Moisture Protection and Taste-Masking with Polymethacrylate Coatings

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Sr. Research Scientist
Pharma Polymers
- Eudragit® E Polymer Properties
- Moisture Protection
- Taste Masking

EVONIK INDUSTRIES
Drug Release in the Upper GI Tract

- **pH differences**
  - Dissolution of cationic barrier coatings at low pH

- **Ionic strength and volume**
  - Ion exchange for taste masking

<table>
<thead>
<tr>
<th>Location</th>
<th>pH Range</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouth</td>
<td>pH 5-7</td>
<td>&lt;1 min</td>
</tr>
<tr>
<td>Esophagus</td>
<td>pH 1-5</td>
<td>0.5-2 h</td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
EUDRAGIT® E 100 and EUDRAGIT® E PO

Chemical properties:
• $R = \text{methyl, butyl } (1:1)$
• cationic properties
• swellable and permeable above pH 5, soluble below pH 5

Physical properties:
• $T_g \text{ (DSC)}: 50 ^\circ C$
• Elongation at break* 200 %
• $pK_a 10.0 \text{ (water)}$
• Particle size EUDRAGIT E PO:
  Spec: >90 % smaller than 315 $\mu$m
  $V_{50} : 7 - 10 \mu m, V_{95} : \text{max. } 20 \mu m$
  * with 10% triacetine

$\Rightarrow$ Highly flexible and acid soluble!
# Aqueous EUDRAGIT® E PO Formulation

<table>
<thead>
<tr>
<th></th>
<th>EUDRAGIT® E PO</th>
<th>On dry polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUDRAGIT® E PO</td>
<td>150.8 g</td>
<td></td>
</tr>
<tr>
<td>SLS (Sodium laurylsulphate)</td>
<td>15.1 g</td>
<td>10 %</td>
</tr>
<tr>
<td>Stearic acid, powder</td>
<td>22.6 g</td>
<td>15 %</td>
</tr>
<tr>
<td>Mg-stearate, or Talc</td>
<td>52.8 g</td>
<td>35 %</td>
</tr>
<tr>
<td>Aqua pur.</td>
<td>1258.7 g</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1500.0 g</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Polymer:**
- 10 % (w/w)

**Solids:**
- 16 % (w/w)

⇒ Recommended polymer weight gain 1 – 10 mg/cm²
EUDRAGIT® E PO Coating Suspension

- Na-laurylsulfate: 5 min Ultra Turrax
- Aq. pur + SLS: 15 min Ultra Turrax
- EUDRAGIT® E PO: 10 - 20 min Ultra Turrax
- Aq. pur + SLS + stearic acid: 10 - 20 min Ultra Turrax
- Glidant, Pigments (optional): 10 - 20 min Ultra Turrax

⇒ 40 - 60 min dispersion time with homogenizers!

EUDRAGIT® E PO Coating suspension
EUDRAGIT® E PO – Homogenizing Equipment

Silverson

Ultra Turrax
- Eudragit® E Polymer Properties
- Moisture Protection
- Taste Masking
Moisture Protection by Coatings

Water Vapour Permeability [g water/m²*d]

- EUDRAGIT® E PO, 10% SLS, 15% St. A.
- EUDRAGIT® L 100-55
- EUDRAGIT® RS 100
- EUDRAGIT® E 100
- EUDRAGIT® NE 30 D
- EUDRAGIT® E PO, 7% SLS, 10% DBS
- EUDRAGIT® RL 100

∀ EUDRAGIT® E PO provides lowest WVP!
# Materials (I): Tablet Cores

<table>
<thead>
<tr>
<th></th>
<th>Placebo (%)</th>
<th>Quinidine sulfate (%)</th>
<th>Silica (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine sulfate</td>
<td>- -</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Lactose</td>
<td>64.5</td>
<td>61.5</td>
<td></td>
</tr>
<tr>
<td>Avicel® PH 102</td>
<td>30.0</td>
<td>30.0</td>
<td></td>
</tr>
<tr>
<td>Primojel®</td>
<td>5.0</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Mg-stearate</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Property</th>
<th>Placebo</th>
<th>Quinidine sulfate</th>
<th>Silica</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (mm)</td>
<td>10</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Weight (mg)</td>
<td>300</td>
<td>300</td>
<td>409.3</td>
</tr>
<tr>
<td>Hardness (N)</td>
<td>119</td>
<td>80</td>
<td>151</td>
</tr>
<tr>
<td>Disintegration (water, min)</td>
<td>&lt; 2</td>
<td>&lt; 2</td>
<td>n. t.</td>
</tr>
<tr>
<td>Disintegration (0.1 N HCl, min)</td>
<td>&lt; 2</td>
<td>&lt; 2</td>
<td>n. t.</td>
</tr>
</tbody>
</table>
Moisture Protection with EUDRAGIT® E PO Various Coating Levels

