Extrusion - Spheronization
Pharmaceutical Applications
There are many solid dosage forms......

Why pellets?
Two Ways to Make Drug Pellets

Drug Layering (DL) vs. Extrusion-Spheronization (ES)
Pellets by DL

Inert Spherical Core (non-pareils, MCC, etc)

Drug Layer

Control Release Polymer

Protective Coating
Pellets by Extrusion Spheronization

1. Drug
2. Mixing
3. Extrusion
4. Spheronization
Choosing DL vs. ES

Generally used for low API pellets
- Processing in Fluid Bed dryer/Coater
- Slow process due to multiple layers
- Single pot processing

Generally used for high API pellets
- API, excipients, MR polymers in core
- Fast process; high quantities
- Ideal for matrix pellets
- Multi-step process
Why Pellets?

Physical Advantages

- Improved flow properties
Why Pellets?

Physical Advantages

- Improved flow properties
- Narrow particle size distribution
Why Pellets?

Physical Advantages

• Improved flow properties
• Narrow particle size distribution
• Smooth, coatable surface
Physical Advantages

- Improved flow properties
- Narrow particle size distribution
- Smooth, coatable surface
- Low friability
Why Pellets?

Physical Advantages

• Improved flow properties
• Narrow particle size distribution
• Smooth, coatable surface
• Low friability

• Uniform packing characteristics
Why Pellets?

Therapeutic Advantages

- High drug loading (ES)

FAST FACTS

- API incorporated in the core
- ES Pellets with 90% API are possible
- High API = Less frequent drug administration
Why Pellets?

**Therapeutic Advantages**

- High drug loading (ES)
- **Modified drug release (ES)**

**FAST FACTS**

- Modified release excipients can be incorporated into the drug core
- May minimize (eliminate) the need for further coating
Why Pellets?

Therapeutic Advantages

- High drug loading (ES)
- Modified drug release (ES)

- **Disperse-freely in GI Tract**
  - Minimizing dose dumping
  - Avoiding high local concentration of drug

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GI Tract  TABLET  vs
Why Pellets?

Therapeutic Advantages

- High drug loading (ES)
- Modified drug release (ES)
- Disperse-freely in GI Tract
  - Minimizing dose dumping
  - Avoiding high local concentration of drug

- Maximum drug absorption
  - Minimum peak plasma fluctuations

GI Tract
Why Pellets?

Therapeutic Advantages

• High drug loading (ES)
• Modified drug release (ES)
• Disperse-freely in GI Tract
  o Minimizing dose dumping
  o Avoiding high local concentration of drug
• Maximum drug absorption
  o Minimum peak plasma fluctuations

• Combination of incompatible API’s
Formulations for Extrusion Spheronization
Components of ES Formulations

**Primary Components**

- Active Ingredient(s)
- Extrusion/Spheronization Aid
- Water (or solvent)

**Secondary Components**

- Binders (natural and synthetic)
- Modified Release Excipients (CR, DR, ER, etc)
- Fillers/Diluents
- Disintegrants
Extrusion/Spheronization Aid

### FAST FACTS
- 15-20% minimum
- Higher levels improve ES process
- MCC acts as a sponge; absorbs and evenly distributes moisture creating a homogenous wet mass

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Trade Name/Grade</th>
<th>Particle Size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMC BioPolymer</td>
<td>Avicel™ PH-101</td>
<td>50</td>
</tr>
<tr>
<td>JRS Pharma</td>
<td>Vivapur® 101, Emcocel® 50M</td>
<td>65</td>
</tr>
<tr>
<td>Blanver</td>
<td>Microcel MC 101</td>
<td>50</td>
</tr>
</tbody>
</table>
### Binders (Natural and Synthetic)

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Trade Names</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxypropylcellulose (HPC)</td>
<td>Klucel®</td>
<td>Synthetic polymer</td>
</tr>
<tr>
<td>Hydroxypropylmethyl Cellulose (HPMC)</td>
<td>Methocel™</td>
<td>Synthetic polymer</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone (PVP)</td>
<td>Kollidon®, Povidone®</td>
<td>Synthetic polymer</td>
</tr>
<tr>
<td>Pregelatinized Starch</td>
<td>Starch® 1500</td>
<td>Natural polymer</td>
</tr>
<tr>
<td>Ethylcellulose (EC)</td>
<td>Ethocel™</td>
<td>Synthetic polymer</td>
</tr>
</tbody>
</table>

**FAST FACTS**

- 2 – 5 % typically
- Stronger extrudates; less fines; higher overall process yield
## Modified Release Excipients

