First Commercial Injectable Microparticle Product

Launched 1986

Evonik photo
Lupron Depot® – Microparticles

Blockbuster product
• Launched 1989
• 1-, 3-, 4-, 6-month formulations (vials)
• Dual chamber syringe (1-month)
• 7.5 mg / month leuprolide (highly potent peptide)

Intramuscular injection
Treatment – prostate cancer

www.lupronprostatecancer.com
Complex Parenteral Products
Extended-Release Microparticle Products
Propel™ – Drug-Eluting Device

• Approved 2011
• 1 month formulation
• Device self-retaining against mucosa
• Mometasone fluroate (370 μg)
  • Anti-inflammatory drug substance
  • Steroid coated on device surface
• Local delivery – inserted into sinus cavity after functional endoscopic sinus surgery

(surgeon compresses implant in delivery system just before use)
Complex Parenteral Products
Extended-Release Implants and Other Products

www.preciolandia.com
www.allergan.com
www.intersectENT.com
www.merck-animal-health-usa.com
www.vascular.abbott.com
www.beefmagazine.com
www.medhelp.org

6 Complex Parenteral Products  May 2017 | Dr. Tom Tice | Copyright Evonik
### Extended-Release Lactide/Glycolide Products

<table>
<thead>
<tr>
<th>Product name</th>
<th>Dosage Form</th>
<th>Distributor</th>
<th>Active</th>
<th>OEB</th>
<th>Duration, months</th>
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<tr>
<td>Decapeptyl®</td>
<td>Microparticle</td>
<td>Ferring</td>
<td>Triptorelin acetate</td>
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* Duration of efficacy
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Edge Therapeutics local delivery for neurosurgical clipping in brain

- Nimodipine – PLG microparticles suspended in hyaluronic acid carrier
- Applied directly to the injury site (intracisternally) during surgical clipping to secure the bleeding aneurysm
- The highly viscous microparticle suspension (gel) stays at the surface of the vessel and prevents delayed cerebral ischemia
- Provides consistent and therapeutic concentrations of nimodipine over 14 days
- Positive clinical outcomes
Poly(lactide-co-glycolide) Synthesis

Resorbs by hydrolysis to lactic acid and glycolic acid
and eventually to carbon dioxide and water
Resorption of Lactide/Glycolide Polymers

- Resorption of poly(DL-lactide-co-glycolide) microparticles in rats
  (polymer inherent viscosity of ~ 0.7 dL/g)
Generic Degradation Path
PLG Polymer Flexibility

Composition      Molecular Weight      Initiator Type      Microstructure

Tailoring Polymers to Control Properties

Mechanical Properties      Degradation Rate      Solubility      Water Uptake      Release Profile
PLG Polymer Flexibility – property relationships

Tailoring Polymers to Control Properties

- Composition
  - • Residual solvent
  - • Stability towards peptide chemistry
- Molecular Weight
  - • Encapsulation efficiency
  - • Strength towards osmotic pressure
  - • Rate of molecular weight decrease
- Initiator Type
- Microstructure
  - • Glass transition temperature above body temperature and PLG microparticle storage
  - • Free flowing powder
- Mechanical Properties
  - • Polymer blends molecular weights lactide/glycolide end groups
- Degradation Rate
- Polymer Solubility
  - • Peptide loading
  - • Injection volume
  - • Amount of PLG needed
- Water Uptake
- Release Profile

• Rate of molecular weight decrease
# Long-Acting Injectable / Implantable Products with Other Excipients

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<td>Chemotherapy-induced nausea/vomiting</td>
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</table>
Implanon – 3-Year Releasing Implant

Nexplanon®
(etonogestrel implant) 68 mg
Radiopaque

Core: 40% EVA
60% etonogestrel
Membrane: 100% EVA

Rate-controlling membrane (0.06mm)

