1 – Introduction and Objectives

• Acceptance of taste is one of the important criteria in pediatric drug delivery (many compounds inherit a bitter or unfavorable taste).
• Film-coated MiniTablets (MTs) are an advantageous drug delivery form for children from 4 years onwards (smaller children might chew miniTablets).
• Advantages: high dosage flexibility, application of standard coating technologies and often better drug stability requiring less restrictive storage conditions compared to liquid dosage forms [1].
• Challenges for the industrial formulation and process development:
  - choice and amount of the right polymer resp. coating formulation
  - selecting the most suitable coating technology (drum vs. fluid-bed coating) and adjustment of process parameters

Objectives:

- Formulation and process development of taste masked miniTablet formulations with 2 model drugs at high and respectively low drug load by using direct compression and film coating
- Feasibility trials of two coating technologies: fluidized bed and modified drum coating
- Identification of potential critical material attributes (pCMAs) and potential critical process parameters (pCPPs) of the coating process in a quality risk assessment (QRA)

2 – Materials and Methods

Material:

- All used excipients were of pharmacopoeial grade. Batch sizes were between 300 to 1000 g.
- pH dependent Polyethylene-based Polymers: Eudragit E PO® (EPO), Kollicoat Smartseal 30D (SMA)
- pH independent Ethylcellulose-based Polymers: Surelease® and Opadry II as a Poreformer

Manufacturing:

- Direct compression: rotary press (Korsch XL100, Korsch AG), 4 x 2.5 mm concave multiple-tip punches (24 tips per punch)
- Coating equipment: Fluidized bed (MiniGlatt), drum coater (GMPC-1, Glatt GmbH)
- Drum coater insert (Korsch, 1.6l perforated drum)
- Process parameters (DoE): atomization pressure 1.25 bar, spray rate 1-3 g/min, inlet air temperature: 58-71°C, air volume rate 100 m³/h

A thermodynamic model (2) was used to transfer the coating process from the fluidized bed to the drum coating process.

Analytical testing:

- Antiviral saliva (AS): in-vitro taste assessment; orbital shaker, screw cap vial with 5 ml of saliva [3], 10rpm, 33°C
- Simulated gastric fluid (SGF): dissolution [4]; µDiss ProfilerTM, 50 rpm, 37°C
- Coating layer & morphology: SEM, X-Ray µCT

3 – Results and Discussion

3.1 – Formulation Development

Direct compression formulations were developed as shown in Table 1 and 2. The therapeutic dose for children between 2-6 years is 200 mg for acetaminophen (equals 28 MTs) resp. 2.5 mg for cetirizine (equals 3 MTs).

Table 1: MiniTablet formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Acetaminophen</th>
<th>Cetirizine</th>
<th>Tapped Density [g/cm³]</th>
<th>Hausner factor</th>
<th>Compressibility [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acet. core</td>
<td>53.0</td>
<td>7.19</td>
<td>0.61</td>
<td>1.44</td>
<td>30.6</td>
</tr>
<tr>
<td>Granules</td>
<td>5.0</td>
<td>0.83</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acet. PR 110</td>
<td>43.5</td>
<td>0.67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acet. PR 112</td>
<td>34.8</td>
<td>0.87</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FixedLC 100</td>
<td>-</td>
<td>-</td>
<td>0.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acet. 1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acet. 0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ctr. 100</td>
<td>14.37</td>
<td>10.67</td>
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</table>

Table 2: MiniTablet properties

<table>
<thead>
<tr>
<th>Compression</th>
<th>Acetaminophen</th>
<th>Cetirizine</th>
<th>Tapped density [g/cm³]</th>
<th>Hausner factor</th>
<th>Compressibility [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tapped density [g/cm³]</td>
<td>0.53</td>
<td>0.81</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tapped density [g/cm³]</td>
<td>0.53</td>
<td>0.81</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compressibility [%]</td>
<td>30.6</td>
<td>22.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6.7</td>
<td>20.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.2 – Coating trials acetaminophen miniTablets

In cross functional team-based QRA the following pCPPs and pCMAs were identified:

- Selection of the right taste masking approach requires careful, individual selection of polymer and amount [mg/cm²], spray rate (g/min) and coating suspension composition.
- pH dependent polymers:
  - Efficient taste masking in AS was achieved with 4±0.5 mg/cm² (Figure 5) and immediate release even at highest coating level (Figure 6).
  - MT with a coating level of 1.5 mg/cm² has a homogenous and continuous coating layer (Figure 4). Nevertheless, due to water-permeable polymer MCC in tablet cores swell, internal pressure caused burst of coating and insufficient taste masking.

3.3 – Coating trials cetirizine dihydrochloride miniTablets

Coating trials with cetirizine dihydrochloride miniTablets were conducted with the pH independent polymer Surelease® (avoiding chemical incompatibility expected with pH dependent polymers). Due to the capability of Surelease® to also extend the drug release, development work needs to find a compromise between efficient taste-masking and immediately release requirements. A two level full factorial design (2³) with 3 Center Points (CPs) was performed (Table 3).

Table 3: Factor level setting

<table>
<thead>
<tr>
<th>pH independent polymer:</th>
<th>Low level</th>
<th>High level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit E PO®</td>
<td>75%</td>
<td>85%</td>
</tr>
<tr>
<td>Cetirizine MT:</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>pH dependent polymer:</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

- Biggest influence on taste masking: spray rate, followed by spray time and the interaction of both factors (determining the coating weight gain)
- Polymer/pore former ratio in examined range has no significant influence on taste masking
- CP represents the optimum between taste masking, dissolution and coating uniformity

4 – Conclusion

Selection of the right taste masking approach requires careful, individual selection of polymer and formulation (CMAs) and optimization of CPPs.

Acetaminophen MT:
- pH dependent polymers (Eudragit E PO® and Kollicoat Smartseal® 30D): efficient taste masking reached with no drug release in AS after 6 minutes and immediate release in SGF, min. coating level of 4mg/cm² necessary
- pH independent polymer Surelease®: taste masking achieved for 60 s

Cetirizine MT:
- pH independent polymer Surelease® was chosen to avoid chemical incompatibilities
- Compromise between taste masking and immediate drug release
- DoE: Optimum Polymer to pore former ratio 80:20, Spray rate 3g/min, Spray time 70min

5 – References


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