pH responsive raft gel forming tablet of risedronate for reducing risk of gastroesophageal irritation of bisphosphonate

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ABSTRACT SUMMARY
pH responsive raft gel forming tablet of sodium risedronate was developed for reducing the risk of gastroesophageal irritation of bisphosphonate.

pH responsive raft gel forming tablet is effervescent formulation which is characterized by having complimentary mechanisms, both pH control with a buffering agent and prevention of gastric reflux with pH responsive raft gel.

pH responsive raft gel system consists of pH responsive natural polymers, gas forming agents, and buffering agents. It can be formulated into an effervescent tablet by adding appropriate additives.

It can be easily dissolved in a small volume of water (100-120 ml) to make raft gel forming solution. When it contacts with acidic medium (50 ml) simulating various conditions of gastric juice, raft gel is formed depending on pH.

It has strong potential to provide more convenient dosing than Actonel® without maintaining upright position while ingesting.

INTRODUCTION
Sodium Risedronate is a bisphosphonate used for treatment and prevention of osteoporosis, which is marketed as a name of Actonel®.

It is known to be irritative to mucosal membrane in GI tract. In this case, Actonel® should be swallowed with a full glass of water (170-230 ml) and patients should maintain upright position for more than 30 minutes to prevent adverse events in esophageal irritation with gastric reflux.

It is reported that bisphosphonate causes esophageal irritation with gastric reflux at pH less than 3.5, where most of drugs exist as an ionized form. This means gastric pH control more than 3.5 has strong potential to provide no need of maintaining upright position¹.

pH responsive raft gel forming effervescent tablet of sodium risedronate was developed using sodium alginate, a pH responsive natural polymer, and the ability of raft gel forming was evaluated in acidic medium with different ionic strengths.

EXPERIMENTAL METHODS
pH responsive raft gel tablet of sodium risedronate was formulated by making an effervescent tablet containing sodium risedronate, pH dependent natural polymer including sodium alginate, buffering agents such as sodium citrate and citric acid, gas forming agents such as sodium bicarbonate and other additives for producing a tablet.

Raft gel forming tablet was dissolved in 120 ml of water to make a raft gel forming solution. Then, the buffer capacity was evaluated with regard to an improved in vitro method for the evaluation of antacids with in vivo relevance. At this point, 120 ml of raft gel forming solution was poured into 250 ml of 0.02 M HCl and pH was estimated after 4 and 20 minutes. The buffer capacity and the neutralizing capacity were also measured by titrating with 0.1 M HCl until pH was dropped to 2.5².

Then, the raft gel forming solution was poured into 50 ml of acidic medium with different ionic strengths. Raft gel forming pH range was checked and the raft gel strength was measured with a texture analyzer.

Dissolution rate was also determined from Raft gel forming solution containing 150 mg of sodium risedronate in 900 ml of acidic medium in order to compare with market product, Actonel®. From this method, it was enough to measure its rate.
RESULTS AND DISCUSSION
Raft gel forming tablet was dissolved within 3 minutes when it poured into 120 ml of water to make a raft gel forming solution.

Raft gel forming solution showed an appropriate buffer capacity from the test according to in vitro method for evaluating antacid with in vivo relevance (Table 1).

After raft gel forming solution (120 ml) was poured into various acidic medium (50 ml), resultant pH and raft gel forming ability were observed. When pH was controlled more than 3.5 by buffer capacity, there was no reaction in resultant medium, however, when pH dropped less than 3.5, pH responsive raft gel was formed on top of resultant solution (Fig 1).

Dissolution rate of sodium risedronate from raft gel forming solution was same regardless of whether raft gel formed or not.

Table 1. Buffer Capacity of Raft gel forming solution, prepared by dissolving pH responsive raft gel forming tablet in 120 ml of water.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt; 2.5</td>
<td>5.49</td>
</tr>
<tr>
<td>pH 20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt; 7.0</td>
<td>5.62</td>
</tr>
<tr>
<td>Neutralizing capacity&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&gt; 8.0 meq</td>
<td>9 meq</td>
</tr>
<tr>
<td>Buffer Capacity&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&gt; 10.0 meq</td>
<td>18.6 meq</td>
</tr>
</tbody>
</table>

<sup>a</sup>pH value 4 minutes after titration was initiated.
<sup>b</sup>pH value 20 minutes after titration was initiated.
<sup>c</sup>The amount of HCl required for adjusting pH from 4.5 to 2.5 by titration with 0.1 M HCl.
<sup>d</sup>The amount of HCl required for adjusting pH from the initial value to 2.5 by titration with 0.1 M HCl.

CONCLUSION
pH responsive raft gel forming tablet of sodium risedronate has complementary mechanisms, both pH control and prevention of gastric reflux with pH responsive raft gel. It has strong potential to provide more convenient and safe dosing than Actonel® without maintaining upright position while ingesting.

REFERENCES

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