Characterization of Newly Developed Micronized Poloxamers for Poorly Soluble Drugs

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Poloxamers are block-copolymers consisting of Polyethylene-(POE-) and Polypropylene-(POP-) units.

Chemical composition:

![Chemical structure of Poloxamer 188 and Poloxamer 407](image)

<table>
<thead>
<tr>
<th>Pharmacopoeial name</th>
<th>a</th>
<th>b</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poloxamer 188</td>
<td>79</td>
<td>28</td>
<td>Lutrol® F 68</td>
</tr>
<tr>
<td>Poloxamer 407</td>
<td>98</td>
<td>57</td>
<td>Lutrol® F 127</td>
</tr>
</tbody>
</table>
## Lutrol® F Grades

### Brand Name
- Lutrol F68NF
- Lutrol F127NF

### Pharmacopeial Name
- Poloxamer 188
- Poloxamer 407

### Also Available
- Lutrol F87NF
- Lutrol L44NF
- Lutrol F108NF
- Poloxamer 237
- Poloxamer 124
- Poloxamer 338
Poloxamers Characteristics

The character of each poloxamer in terms of:
- molecular weight
- appearance
- hydrophilicity / hydrophobicity
- solubility

is determined by the chain length of the

AND

- polyoxyethylene-(EO-) units
- polyoxypropylene-(PO-) units
Poloxamer Grid

Molecular weight of PO-part vs. Percentage EO-part (%)
## Poloxamer grades
### Definition of Number Code

<table>
<thead>
<tr>
<th></th>
<th>M&lt;sub&gt;w&lt;/sub&gt; of PO-part</th>
<th>EO-part (Wt.%).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poloxamer 18 8</td>
<td>18 x 100 = 1800</td>
<td>8 x 10 = 80</td>
</tr>
<tr>
<td>Poloxamer 40 7</td>
<td>40 x 100 = 4000</td>
<td>7 x 10 = 70</td>
</tr>
</tbody>
</table>
Lutrol® Grid

Molecular weight

Percentage EO-part (%)

- Actives
- Excipients
- Contract Manufacturing
- Value Added
### Lutrol® F Grades Nomenclature

<table>
<thead>
<tr>
<th>Lutrol F</th>
<th>M&lt;sub&gt;w&lt;/sub&gt;</th>
<th>EO-part (Wt.%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F6 8</td>
<td>6 x 1000</td>
<td>8 x 10 = 80</td>
</tr>
<tr>
<td></td>
<td>= 6000</td>
<td></td>
</tr>
<tr>
<td>F12 7</td>
<td>12 x 1000</td>
<td>7 x 10 = 70</td>
</tr>
<tr>
<td></td>
<td>= 12000</td>
<td></td>
</tr>
</tbody>
</table>
Lutrol® F Grades
Molecular Weight

<table>
<thead>
<tr>
<th></th>
<th>Mw</th>
<th>Mn</th>
<th>(Mw/Mn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot-No. 89-0823</td>
<td>8,600</td>
<td>7,600</td>
<td>1.4</td>
</tr>
<tr>
<td>Lot-No. 87-0807</td>
<td>9,000</td>
<td>8,100</td>
<td>1.4</td>
</tr>
</tbody>
</table>
## Lutrol® F127 Molecular Weight

<table>
<thead>
<tr>
<th></th>
<th>Mw</th>
<th>Mn</th>
<th>(Mw/Mn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot-No. 41-0805</td>
<td>13,400</td>
<td>9300</td>
<td>1.4</td>
</tr>
<tr>
<td>Lot-No. 64-0806</td>
<td>13,500</td>
<td>9500</td>
<td>1.4</td>
</tr>
</tbody>
</table>
Lutrol F127
Reason for Bimodal Distribution

- The molecular weight distribution is dependant on side reactions, which occur during propylene oxide polymerization.

- During formation of POP block, a fraction of propylene oxide may be converted to allyl alcohol which will further react with PO and EO producing a polymeric material about half the molecular weight of the main product. This segment constitute the unsaturation part of Lutrol F127 (0.048 meq/gm).

