Extended Release Tablets Containing High Levels of Carbomer Homopolymer

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OBJECTIVE
To identify the feasibility of incorporating high levels (up to 20 w/w%) of Carbopol® 971P NF polymer (Carbomer Homopolymer Type A) as an extended release matrix former in tablets.

METHODOLOGY
Materials
Guaiifenesin (Delta Synthetic Co. Ltd., Taiwan), Carbopol® 971P NF polymer (Lubrizol Advanced Materials, Inc., Cleveland, OH, USA), Emcocel® 50M microcrystalline cellulose (JRS Pharma LP, Patterson, NY), Lactose monohydrate (Sheffield Pharma Ingredients, Norwich, NY), Synpro® magnesium stearate (Ferro Corporation, Walton Hills, OH) Ketoprofen (Medica Inc., Plattsburgh, NY), Talc (Acros Organics USA, Morris Plains, NJ), Cab-O-Sil® M5 fumed silica (Cabot Corporation, Billerica, MA).

Methods
Several formulations containing guaiifenesin or ketoprofen as model water soluble and low water soluble drugs, respectively, and polymer levels ranging from 5 to 20% w/w were prepared (Table 1). The formulations were wet granulated with a rate-controlled addition of deionized water in a high shear granulator (Glatt, E-150). The wet granules were tray-dried, sized and after magnesium stearate spraying compressed into tablets on a rotary tablet press (Korsch, PH-103). The granules were evaluated for flow rate, critical orifice diameter, bulk and tapped densities and Carr’s compressibility index. The tablets were evaluated for weight variation, hardness, friability and disintegration properties.

Table 1. Composition of tablet formulations
<table>
<thead>
<tr>
<th>Batch</th>
<th>Guaiifenesin</th>
<th>Ketoprofen</th>
<th>Carbopol® 971P NF polymer</th>
<th>Emcocel® microcrystalline cellulose</th>
<th>Lactose monohydrate</th>
<th>Synpro® magnesium stearate</th>
<th>Talc</th>
<th>Cab-O-Sil® M5 fumed silica</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 (5%)</td>
<td>800.74</td>
<td>6.60</td>
<td>5.0</td>
<td>4.97</td>
<td>10.0</td>
<td>0.51</td>
<td>0.23</td>
<td>0.09</td>
</tr>
<tr>
<td>G2 (10%)</td>
<td>800.09</td>
<td>6.60</td>
<td>9.0</td>
<td>4.97</td>
<td>10.0</td>
<td>0.51</td>
<td>0.23</td>
<td>0.09</td>
</tr>
<tr>
<td>G3 (15%)</td>
<td>800.44</td>
<td>6.60</td>
<td>13.5</td>
<td>4.97</td>
<td>10.0</td>
<td>0.51</td>
<td>0.23</td>
<td>0.09</td>
</tr>
<tr>
<td>G4 (20%)</td>
<td>800.74</td>
<td>6.60</td>
<td>18.0</td>
<td>4.97</td>
<td>10.0</td>
<td>0.51</td>
<td>0.23</td>
<td>0.09</td>
</tr>
</tbody>
</table>

For guaiifenesin formulations, increasing the polymer level from 5 to 20% w/w resulted in a progressive retardation of drug release with a reduction in intra-batch variability. These effects were found to be consistently reproducible in pH = 6.8 phosphate buffer and 0.1N HCI. For ketoprofen formulations, increasing polymer levels from 5 to 20% w/w showed the drug release with a reduction in intra-batch variability. Inclusion of 20% w/w polymer resulted in a robust formulation.

