The Influence Dissolution Media pH on Drug Release from Ethylcellulose Coated Multicaptilates

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Abstract Summary
The influence of dissolution media pH on drug release from ETHOCEL™ coated drug was investigated. Drug release was found to be independent of dissolution media pH.

Introduction
In order to achieve a consistent extended drug release, it may be necessary to maintain similar drug release while dosage formulation across the physiological pH range. The objectives of this work was to carry out a comparative evaluation of drug release from ethylcellulose coated multiparticulates in both gastric and intestinal media for ionic or non-ionic drugs.

Experimental Methods

Drug Layering of Sugar Spheres
Four model drugs; chlorpheniramine maleate (CPM), guaifenesin (GUA), acetaminophen (APAP) and amlodipine besylate (AMD) in a solvent mixture comprising isopropanol and water (90:10) was used in this study. The four model drugs are characterized below (Table 1).

Table 1. Model Drug Characteristics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Model Drug Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pKa</td>
</tr>
<tr>
<td>CPM</td>
<td>2.8</td>
</tr>
<tr>
<td>GUA</td>
<td>3.2</td>
</tr>
<tr>
<td>APAP</td>
<td>4.0</td>
</tr>
<tr>
<td>AMD</td>
<td>6.5</td>
</tr>
</tbody>
</table>

The model drugs coated were ethos TELOCEL™ coated chlorpheniramine maleate beads (ETHOCEL™ coated chlorpheniramine maleate beads), ETHOCEL™ coated amlodipine besylate beads (ETHOCEL™ coated amlodipine besylate beads) and ETHOCEL™ coated atorvastatin calcium beads (ETHOCEL™ coated atorvastatin calcium beads) for dissolution testing (Table 3).

Table 3. Coating Parameters used for EC Coating

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CPM</th>
<th>GUA</th>
<th>APAP</th>
<th>AMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomization pressure (bar)</td>
<td>1.5</td>
<td>1.2-1.5</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Fluid delivery rate (g/min)</td>
<td>8-10</td>
<td>8-10</td>
<td>2-3</td>
<td>2-3</td>
</tr>
<tr>
<td>Product temperature (°C)</td>
<td>45-48</td>
<td>48-48</td>
<td>38-40</td>
<td>38-40</td>
</tr>
<tr>
<td>Inlet temperature (°C)</td>
<td>65-70</td>
<td>52-58</td>
<td>43-48</td>
<td>42-45</td>
</tr>
</tbody>
</table>

The coatings were applied at slow drying conditions (Figure 1).

Table 2. Drug Layering Process Parameters

<table>
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<tr>
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The drug release across a barrier membrane is expected to occur via diffusion through the polymer network, diffusion or sorption of the drug in the coating. A partitioning of drug in a polymeric film coat is generally dependent on the state of ionization of the drug, molecular affinity (determined by solubility parameter) and its aqueous solubility. The degree of ionization of a drug depends on its pKa and the pH of the aqueous solution in which it is dissolved. Chlorpheniramine, a weak organic acid (pKa=2.8) is expected to be essentially non-ionized at physiological pH (pH between 0.1-0.1 M HCl and pH 7.4 buffer). Acetaminophen solubility does not vary from pH 1.2-8.0 corresponding to the in vivo range in the GIT. As expected, a pH independent behavior was observed in the case of acetaminophen.

In conclusion, a neutral medium, with an absence of any ionizable groups in the molecule also showed pH independent drug release. Guaifenesin is less soluble in a more acidic environment, while in a higher pH environment, guaifenesin is readily soluble. Chlorpheniramine maleate (pKa=2.8), salt of the weak base chlorpheniramine and maleic acid is reported to have similar solubility, in both 0.1 M HCl and in pH 7.4 phosphate buffer at 25°C also showed pH independent release behavior (Figure 1).

Amlodipine besylate, salt of a weak base amlodipine, has mixed ionization within the physiological pH range. Drug release from coated pellets, however, was found to be independent of pH (Figure 4). Amlodipine has a maximum solubility in acidic pH.

Drug release from ETHOCEL™ coated pellets was found to be independent of the dissolution medium for a range of actions with varying solubility.

References
1. USP 35, Appendix VI, October 21, 2010
5. US patent 6737252

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