Test conditions: 40°C, 75% rel. humidity, open

Increasing coating thickness improves protection!
# Materials (II): Coating formulations

| Ingredient             | EUDRAGIT®  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E PO</td>
</tr>
<tr>
<td>Polymer [g]</td>
<td>285.0</td>
</tr>
<tr>
<td>SLS [g]</td>
<td>28.5</td>
</tr>
<tr>
<td>Stearic acid [g]</td>
<td>42.8</td>
</tr>
<tr>
<td>Mg-stearate / talc [g]</td>
<td>99.8</td>
</tr>
<tr>
<td>Water [g]</td>
<td>1982.9</td>
</tr>
<tr>
<td>Total</td>
<td>2439.0</td>
</tr>
</tbody>
</table>

**Cores:**

2750 g placebos and 250 g Silica tablets
Coating pan : 35 cm diameter  
Spray gun: Walther WA 1 NBA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nozzle diameter [mm]</td>
<td>1.2 mm</td>
</tr>
<tr>
<td>Spray rate [g/min]</td>
<td>8.4 g/min</td>
</tr>
<tr>
<td>Atomizing air pressure [bar]</td>
<td>0.8 bar</td>
</tr>
<tr>
<td>Inlet air temp [°C]</td>
<td>40 – 50°C</td>
</tr>
<tr>
<td>Bed temp [°C]</td>
<td>31 - 37°C</td>
</tr>
<tr>
<td>Coating time [min]</td>
<td>291 min</td>
</tr>
</tbody>
</table>

**EUDRAGIT® E PO**
- Eudragit® E Polymer Properties
- Moisture Protection
- Taste Masking
Taste Masking for Improved Compliance

• Aqueous film coating
  - tablets,
  - multiparticular systems

• Fine powders
  - ionic interactions between polymers and actives
  - alternative production processes

⇒ Chances for innovative formulations!
Cores:
Placebo tablets and quinidine sulphate tablets (1%),
10 mm Ø, 4 mm height, 301 mg weight
Batch size: 8 kg

Equipment:
Accela Cota 10

Parameters:
Nozzle bore: 1.0 mm (Watson Marlow)
Spray rate: 3-5 g/min/kg
 Atomizing air pressure: 1.5 bar
 Inlet air temp: 35-50°C
 Bed temp: 29-31°C
 Coating time: 50 min
Characteristics of EUDRAGIT® EPO Coatings
Example: Quinidine sulfate tablets (stearic acid, SLS)

⇒ Rapid disintegration in artificial gastric fluid!
EUDRAGIT® E PO – Post Coating Treatment

Placebo tablets, 4 mg/cm² polymer weight gain
water, 37 °C

Disintegration time [min]

Curing time [h]

RT trays
40°C trays
50°C trays
Storage Stability

25°C, 60% rel. humidity, open

Disintegration in water
Disintegration in 0.1 N HCl

Placebo tablets, 4 mg / cm² polymer weight gain
Storage Stability

40°C, 75% rel. humidity, closed

Disintegration time [min]

Time [weeks]

Disintegration in water
Disintegration in 0.1 N HCl

Placebo tablets, 4 mg / cm² polymer weight gain
Storage Stability Under Stress

40°C, 75% rel. humidity, open

Disintegration in 0.1 n HCl

Placebo tablets, 4 mg / cm² polymer weight gain
Taste Masking by Particle Coating

Paracetamol Special Granular
Mallinkrodt Inc.
Particle size: 99.5% 150 - 420µm
Surface area (Blaine): 259.4 cm²/g
Particle Coating with EUDRAGIT® E PO

Glatt WSG 5 with 2kg insert (top-spray)

Nozzle diameter
1.2 mm
Atomizing pressure
2.0 bar
Distance nozzle - products
15 cm
Inlet air temperature
26 ~ 38 °C
Outlet air temperature
22 ~ 30 °C
Air flow rate
1.0 ~ 2.0 m/s
Drug Release from Coated Paracetamol Granules

\[ \Rightarrow \text{pH-dependent solubility:} \]
\[ \text{Release testing in acid media!} \]
### Model for Chewable Tablets