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Trade Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxypropylmethyl Cellulose (HPMC)</td>
<td>Methocel™ CR</td>
<td>Synthetic polymer</td>
</tr>
<tr>
<td>Ethylcellulose (EC)</td>
<td>Ethocel™</td>
<td>Synthetic polymer</td>
</tr>
<tr>
<td></td>
<td>Aqualon® T10</td>
<td></td>
</tr>
<tr>
<td>Acrylic Polymers</td>
<td>Eudragit RL</td>
<td>Synthetic polymers</td>
</tr>
<tr>
<td></td>
<td>Eugradit RS</td>
<td></td>
</tr>
<tr>
<td>Hydroxypropylcellulose (HPC)</td>
<td>Klucel® HXF</td>
<td>Synthetic polymer</td>
</tr>
<tr>
<td>Hydroxyethylcellulose (HEC)</td>
<td>Natrosol® HHX</td>
<td>Synthetic polymer</td>
</tr>
<tr>
<td></td>
<td>Natrosol® HX</td>
<td></td>
</tr>
</tbody>
</table>

**FAST FACTS**

- Integrated directly into wet granulation step
- Added as a solid or a solution (depends on excipient)
# Fillers/Diluents

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose Monohydrate</td>
<td>Sugar</td>
</tr>
<tr>
<td>Maltodextrins</td>
<td>Saccharide polymers</td>
</tr>
<tr>
<td>Mannitol, Sorbitol, Xylitol</td>
<td>Compressible sugars</td>
</tr>
<tr>
<td>Dicalcium Phosphate Trihydrate</td>
<td>Salt</td>
</tr>
<tr>
<td>Pregelatenized Starch</td>
<td>Natural Polymer</td>
</tr>
</tbody>
</table>

**FAST FACTS**

- Bulking agents
- % in formulation depends on API and MCC levels
## Superdisintegrants

**FAST FACTS**
- 1% or less
- May be needed to counteract effects of binder addition

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Trade Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-linked Polyvinylpyrrolidone</td>
<td>Kollidon® CL, Crosspovidone®</td>
<td>Synthetic polymer</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>Primojel®</td>
<td>Synthetic polymer</td>
</tr>
<tr>
<td></td>
<td>Explotab®</td>
<td></td>
</tr>
<tr>
<td>Sodium Croscarmellose</td>
<td>Primellose®</td>
<td>Synthetic polymer</td>
</tr>
<tr>
<td></td>
<td>AcDisol®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vivasol®</td>
<td></td>
</tr>
</tbody>
</table>
Formulation Example 1

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Percentage</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem HCl</td>
<td>40%</td>
<td>API (high solubility)</td>
</tr>
<tr>
<td>MCC (50µ)</td>
<td>30%</td>
<td>ES Aid</td>
</tr>
<tr>
<td>L-HPC 20</td>
<td>30%</td>
<td>Filler</td>
</tr>
<tr>
<td>Moisture Content</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>Final Product</td>
<td>1.0 mm pellets</td>
<td></td>
</tr>
</tbody>
</table>
## Formulation Example 2

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Percentage</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpheniramine</td>
<td>50%</td>
<td>API (high solubility)</td>
</tr>
<tr>
<td>MCC (50µ)</td>
<td>40%</td>
<td>ES Aid</td>
</tr>
<tr>
<td>Pregelatinized Starch</td>
<td>3.8%</td>
<td>Binder</td>
</tr>
<tr>
<td>Ethyl Cellulose</td>
<td>6.2%</td>
<td>Modified Release</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moisture Content</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Final Product</td>
<td>1.2 mm MR pellets</td>
<td></td>
</tr>
</tbody>
</table>
### Formulation Example 3

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Percentage</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>39%</td>
<td>API (low solubility)</td>
</tr>
<tr>
<td>MCC (50µ)</td>
<td>60%</td>
<td>ES Aid</td>
</tr>
<tr>
<td>Povidone K90</td>
<td>1%</td>
<td>Binder</td>
</tr>
<tr>
<td>Moisture Content</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td><strong>Final Product</strong></td>
<td>1.0 mm pellets</td>
<td></td>
</tr>
</tbody>
</table>
The Extrusion Spheronization Process
Mixing

1. Mixing
2. Extrusion
3. Spheronization
4. Drying/Coating
Production Mixers

FAST FACTS

- Most often used in production
- Top or bottom driven

High Shear Granulators (HSG)
Mixing Variables

GOAL

- A wet, homogenous mass
- Soft wet mass, but still needs to hold its shape under low pressure
- Enough gliding properties to enable low pressure extrusion

**Liquid Addition Rate**

- **Minimize** addition time
- Longer rates = higher density

**Mixing Speed/Intensity**

- **Lower** chopper/impeller speeds
- Higher speeds = higher density

**Massing Time**

- **Minimize**; No need to fully granulate
- Longer massing time = higher density
Extrusion