- In the USP, the average molecular weight is 9840 to 14600.
Formation of Unsaturation

Unsat. in USP/NF for 407 = 0.048 ± 0.017 mEq/g
Functionality of Poloxamer 407

\[
\text{CH}_3 \\
\text{HO-} (\text{CH}_2\text{-CH}_2\text{-O})_x\text{-} (\text{CH}_2\text{-CH-O})_y\text{-} (\text{CH}_2\text{-CH}_2\text{-O})_x\text{-H}
\]

where \(x = \text{approx. } 98\) and \(y = \text{approx. } 57\)

Poloxamer is terminated with hydroxyl group - therefore further reactions will not occur (will not self polymerize)
Principle of Micellization

- Surfactant Molecule
- Polar Solvent
As a Solubilizer

Solubilization capacity of a poloxamer is believed to be dictated by the hydrophobic portion.

One theory is that in water, the poloxamer molecules arrange themselves in an “umbrella” like configuration:

![Diagram of poloxamer molecule with POP and POE groups](image)

POE Group

POP Group

One Poloxamer molecule
Limiting Aggregation Concentration

From the available literature:

• Poloxamer 188 (Lutrol F 68)  6.0  micromoles/ liter
• Poloxamer 338 (Lutrol F 108)  4.74  micromoles/ liter
• Poloxamer 407 (Lutrol F 127)*  2-3  micromoles/liter

* Estimated, no published literature.
Lutrol® F Grades
Applications

Solubilizer
Gels
Suspension Stabilizer
Melt / Spray Granulations
# Lutrol® F Grades (Poloxamers)

## Prill
- Lutrol F68 Prill
- Lutrol F127 Prill

## Microprill
- Lutrol 68*micro
- Lutrol 127* micro
- Particle Size Range
  - \( d (0.5) = 50 \text{micron} \)
  - \( d (0.9) = 90 \text{micron} \)
- *Development Product

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**Pharma Solutions**

- Actives
- Excipients
- Contract Manufacturing
- Value Added
Advantages of Microprilling

- Average particle size 50 micron
- Stronger solubilization activities
- Controlled dissolution rate
- Reduction of die-wall friction
- Achievement of homogeneous blend
- Elimination of dose dumping
- Effective water soluble lubricant
Microprill Lutrol®
Particle Size Specification

Microprill meets the following specification

- Max. 10% retain in 106 micron (#140 Screen)
- Max. 50% retain on 53 micron (#270 Screen)

- Using Alpine Air Jet Sieve Analysis

- Chemical Specification is identical to regular prill and complies with USP/NF specification
Lutrol® F68 Prill
x50 magnification

Lutrol® 68 Microprill
x500 magnification
Particle Size
Using Malvern Mastersizer 2000

Lutrol® F68 Prill

Lutrol® 68 Microprill
<table>
<thead>
<tr>
<th>Sample</th>
<th>BET Surface (m²/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutrol® F68 Lot # 55-0003</td>
<td>Not Possible</td>
</tr>
<tr>
<td>Lutrol® 68 Microprill Lot # WPNZ-664BMP</td>
<td>0.18</td>
</tr>
<tr>
<td>Material</td>
<td>Bulk Density (g/cm³)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Lutrol® F68 Prill Lot # WPDX-577B</td>
<td>0.56</td>
</tr>
<tr>
<td>Lutrol® 68 Microprill Lot # WPNZ-664BMP</td>
<td>0.52</td>
</tr>
</tbody>
</table>
### Melt Viscosity

<table>
<thead>
<tr>
<th>Viscosity (cps)</th>
<th>F68 Prill</th>
<th>68 Microprill</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>807</td>
<td>730</td>
</tr>
<tr>
<td>Stabilized</td>
<td>783</td>
<td>720</td>
</tr>
</tbody>
</table>

**Equipment:** Brookfield RVT-DVII with Thermoseal & Temperature Controller  
Temperature Set and Maintained at 80°C, Spindle #27
### Molecular Weight Distribution (GPC)