#### Compositions

<table>
<thead>
<tr>
<th></th>
<th>15 % polymer weight gain [mg]</th>
<th>30 % polymer weight gain [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>300.0</td>
<td>300.0</td>
</tr>
<tr>
<td>as coated</td>
<td>371.7</td>
<td>447.8</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>216.8</td>
<td>261.2</td>
</tr>
<tr>
<td>Na-carboxymethyl starch</td>
<td>31.0</td>
<td>37.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>619.5</strong></td>
<td><strong>746.3</strong></td>
</tr>
</tbody>
</table>

#### Manufacture & Characteristics

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression pressure (kN)</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Tablet hardness (N)</td>
<td>61-68</td>
<td>60-79</td>
</tr>
<tr>
<td>Weight (mg)</td>
<td>731-747</td>
<td>615-622</td>
</tr>
<tr>
<td>Height (mm)</td>
<td>8.5</td>
<td>7.2</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td>12.0, radius of curvature 9.0</td>
<td></td>
</tr>
</tbody>
</table>
Dissolution Profiles of Particles and Tablets

15% polymer weight gain
- Particles
- Tablets

30% polymer weight gain
- Particles
- Tablets

Coatings resist compression due to high flexibility!
EUDRAGIT® E PO – Colored coatings

- **Compatibility with iron oxide pigments**
- **Povidone K 25** and **Poloxamer 188** can be used to stabilize spray suspensions containing aluminum lakes
- **Moisture protective film coatings** might require higher weight gains.

Kucera and Assmus. Presented at the 2007 Meeting of the American Association of Pharmaceutical Scientists, San Antonio, TX
Applications where EUDRAGIT® E PO is combined with a pigment are especially attractive due to the pharmaceutical elegance of the final dosage form.

Lakes are formed by the precipitation and absorption of a water-soluble dye onto an insoluble substrate, such as aluminum hydroxide.

When added to polymethacrylate coating systems, it is possible for a lake to cause coagulation due to the action of the water soluble dye as strong electrolyte.
EUDRAGIT® E PO solutions were prepared and then mixed with red (E127), blue (E132), or yellow (E104) aluminum lakes in the presence of polymeric additives.

The suspensions were agitated for 10 hours via a magnetic stirplate and then passed through a 0.2 mm sieve to observe the effect of polymeric additives on coagulum content.
## Formulation

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUDRAGIT® E PO</td>
<td>7.37%</td>
</tr>
<tr>
<td>Sodium Lauryl Sulfate</td>
<td>0.74%</td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>1.10%</td>
</tr>
<tr>
<td>Talc</td>
<td>3.70%</td>
</tr>
<tr>
<td>Titanium Dioxide</td>
<td>0.74%</td>
</tr>
<tr>
<td>Aluminum Lake Pigment</td>
<td>1.10%</td>
</tr>
<tr>
<td>Stabilizing Excipient</td>
<td>0.74%</td>
</tr>
<tr>
<td>Water</td>
<td>84.50%</td>
</tr>
</tbody>
</table>

% Solids: 15.5%

Polymer Applied: 4 mg/cm²

Solids Applied: 8.4 mg/cm²
Coating Equipment

- Erweka AR400 Coating Pan
- Schlick 970/7-1 S 53 Spray Gun
- Watson-Marlow 505 S Peristaltic Pump
Coating Parameters

Inlet Air Temperature (°C): 34 ± 2
Product Temperature (°C): 26 ± 1
Atomizing Air Pressure (bars): 0.8
Pan Rotation Speed (rpm): 50
Coating Time (min): 120 ± 8
Spray Rate (g/min/kg): 3.2 ± 0.2
Placebo Tablets Coated with EUDRAGIT® E PO, 10% Kollidon® K25, and 15% Aluminum Lake
Placebo Tablets Coated with EUDRAGIT® E PO, 10% Kollidon® K25, and 15% Aluminum Lake
Placebo Tablets Coated with EUDRAGIT® E PO, 10% Kollidon® K25, and 15% Aluminum Lake
EUDRAGIT® E PO provides an effective moisture barrier coating system

Aqueous EUDRAGIT® E PO dispersions provide efficient taste masking by spray coating on tablets and particles

Coatings are flexible and coated particles may be compressed into rapidly disintegrating tablets