Poly(methacrylic acid-co-ethyl acrylate): comparing three different grades in regard to preparation and functionality features in enteric release-coating applications

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INTRODUCTION

Various active pharmaceutical ingredients (APIs) are either aggressive to the stomach’s mucosa or vulnerable to the acidic nature of the gastric juice. Solid oral dosage forms carrying one of these APIs therefore require gastric resistant functionality to prevent drug libera-
tion and drug up-take in the stomach. In order to introduce this release pattern to a formulation, poly(methacrylic acid-co-ethyl acrylate) based film-coating formulations are most frequently applied [1]. Poly(methacrylic acid-co-ethyl acrylate) [MAE] is available in three different grades: as aqueous dispersion, and as spray dried non-
neutrallised material, and partly (8 mol%) pre-neutrallised powder. The latter grades allow coating formulations based on organic sol-
vents. However, both powders are typically redispersed in water for processing, due to higher solid matter contents possible with aque-
ous based formulations.

The aim of this study was to compare the three different polymer grades in regard to their individual handling during preparation of their aqueous film-coating dispersion, and their respective applica-
tion and functionality features.

MATERIALS AND METHODS

Proton-pump inhibitors are known to require enteric release coat-
ings, due to their sensitivity to acid. Therefore, pantoprazole (prone to degradation when exposed to acid) was selected as model ac-
tive pharmaceutical ingredient. Round shaped tablets (Ø=9.0 mm), containing 40 mg API (Formulation Table 1) were produced, using a rotary press (XL 100, Korsch).

In order to prevent interactions in-between API and the carboxylic acid group of the functional polymer (MAE), an instant release sub-
coat based on poly(vinyl alcohol)-polyethylene glycol) graft copoly-
mer (Kollisolve® IR, BASF) was sprayed onto the tablets. Subse-
quently, the enteric release top-coat was applied based on one of the three products investigated in this study; methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30% per cent (Kollisolve® MAE 30 DP, BASF), methacrylic acid – ethyl acrylate copolymer (1:1) type A (Kollisolve® MAE 100-55, BASF), and methacrylic acid – ethyl acry-
late copolymer (1:1) type B (Kollisolve® MAE 100 P, BASF).

All formulations were prepared as aqueous dispersions, holding a solid matter content of 25% and being characterised with triethyl citrate (TEC), added in a concentration of 10% (based on the polymer) [2].

All coating trials were conducted in a side vented pan coater (XL Lab G1, BOSCH Maschey) equipped with one OptiCoat nozzle (further details Table 2).

RESULTS AND DISCUSSION

Dispersing water insoluble particles in a liquid leads to structure viocose flow characteristics. Consequently, one needs to apprec-
iate a reading error when applying standard rotational rheological measurements to determine dynamic viscosity. Nevertheless, the method was suitable to investigate the differences in the preparation characteristics of the three Kollisolve® MAE products. The aqueous dispersion could directly be diluted and mixed with the plasticiser TEC. The spray dried product needed to be partly neu-
trallised (4 to 6 mol% of the carboxylic acid groups) to allow its read-
ily re-dispersion in aqueous media. Sodium hydroxide or ammonia could be used for this purpose. The partly pre-neutrallised powder allowed its re-dispersion without further additives. However, due to its pre-neutrallisation, dynamic viscosity increased, before it levelled off in the same range as the other two products (Figure 1).

The resulting mobility (or zeta-potential) of all three dispersions was very identical. This suggested that all products offered quite similar functionality in regard to shear stress, additives or changes in the pH-value (Figure 2).

The overall preparation time was roughly the same for all formula-
tions. Even though, the powders needed to be re-dispersed, the lim-
iting factor was the generally recommended 2 hours’ incorporation time of the plasticiser.

All three formulations showed the same processing characteristics. A coating level of about 3 mg/cm² resulted in a sealed core, not allowing any API liberation in 2 hours’ dissolution testing in artifi-
cial gastric juice. However, partly pre-neutrallisation of the carbox-
ylic acid groups improved the solubility of the polymer, allowing a quicker dissolution at pH 6.8 (Figure 3).

