A comparison of the dissolution properties of 2 HPMC (hypromellose) capsules filled with basic compounds in acid media

Yoshiro Osaki, Toshimitsu Usui and Tohru Kokubo
Capsule R&D, QualiCaps Co. Ltd., Japan

BACKGROUND
There are two types of hypromellose capsules that are manufactured by different methods. 1) The ‘cold dip’ method - forming HPMC capsules at ambient temperatures and requires a gelling agent 2) The ‘thermal gelling’ method - utilizing HPMC at higher temperatures without a gelling agent. We previously compared capsules made by both methods and reported that capsules made by the 'cold dip' method were superior in terms of capsule strength and drug dissolution rate (Poster, AAPS Annual Meeting, 2010, New Orleans, W4188).

PURPOSE AND HYPOTHESIS
In this study, we investigated dissolution from 2 types of hypromellose capsules to clarify these claims and to find out if basic groups interfere with dissolution from capsules manufactured with carrageenan.

MATERIALS AND METHODS
Capsules: Two 3-hypromellose capsules were obtained from the Japanese market: Capsule A (Quad-X®, made by ‘cold dip’ method) with carrageenan/ KCl Capsule B (Vcaps Plus®, prepared by ‘thermal gelling’ method) without a gelling agent

Dissolution test:
Equipment: Distek Dissolution Apparatus Model 2100C with a fiber-optic UV detection system was employed. Uvita were collected from 6 samples and were submitted for analysis. Conditions: Paddle method at 50 rpm in 900 mL of 0.1N HCl, 34mM NaCl (1st fluid), pH 1.2 at 37°C. P-filters were used to keep capsules submerged.

Solubility test:
Capsule contents: HPMC capsules were filled with each neat API (Hydralazine HCl : 50 mg, Pilocarpine HCl : 5 mg, Ampicillin trihydrate : 100 mg).

RESULTS

<table>
<thead>
<tr>
<th>Compound</th>
<th>Release at 60 min</th>
<th>Release at 150 min</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine</td>
<td>50%</td>
<td>80%</td>
<td>Excellent dissolution</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>50%</td>
<td>80%</td>
<td>Excellent dissolution</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>50%</td>
<td>80%</td>
<td>Excellent dissolution</td>
</tr>
</tbody>
</table>

CONCLUSIONS
This study showed that the dissolution rate from hypromellose capsules made with carrageenan filled with basic compounds in acid media was superior to those made by the ‘thermal gelling’ method. Carrageenan that is included in these capsules appears to act as a promoter of dissolution.

BIBLIOGRAPHY
3) Yoshiro Osaki, Toshimitsu Usui and Tohru Kokubo (Int. J Pharm., 2011, 416(1), 16-24) recently claimed that hypromellose capsules made by 'cold dip' method showed retarded dissolution profiles in the following conditions: 1) Dissolution in acidic media 2) When API is a basic compound with two different pKa's.

SUMMARY TABLE OF CAPSULE COMPARISON STUDIES

<table>
<thead>
<tr>
<th>Capsule</th>
<th>Film Strength</th>
<th>Capsule Strength</th>
<th>Disintegration</th>
<th>Dissolution in Acid Media (Basic compounds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>B</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
</tbody>
</table>

Dissolution tests in acidic media showed that Capsule A (with carrageenan) compared to Capsule B (no gelling agent) had shorter rupture times and improved dissolution rates, for the three structurally different APIs. The dissolution profiles of Capsule A were faster and with less variation especially during the initial stage of the test. The result indicated there is no general charge interactions between carrageenan and basic groups of compounds that could interfere the dissolution in acid conditions.

Hydralazine

Pilocarpine

Ampicillin

Compounds used in this study

<table>
<thead>
<tr>
<th>Cpd</th>
<th>Form</th>
<th>npH</th>
<th>Fill Weight (mg)</th>
<th>Solubility in medium (mg/mL)</th>
<th>Sink ratio</th>
<th>Paddle speed (rpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine</td>
<td>Salt</td>
<td>Low</td>
<td>0.1N HCl</td>
<td>45</td>
<td>810</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>1.6, 7,1</td>
<td>34mM NaCl</td>
<td>418</td>
<td>75,240</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>5, 7,3</td>
<td>100</td>
<td>124</td>
<td>1,116</td>
<td></td>
</tr>
</tbody>
</table>

Film Strength

Capsule Strength

Disintegration

Disolution (Acetaminophen)

Disolution in Acid Media (Basic compounds)

Solubility in Acid Media

Dissolution rate and variation of Capsule A was excellent in Acid Media.

Hydralazine

Pilocarpine

Ampicillin

Structure of kappa-carrageenan (CA) utilized in Capsule A

Dissolution reported by Ku et al. (2011)