1. Mixing
2. Extrusion
3. Spheronization
4. Drying/Coating
**Terminology**

**Extrudates**
- Particles produced by an extruder
- Mostly cylindrical in shape

**Pellets**
- Cylindrical particles or spheres
- Term is used interchangeably

**Beads**
- Spheres produced by a spheronizing device
- Inert cores (Nonpareils, or MCC)
- Other terms: beadlets, marumes, spheroids
Dome Extrusion

Dome  Axial

Radial  Basket
Twin Dome Extruder Schematic

FAST FACTS

- Twin screw
- Short residence time
- Plug Flow (1st in, 1st out)
- Consistent pressure profile across the die
- Adjustable extrusion gap
- High capacity
- Simple to operate
Twin Dome Video
Extrusion Variables

**GOAL**

To Produce Extrudates Suitable for Spheronization

- NOTE: Variables apply to Dome, Radial, and Basket extrusion

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### Moisture Content

- Higher moisture = Higher extrusion rate
- Higher moisture = Longer extrudates
- Higher moisture = Less work, pressure, temperature, power
- Excessive moisture = Secondary agglomeration (extruder & spheronizer)

### Extrusion Gap

- Smaller gap = Less compaction
- Smaller gap = Little to no heat generation
- Smaller gap = Less build-up and hardening of material

### Die Hole Diameter

- Larger Diameter = Higher extrusion rate
- Larger Diameter = Softer extrudates (less compaction)

### Die Thickness

- Thicker Die = Harder extrudates (more compaction)
Spheronization

1. Mixing
2. Extrusion
3. Spheronization
4. Drying/Coating
Spheronization Mechanisms

**Mechanism 1**

**Mechanism 2**
Spheronizer in Operation Video
Mechanism of Spheronization

3 Types of Collisions

1. Particles with Plate
2. Particles with Wall
3. Inter-particle

> Tumbling action
> Twisting Rope

- Tumbling action
- Twisting Rope
Friction Plate Designs

2 mm CH plate

3 mm CH plate

5 mm CH plate

Radial plate
**Spheronization Variables**

**GOAL**

- To produce the most spherical product (aspect ratio closest to 1.0)
- Narrow Particle Size Distribution (PSD)
- Product densification

**Friction Plate Speed**
- Affects product sphericity (shape)
- Affects product density

**Processing Time**
- Affects product sphericity
- Affects PSD

**Moisture Content**
- Proper level required for strength, product pliability
- Excessive level can cause larger spheres; secondary agglomeration
- Affects sphericity (shape)
- Affects product porosity

**Friction Plate Configuration**
- Impart more energy, stronger collisions
- Can produce more fines
Drying/Coating

1. Mixing
2. Extrusion
3. Spheronization
4. Drying/Coating
Drying/Coating

Fluid Bed Dryers/Coaters

Bottom Spray for coating
Temperature Rise in Process

- **Mixing**: 2° - 8°F
- **Extrusion**: 2° - 15°F
- **Spheronization**: 2° - 6°F
- **Drying/Coating**: MINIMAL
Continuous Drug Pelleting Systems
LCI Continuous Drug Pelleting System
(Shown with Radial Extruder)
Laboratory Equipment
MG-55 Multi Granulator

FAST FACTS

• 15-20 kg/hr extrusion rate

• Easily converts into a dome, radial or axial extruder
QJ-230T Marumerizer

FAST FACTS

• 230 mm diameter friction plate
• 1 liter nominal batch size
• Manual discharge
• Laboratory
FAST FACTS

- 5 liters vessel
- 25 g – 5 kg batches
- 2 kW electric heater
- 11-78 cfm air blower
- Temperature/Humidity probe
- Maximum Temperature: 200°C
- Programmable
Conclusion
Final Dosage Examples

Capsules

- CR/SR coated pellets
- DR coated pellets (e.g. enteric)
- MR coated pellets (e.g. pulsatile)
- Matrix pellets (coated or uncoated)
- Multi-Particulates

Tablets

- Disintegrating tables (made of coated pellets)

Sachets

- Sprinkle Drugs (taste masked pellets for pediatric/geriatric drugs)
### Commonly Pelleted Drugs

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>Ibuprofen</td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Ketoprofen</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Propranolol HCl</td>
<td>Acetaminophen</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Diltiazem HCl</td>
<td>Hydrochlorothiazide</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Venlafaxine HCl</td>
<td>Diphenhydramine</td>
</tr>
</tbody>
</table>
Recommended Publications

1. Influence of material characteristics on the extrusion and spheroidization behavior of wet mass. M. Gill, J. Huang, K. Chow: GSK, Patheon and University of Toronto.


Questions
LCI GRANULATION TEAM

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