Continuous Granulation
Using a Twin-Screw Extruder

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What is a twin screw extruder and how to use it for continuous granulation?

Dry feed: blend or feed by separate feeders

Liquid feed: binder solution

Barrel temperature individually controlled

Understand the modular design in screw configuration to meet process needs
Batch Granulation vs. Continuous Granulation

- More streamlined and efficient process
- Significantly reduced cost, resource and time related to scale up for product launch
- Less material handling
- More robust process and improved product quality
Case Study: Feasibility and Process Evaluation of Wet and Melt Granulation for Manufacturing Extended Release Matrix Tablets Using a Twin-Screw Extruder
Drug substances are homogeneously mixed with hydrophilic rate-controlling materials

Rate-controlling materials

- Non-ionic soluble cellulose ethers: HPMC, HPC, HEC
- Non-ionic homopolymers of ethylene oxide: polyox
- Others: water-insoluble natural gums, Carbopol®, Kollidon SR, cross-linked high amylose starch, Eudragit L30D, FS30D

Common manufacturing process

- Granulation
- Direct compression

Extended-Release Hydrophilic Matrices

Ingestion of Tablet (as is or in capsule)

Hydration, gel formation, continued water ingression, expansion of gel layer/polymer dissolution, drug release controlled by diffusion and erosion

Complete hydration, continued tablet erosion and drug release

Dry core

Complete drug release and tablet erosion

Dry core
Model Drug Compound

- Commercial products manufactured using high-shear wet granulation (> 15 yrs)
- High drug-loading: up to 50%
- Matrix polymer: HPMC K100LV
- High m.p. ~ 200 °C, thermally stable
- High-shear wet granulation
  - water/powders = ~35% (w/w)
  - Batch size: 1 ton (1,000,000 tablets)

8-12 granulation sub-batches
Continuous Melt Granulation

- Dry feed: blend or feed by separate feeders. Binder can also be fed in a powder form.
- Pre-melted binder solution.
- No drying is needed.
- Barrel heated to maintain the binder in molten state.
- Understand the modular design in screw configuration to meet process needs.
Plasticizer Selection for HPMC

- HPMC
  - Commonly used polymer in hydrophilic matrices
  - High Tg (182 °C)

- Multiple plasticizer evaluated
  - Propylene glycol
  - Glycerin
  - Triethyl citrate
  - TPGS
  - Stearic acid

- Differential scanning calorimetry (DSC) used for selection of plasticizer
Stearic acid was found to be miscible with HPMC and can effectively decrease the Tg of HPMC.

Phase separation observed when stearic acid is ~ 20%.
Continuous Melt Granulation Results

- IVIVR based method: *USP II, 0.05M phosphate buffer, pH 6.0, 75 rpm*
- Stearic acid accelerated *in vitro* drug release
  - *Possible effect on polymer hydration/gelation*
- Release mechanism: erosion controlled
- Uniform sieve cut potency

![Graph showing cumulative release over time for different formulations and mesh sizes.](image-url)

- F1 (SA 2.2%)
- F2 (SA 4.4%)
- Control (BioLot)

- >40 mesh: Potency 70.7%
- <40 mesh: Potency 68.6%
Continuous Wet Granulation

- Dry feed: blend or feed by separate feeders
- Binder can also be fed in a powder form
- Multiple locations for injection of binder solution or water
- Barrel not heated
- More efficient Drying

Understand the modular design in screw configuration to meet process needs
Study Variables and Responses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Granule</th>
<th>Blend</th>
<th>Tablet</th>
</tr>
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<tbody>
<tr>
<td>Solid Feed Rate</td>
<td>Granule Size</td>
<td>PSD</td>
<td>Solid Fraction</td>
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<tr>
<td>Barrel Temp.</td>
<td>Granule Strength</td>
<td>Powder Density</td>
<td>Hardness</td>
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<tr>
<td>Screw Config.</td>
<td></td>
<td></td>
<td>Dissolution</td>
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<td>Screw Speed</td>
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<td></td>
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</tr>
<tr>
<td>Liquid Feed Rate</td>
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<tr>
<td>Liquid Injection Position</td>
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</tbody>
</table>
Screw Configurations and Injection Positions

