Microparticles as Controlled Release Drug Delivery Systems

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Introductions

• Located in Bethlehem, PA, ~50,000 sq ft integrated facility, 90+ employees
• Full service CDMO including commercial production and traditional CMC services
• Wide range of dosage forms, specialize in complexity
• 7,000+ sq. ft. of GMP production suites: sterile, non-sterile, and high potency
• FDA registered, DEA licensed
Agenda: Microparticles as Controlled Release Drug Delivery Systems

- What are microparticles?
- Why choose microparticles?
- Commercial microparticulate products
- Methods of preparation
- Preparation considerations
- Particle Sciences’ microparticle capabilities
What Are Microparticles?
Microparticle Drug Delivery Systems Can Align with Important Goals

- Controlled release from single injection-tunable duration of efficacy
- Biodegradable/biocompatible GRAS carrier materials
- Small molecules and biologics
- Range of loading capability
- Delivery of water soluble or insoluble products
Why Choose Microparticles?

- Protect unstable drugs
  - Before and after administration
- Provide accurate delivery of small quantities of potent drugs
- Provide ability to manipulate:
  - pK profile
  - Cellular and tissue interactions
  - *In vivo* action of drugs
- Enable controlled release
Microparticle Advantages

- Improved Safety
- Improved Patient Compliance
- Improved Efficacy
- Improved Patient Compliance
- Improved Outcomes
- Life Cycle Management
- Cost Reduction

Why MPs?

Sustained and Controlled delivery of an active over long periods of time
Microparticle Advantages

• Effective delivery of insoluble actives
• Bolus delivery instead slower IV administration
• Targeted drug delivery to specific sites
• Reduction of dose frequency and toxicity
• Ability to maintain drug in amorphous form
• Reduction of local side effects
• Maintenance of therapeutic plasma concentrations
# Examples of FDA-Approved Microparticulate Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Active Ingredient</th>
<th>Route of Administration</th>
<th>Approval Date</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vivitrol® by Alkermes</strong></td>
<td>Naltrexone</td>
<td>Intramuscular</td>
<td>1984</td>
<td>Indicated for the treatment of alcohol/opioid dependence</td>
</tr>
<tr>
<td><strong>Sandostatin® LAR Depot by Novartis</strong></td>
<td>Octreotide</td>
<td>Subcutaneous</td>
<td>1998</td>
<td>Indicated for treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors and VIP-secreting tumors</td>
</tr>
<tr>
<td><strong>Arestin® by OraPharma</strong></td>
<td>Minocycline HCl</td>
<td>Periodontal</td>
<td>2001</td>
<td>Indicated as an adjunct to scaling and root planing (SRP) procedures for reduction of pocket depth in patients with adult periodontitis</td>
</tr>
<tr>
<td><strong>Risperdal Consta® by Janssen</strong></td>
<td>Risperidone</td>
<td>Intramuscular</td>
<td>2003</td>
<td>Indicated for the treatment of schizophrenia and bipolar I disorder</td>
</tr>
<tr>
<td><strong>Lupron Depotstin® by AbbVie</strong></td>
<td>Leuprolide acetate</td>
<td>Intramuscular</td>
<td>1989</td>
<td>Multiple indications including prostate cancer, central precocious puberty, fibroids and endometriosis</td>
</tr>
</tbody>
</table>

## Dosing Frequency

- **Vivitrol® by Alkermes**: Every 4 weeks
- **Sandostatin® LAR Depot by Novartis**: Every 4 weeks
- **Arestin® by OraPharma**: Variable
- **Risperdal Consta® by Janssen**: Every 2 weeks
- **Lupron Depotstin® by AbbVie**: Every 1, 3 or 6 months
Methods of Preparation

Preparation of Microparticles via Emulsion

- Distilled Water Emulsifiers
- Drug + Polymer + Solvent
- Stirring
- High Shear Mixer
- O/W Emulsion
- Solvent Evaporation or Extraction
- Microparticle Suspension Ready for Additional Processing
- Drug Loaded Microparticles

Spray Drying

- Feed
- Gas (in)
- Drying Chamber
- Gas (out)
- Cyclone
- Powder Product
Methods of Preparation

Jet Milling

Augmented Drip Casting

Compressed Grind Air or Gas

Grinding Chamber

Micronized Product Outlet

Feeder
Preparation Considerations

Water Insoluble API

Water Soluble API

Liquid / Solution Encapsulation

Solid Encapsulation

Water Immiscible Solvent

Emulsion-Solvent Evaporation
Emulsion-Solvent Extraction
Spray Drying

Water Miscible Solvent

Coacervation/Phase Separation
Spray Drying

Washing
Filtration
Drying/Lyophilization
Sterilization
Resuspension for Dosing
Over 20 microparticle formulations in development at PSI over past 18 months from R&D through clinical production
PSI Processing Capabilities

Buchi

Retsch

Microfluidics

Buchi

Sturtevant
When it comes to microparticulate formulations, Particle Sciences has the:

**Equipment**
- Fully equipped for development services and moving into commercial-scale equipment

**Facilities**
- 7,000+ sq. ft. of GMP production suites to accommodate 1 - 2 kg commercial batches

**Personnel**
- Decades of cumulative experience formulating and manufacturing microparticulate formulations
Concept to Commercialization

We Deliver®