and sodium bicarbonate. Thus combination of both in suitable concentration might increase the %CDR at 12th hour of the floating tablet.

Figure 5: Contour plot showing the effect of Polyox WSR 303 and Sodium Bicarbonate on lag time.

Figure 6: Response surface plot (3D) showing the effect of Polyox WSR 303 and Sodium Bicarbonate on lag time.

Table 5: Design Summary.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Factor 1 (X1) : Polyox WSR 303 (%)</th>
<th>Factor 2 (X2) : Sodium Bicarbonate (%)</th>
<th>Response 1 Lag time (Sec)</th>
<th>Response 2 % CDR at 12th hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>22</td>
<td>5</td>
<td>31.12</td>
<td>85.23</td>
</tr>
<tr>
<td>S2</td>
<td>22</td>
<td>10</td>
<td>28.74</td>
<td>87.12</td>
</tr>
<tr>
<td>S3</td>
<td>22</td>
<td>15</td>
<td>24.22</td>
<td>99.69</td>
</tr>
<tr>
<td>S4</td>
<td>25</td>
<td>5</td>
<td>48.18</td>
<td>80.49</td>
</tr>
<tr>
<td>S5</td>
<td>25</td>
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<td>42.11</td>
<td>82.6</td>
</tr>
<tr>
<td>S6</td>
<td>25</td>
<td>15</td>
<td>36.39</td>
<td>89.76</td>
</tr>
<tr>
<td>S7</td>
<td>28</td>
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<td>59.48</td>
<td>74.36</td>
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<td>S8</td>
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<td>10</td>
<td>50.48</td>
<td>76.34</td>
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<tr>
<td>S9</td>
<td>28</td>
<td>15</td>
<td>39.4</td>
<td>77.25</td>
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</tbody>
</table>
Conclusions

The floating tablets of Ketorolac tromethamine were formulated by direct compression various polymers like Polyox WSR 303 for sustained release and sodium starch glycolate used as a superdisintegrant for immediate release. The results of pre compression and post compression of floating bilayered tablets were in their acceptance range. Batch S3 containing Polyox WSR 303 in 23% with sodium bicarbonate 12% shows the lowest lag time of 24.22 ± 1.02 and the highest % CDR at 12th hr of 99.69%. The results showed that Polyox WSR is promising tool to designing of sustained release formulation.

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Conflict of interest: None declared

References