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>Mn</th>
<th>Mw</th>
<th>MP</th>
<th>Polydispersity</th>
<th>% Area</th>
<th>Area</th>
<th>Retention Time</th>
<th>Project #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutrol® F68 Microprill WPNZ-664BMP (microprill) Date Acquired 10/18/04 9:05:37 AM</td>
<td>8611</td>
<td>9332</td>
<td>9956</td>
<td>1.083755</td>
<td>100.0</td>
<td>2861502</td>
<td>18.411</td>
<td>2S011</td>
</tr>
<tr>
<td>Lutrol® F68 Prill – WPOZ-551BK4 (normal prill) Date Acquired 10/18/04 10:45:31 AM</td>
<td>8809</td>
<td>9656</td>
<td>10288</td>
<td>1.096190</td>
<td>100.0</td>
<td>3711903</td>
<td>18.356</td>
<td>2S011</td>
</tr>
</tbody>
</table>

The diagram shows the Molecular Weight Distribution (GPC) with retention time ranging from 15.00 to 30.00 minutes. The peak at around 18.00 minutes indicates the area of interest for the sample analysis.
### Differential Scanning Calorimetric Data

<table>
<thead>
<tr>
<th>Material</th>
<th>To</th>
<th>Tp</th>
<th>ΔH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutrol® F68 Prill</td>
<td>48.9</td>
<td>51.6</td>
<td>121.7</td>
</tr>
<tr>
<td>Lutrol® 68 Microprill</td>
<td>50.1</td>
<td>52.4</td>
<td>121.7</td>
</tr>
</tbody>
</table>

*To = Extrapolated onset of melting endotherm in °C*

*Tp = Peak of melting endotherm in °C*

*ΔH = Enthalpy of melting endotherm in joules/gram*
DSC

Lutrol® F68 Prill

![DSC graph for Lutrol® F68 Prill]

Lutrol® 68 Microprill

![DSC graph for Lutrol® 68 Microprill]
X-Ray Diffraction

- Lutrol® F68 Prill
- Lutrol® 68 Microprill
Case Study – Effects of micronized poloxamers on poorly water soluble drugs
## Formulations

<table>
<thead>
<tr>
<th>Material</th>
<th>Formulation A (%)</th>
<th>Formulation B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>5.0</td>
<td>-</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>-</td>
<td>5.0</td>
</tr>
<tr>
<td>Lutrol micro®</td>
<td>5.0, 25.0, 50.0</td>
<td>25.0, 50.0</td>
</tr>
<tr>
<td>Di-calcium Phosphate</td>
<td>79.0, 69.0, 59.0, 34.0</td>
<td>-</td>
</tr>
<tr>
<td>Calcium Carbonate 90A</td>
<td>-</td>
<td>59.0, 34.0</td>
</tr>
<tr>
<td>Kollidon CL</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Aerosil 200</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Ibuprofen Capsule Data

Capsules containing Ibuprofen and Lutrol® 127 Micro

% Drug Release

Time (Hrs)

Capsules containing Ibuprofen and Lutrol® 127 Micro

Dissolution Media pH 4.5 buffer
HPLC Column 5µm C18 150mm x 39mm
Mobile Phase: H2O:Acetonitrile (40:60)
Ibuprofen Tablet Data

Tablets containing Ibuprofen and Lutrol® 127 Micro

% Drug Release

Time (hrs)

Dissolution Media pH 4.5 buffer
HPLC Column 5µm C18 150mm x 39mm
Mobile Phase: H2O:Acetonitrile (40:60)
Ibuprofen and Lutrol® F127 Prill vs. Micro grades (1:10)

Ibuprofen tablets containing Lutrol 127 Prill and Micro grades

% Drug Release

0 1 2 3 4 5

0 20 40 60 80 100 120

Time (hrs)

Dissolution Media pH 4.5 buffer
HPLC Column 5µm C18 150mm x 39mm
Mobile Phase: H2O:Acetonitrile (40:60)
Conclusion For Ibuprofen