Table 4. Physical properties of guaiifenesin tablets
<table>
<thead>
<tr>
<th>Batch</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>Friability 100 rot.</th>
<th>Tendancy 300 rot.</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 (5%)</td>
<td>800.74</td>
<td>6.60</td>
<td>5.0</td>
<td>4.97</td>
<td>10.0</td>
<td>0.51</td>
<td>0.23</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2 (10%)</td>
<td>800.09</td>
<td>6.60</td>
<td>9.0</td>
<td>4.97</td>
<td>10.0</td>
<td>0.51</td>
<td>0.23</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3 (15%)</td>
<td>800.44</td>
<td>6.60</td>
<td>13.5</td>
<td>4.97</td>
<td>10.0</td>
<td>0.51</td>
<td>0.23</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G4 (20%)</td>
<td>800.74</td>
<td>6.60</td>
<td>18.0</td>
<td>4.97</td>
<td>10.0</td>
<td>0.51</td>
<td>0.23</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For carbopol formulations, incorporating higher polymer levels (20% w/w) resulted in lower drug loading (6.57% w/w) and an increase in the rate (3.66% w/min) and amount (17.5% w/w) of granulating water (Table 2). The formulations developed showed acceptable granule and tablet properties (Tables 5 and 6). Since the amount of granulating water added depended on the polymer level and is critical to the reproducibility of a formulation, the conditions optimized for incorporating 20% w/w polymer could not be easily extrapolated to formulations containing polymer levels below 15% w/w. At lower polymer levels, the formulations required significantly higher levels (up to 30% w/w) of granulating water. Increasing polymer levels slightly decreased the release of guaiifenesin in phosphate buffer pH = 6.8 (Figure 2).

Table 5. Physical properties of ketoftepone formulations granulations
<table>
<thead>
<tr>
<th>Batch</th>
<th>Carbopol® 971P NF polymer</th>
<th>Flow rate</th>
<th>Tapping density</th>
<th>Tendancy 100 rot.</th>
<th>Tendancy 300 rot.</th>
</tr>
</thead>
<tbody>
<tr>
<td>K1 (5%)</td>
<td>10</td>
<td>3.81</td>
<td>0.385</td>
<td>0.048</td>
<td>21.06</td>
</tr>
<tr>
<td>K2 (15%)</td>
<td>10</td>
<td>4.66</td>
<td>0.345</td>
<td>0.062</td>
<td>19.09</td>
</tr>
<tr>
<td>K3 (20%)</td>
<td>6</td>
<td>5.55</td>
<td>0.465</td>
<td>0.056</td>
<td>19.09</td>
</tr>
</tbody>
</table>

Table 6. Physical properties of ketoprofen tablets
<table>
<thead>
<tr>
<th>Batch</th>
<th>Carbopol® 971P NF polymer</th>
<th>Weight</th>
<th>Thickness</th>
<th>Hardness</th>
<th>Friability 100 rot.</th>
<th>Tendancy 300 rot.</th>
</tr>
</thead>
<tbody>
<tr>
<td>K1 (10%)</td>
<td>299.68</td>
<td>5.10</td>
<td>4.97</td>
<td>0.02</td>
<td>10.01</td>
<td>0.94</td>
</tr>
<tr>
<td>K2 (15%)</td>
<td>299.06</td>
<td>3.81</td>
<td>4.99</td>
<td>0.02</td>
<td>10.26</td>
<td>1.29</td>
</tr>
<tr>
<td>K3 (20%)</td>
<td>277.01</td>
<td>3.25</td>
<td>4.99</td>
<td>0.03</td>
<td>9.93</td>
<td>0.73</td>
</tr>
</tbody>
</table>

CONCLUSIONS
• 20% w/w Carbopol® 971P NF polymer was successfully incorporated into extended-release tablet formulations containing a water-soluble (guaiifenesin) and a low water soluble (ketoprofen) drug.
• Incorporating 20% w/w polymer in formulations containing a water-soluble drug was achieved with a low water level (5% w/w) and a low water spray rate (1.29% w/min), whereas in formulations containing a low water-soluble drug, incorporating 20% w/w polymer required higher water levels (17.5% w/w) at a higher spray-rate (3.66% w/min).
• For guaiifenesin formulations, increasing the polymer level from 5 to 20% w/w resulted in a progressive retardation of drug release with a reduction in intra-batch variability. These effects were found to be consistently reproducible in pH = 6.8 phosphate buffer and 0.1N HCI.
• For ketoprofen formulations, increasing polymer levels from 5 to 20% w/w showed the drug release with a reduction in intra-batch variability. Inclusion of 20% w/w polymer resulted in a robust formulation. The low solubility API required stricter control of the granulating conditions, thus making it more difficult to extrapolate to lower polymer levels (require higher amount of water).

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