In order to meet the additional requirement of preventing acid up-
take during the dwell time in artificial gastric juice, higher coating levels were required. The formulation based on the dispersion mere-
ly needed 5 mg/cm² whereas the higher permeability of the partly pre-neutrallised products led to a required coating level of 8 mg/cm² for these formulations (Figure 4).

REFERENCES

[1] Nollenberger, K.; Albers, J.; Poly(methacrylic acid-co-ethyl acrylate) grades impacted the preparation procedure of the dispersions. However, all three aqueous dispersions were alike in their processing characteristics. A coating level of 3 mg/cm² was required to prevent drug liberation during dissolution testing in artificial gastric juice. A higher coating level was needed to additionally prevent acid up-taking during that time, though.

The required partly pre-neutrallisation (for re-dispersion in aqueous media) of the powder grades improved the solubility of the polymer. As a result, drug release was faster at pH 6.8 and acid permiation was increased. In order to prevent acid up-taking, a coating level of 8 mg/cm² instead of 5 mg/cm² was required.

CONCLUSION

The different physico-chemical properties of the three poly (methacrylic acid-co-ethyl acrylate) grades impacted the preparation procedure of the dispersions. However, all three aqueous dispersions were alike in their processing characteristics. A coating level of 3 mg/cm² was required to prevent drug liberation during dissolution testing in artificial gastric juice. A higher coating level was needed to additionally prevent acid up-taking during that time, though.

The required partly pre-neutrallisation (for re-dispersion in aqueous media) of the powder grades improved the solubility of the polymer. As a result, drug release was faster at pH 6.8 and acid permeation was increased. In order to prevent acid up-taking, a coating level of 8 mg/cm² instead of 5 mg/cm² was required.

Figure 1. Dynamic viscosity as function of time.

Figure 3. Dissolution testing in different media (pH 1.1, pH 6.8).

Figure 4. Tablets after 2 hours dissolution testing (pH 1.1). Blue colour: sub-coat, yellow colour: degraded API.

Table 1. Ingredients and content of tablet formulation.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Functionality</th>
<th>Brand name (source)</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pantoprazole sodium hydroxide</td>
<td>API</td>
<td>Gastrolyt S (Gilead)</td>
<td>12.12%</td>
</tr>
<tr>
<td>Co-processed lactose</td>
<td>Filler</td>
<td>Ludipress® LCE (BASF)</td>
<td>76.88%</td>
</tr>
<tr>
<td>Copovidone</td>
<td>Dry binder</td>
<td>Kollisolve® VA 64 Fire (BASF)</td>
<td>5.00%</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>Disintegrant</td>
<td>Kollisolve® CL (BASF)</td>
<td>5.00%</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>Lubricant</td>
<td>MSG Bel 1 (Blistech)</td>
<td>1.00%</td>
</tr>
</tbody>
</table>

Table 2. Process settings for application of sub- and top-coat.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Settings sub-coat</th>
<th>Settings top-coat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nozzle orifice</td>
<td>1.2 mm</td>
<td>0.8 mm</td>
</tr>
<tr>
<td>Drum diameter</td>
<td>610 mm</td>
<td>406 mm</td>
</tr>
<tr>
<td>Drum speed</td>
<td>7 rpm</td>
<td>12 rpm</td>
</tr>
<tr>
<td>Batch size</td>
<td>20.0 kg</td>
<td>2.5 kg</td>
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<tr>
<td>Net air quantity</td>
<td>400 m³/h</td>
<td>300 m³/h</td>
</tr>
<tr>
<td>Process air temperature</td>
<td>55 °C</td>
<td>55 °C</td>
</tr>
<tr>
<td>Spray rate</td>
<td>27 g/min</td>
<td>10 g/min</td>
</tr>
<tr>
<td>AAPA pressure</td>
<td>1.2 bar/1.6 bar</td>
<td>1.0 bar/1.0 bar</td>
</tr>
<tr>
<td>Product temperature</td>
<td>39 °C</td>
<td>42 °C</td>
</tr>
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</table>