Screw configuration

<table>
<thead>
<tr>
<th>#</th>
<th>Configuration</th>
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</thead>
<tbody>
<tr>
<td>#1</td>
<td>7 x SE24/24 + 7 x SE16/16 + 1 x KB45/5/8(LH) + 1 x KB45/5/8 + 5 x SE24/24 + 1 x SE 16/16</td>
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<tr>
<td>#2</td>
<td>7 x SE24/24 + 7 x SE16/16 + 2 x KB45/5/8(LH) + 2 x KB45/5/8 + 5 x SE24/24</td>
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<tr>
<td>#3</td>
<td>7 x SE24/24 + 7 x SE16/16 + 1 x KB45/5/16 + 5 x SE24/24 + 1 x SE 16/16</td>
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<tr>
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<tr>
<td>#5</td>
<td>7 x SE24/24 + 7 x SE16/16 + 1 x KB45/5/8(LH) + 1 x KB45/5/8 + 3 x SE24/24 + 1 x KB45/5/8(LH) + 1 x KB45/5/8 + 2 x SE24/24</td>
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</table>

Solid feed rate: 1kg/hr

Barrel Temp.: Zone 1-6 @25°C

5 liquid feed rates (0.09-0.582kg/hr) and 4 liquid injection positions

3 screw speeds (120-300rpm)
**Process Impact on Granule and Milled Granule Particle Size**

<table>
<thead>
<tr>
<th>Liquid/Solid (w/w)</th>
<th>Wet granules</th>
</tr>
</thead>
</table>
| 0.582             | ![Granule Image] | liquid% ↑ → wetter → larger granules  
| 0.432             | ![Granule Image] | Screw speed ↑ → smaller granules  
| 0.282             | ![Granule Image] | Less aggressive kneading → smaller granules  
| 0.132             | ![Granule Image] | Milling of granules  
| 0.09              | ![Granule Image] |  
| **Note:** Screw config. #1, 120RPM, Liquid injection position 3-1 |  

Milled granule particle size is not significantly affected by changing other process parameters though observed.
Process Impact on Granule Strength

- Granules strength

Dry granules

- Sieve 1000µm
- Sieve 600µm

- liquid%↑ → granules strength ↑
- Granule strength is similar when other process parameters are changed.
Process Impact on Tablet Porosity and Tablet Strength
Process Impact on Tablet Dissolution

• *In-vitro* drug release
  - Comparable drug release to the bioilot can be obtained
  - Fast release observed for granule with higher L/S ratios

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<tr>
<th>L/S</th>
<th>f2 factor</th>
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Biolot L/S ratio ≈ 35% (w/w)
L/S ratio by wet granulation = 9~28.2% (w/w)

*Lower amount of water required in granulation*
Similar *in-vitro* drug release observed at different screw speeds and liquid injection positions.
Process Impact on Tablet Dissolution

- Similar *in-vitro* drug release observed at different screw configurations.
More Efficient Drying

- Moisture content in wet granules

- Shorter drying cycle due to lower moisture content in the granule
Summary of Case Study

• Melt or wet granulation via extrusion has been shown to be feasible for manufacturing of ER hydrophilic matrix tablets.

• Similar in-vitro drug release can be obtained from tablets manufactured by the extruder and the high-shear granulator.

• Granule size distribution may be altered by varying parameter settings of the extruder.

• The in-vitro drug release, particle size distribution of milled granules and tablet properties are insensitive to screw configuration, screw speed and liquid injection position.
Conclusions

• Granulation through extrusion offers an opportunity for continuous granulation and produces granules with more consistent characteristics and uniformity.

• Continuous granulation offers advantages of efficient modification of API properties, enhanced process control, more efficient scale-up, more robust process and higher throughput.

• Significantly less water can be used in the continuous wet granulation process compared to the high shear wet granulation process, which provides the potential for a shorter drying cycle or potential for eliminating the drying unit operation
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