- The addition of Lutrol® 127 micro improved the dissolution of Ibuprofen

- Tablets showed a greater improvement in dissolution compared to capsules

- The thermoreversible gelling effect, along with the smaller particle size of Lutrol 127 micro gave a controlled release profile
Carbamazepine Formulations Process

- Dissolution studies with tablets via direct compression and solid dispersion were evaluated
- Regular prill used for Solid dispersion and Microprill for Direct Compression
- Tablets compressed using 9.5mm round flat face bevel edge tooling
- Target weight 400mg, target hardness 4-5Kp
- Using Carbamazepine as a model drug, due to its limited solubility in water – dissolution studies were carried out using a co-solvent of water and ethanol (70:30)
Carbamazepine and Lutrol® 127
1:5 ratio

Carbamazepine and Lutrol 127 micro 1:5 Ratio

Dissolution Media 70:30 Ethanol:Water  
HPLC Column 5μm CN 250mm x 4.6mm  
Mobile Phase: H2O:MeOH:THF (85:12:3)
Carbamazepine and Lutrol® 127
1:10 ratio

Carbamazepine and Lutrol 127 micro 1:10 Ratio

Dissolution Media 70:30 Ethanol:Water
HPLC Column 5µm CN 250mm x 4.6mm
Mobile Phase: H2O:MeOH:THF (85:12:3)
Carbamazepine and Lutrol® 68
1:5 ratio

Carbamazepine and Lutrol 68 micro 1:5 Ratio

Dissolution Media 70:30 Ethanol:Water
HPLC Column 5µm CN 250mm x 4.6mm
Mobile Phase: H2O:MeOH:THF (85:12:3)

- Actives
- Excipients
- Contract Manufacturing
- Value Added
Carbamazepine and Lutrol® 68
1:10 ratio

Dissolution Media: 70:30 Ethanol:Water
HPLC Column: 5µm CN 250mm x 4.6mm
Mobile Phase: H2O:MeOH:THF (85:12:3)
Conclusions For Carbamazepine

- Both Lutrol® 68 micro and Lutrol 127 micro improved the dissolution of Carbamazepine

- Solid dispersion techniques appeared to provide incomplete release of Carbamazepine
Case Study 2
Comparing different granulation techniques
Formulation and Process

- Made Carbamazepine tablets using different granulation techniques:
  - Direct Compression
  - Wet Granulation
  - Melt Granulation

- Two ratios evaluated: 1:3 and 1:5 (Drug: Poloxamer)
- **Microprill was used only in Direct Compression**

- Tablets compressed at 400mg, target hardness 5-7Kp
Lutrol® 68 micro
1:5 ratio

Carbamazepine and Lutrol 68 1:5 Ratio

% Drug Release

Time (Hrs)

Direct Compression
Melt Granulation
Wet Granulation
Control

Actives
Excipients
Contract Manufacturing
Value Added
Lutrol® 127 micro
1:3 ratio

Carbamazepine and Lutrol 127 1:3 Ratio
Carbamazepine and Lutrol 127 1:5 Ratio

% Drug Release

Time (Hrs)

Direct Compression
Wet Granulation
Melt Granulation
Control
Lutrol® 127 micro
Dissolution

Comparing 1:5 and 1:3 ratio Lutrol 127 direct compression tablet
Conclusions

- Use of poloxamers, regardless of granulation technique, improved the solubility of Carbamazepine.
- Higher levels of poloxamer create a greater binding effect, which has an impact on dissolution.
- Microprilled Poloxamers exhibit good blend homogeneity and eliminate the segregation problem during direct compression.
- The gelling characteristic of microprilled Poloxamer 407 can be used for controlled release or other drug delivery technology.
- Microprill poloxamer can be a good candidate as a water soluble lubricant for effervescent tablets.
ARE THERE ANY QUESTIONS ????
Ibuprofen Formulations Process

- Dissolution studies with capsules and tablets were evaluated

- Tablets compressed using 11mm round flat face bevel edge tooling

- Target weight 800mg, target hardness 4-5Kp

- Using Ibuprofen as a model drug – dissolution studies were carried out at pH 4.5 (where Ibuprofen has limited solubility)