2mm Core
40mm

www.fullcirclehealthcareinc.com
Probuphine – 6-Month Releasing Implant

- Opioid dependence
- 4 implants
- 80 mg buprenorphine per implant
- EVA excipient
- 26-mm length / 2.5-mm diameter
- Terminally sterilized
- Upper arm, inner side, subdermal
- 6-month delivery
- Implant is retrievable
- FDA approval 2016
Key Learnings

Technical Understandings
Learnings

- Importance of scale up
- Reproducibility of product-by-process manufacturing
- Difficulty developing generics of complex parenteral products
- Importance of reproducible physical and chemical properties of excipient and drug substance
- Challenges of non-standard manufacturing unit operations
- Equipment challenges to perform aseptic manufacturing
- Boundaries of parenteral products
- Controlling drug release (narrower therapeutic windows, managing drug side effects)
- Aligning drug delivery with the biology
- Less risk with established excipients
- Potential toxicity of nanoparticles
- No universal drug delivery technology
- Decoupling drug delivery from device functionality (combination products)
Critcality of Scale Up Microencapsulation Processes

• Batch processing relies on “art” because control of the emulsification, precipitation or evaporation/extraction procedures is difficult.

• Batch processing inadequacies typically are exposed at scale up. (multiple timeline delays and costly experiments jeopardize the product).

• Controlling critical process parameters is key for successful process scale-up and validation.

• Cannot scale up most laboratory processes.
Advantages of Continuous Manufacturing
Control needed throughout run (solvent-removal step)

- Extraction of polymer solvent
- Transport of polymer solvent (rate, amount)
- Polymer precipitation (internal morphology and surface properties)
- Drug precipitation or crystallization (physical properties of drug)
- Movement of drug
- Creation of microparticle surface (morphology, polymer orientation (surface charge, surface hydrophobicity)

FormEZE® Microparticles
Continuos and Batch Manufacturing

- Solvent Extraction
- Phase Separation
- Spray Drying
- Solvent Evaporation
- Spray Chilling
- Solvent Displacement
Scale Up is a Critical Step

Advantages of continuous processes
• Ability to scale up
• Same product made throughout the process

Other considerations
• Time limitation per batch (bioburden)
• Aseptic manufacturing
• Microparticle drying
• Residual solvents
• Powder filling
Parenteral Injection Volumes

• Dose requirements
  • Drug potency
  • Duration (days → months)

• Injection volume limitations for parenterals
  (volume = microparticles + vehicle)

  • 1-2 mL subcutaneous
  • 1-3 mL intramuscular (site dependent)
  • 0.5 mL subcutaneous / intramuscular (pediatrics)
  • 100 µL intravitreal
  • 0.1 mL intradermal
Design by dose Hydrophilic Drug Substance

Design by dose

- 1-mL injection (subcutaneous administration)
- 100 mg microparticles (10 % solids)
- 40 mg drug (dose for 1 month)
- 40 wt% drug content (10% solids)
Increasing Drug Loading Hydrophilic Drug Substances

1 wt% loading
Delayed release with no initial release

10 wt% loading
Extended release with appropriate initial release

40 wt% loading
Burst release

Polymer strength
- Molecular weight
- Matrix structure
- Amount of polymer

Osmotic pressure
- Drug molecular weight
- Number of drug molecules
- Hydrophilic v. hydrophobic drug
Design by Dose Verses Design for Rate of Release Hydrophilic Drug Substances

Design for dose

• 1-mL injection (subcutaneous administration)
• 100 mg microparticles (10% solids)
• 40 mg drug (dose for 1 month)
• 40 wt% drug content (10% solids)

Design for rate of release

• 10 wt% drug content (loading for 1-month release)
• 400 mg microparticles (40% solids)
Approaches to injecting more microparticles

More microparticles injected
(30-50% microparticle solids compared to 10-20%)

- Deliver less potent drugs
- Deliver more drug
- Deliver drug for longer durations
Continuous Melt Extrusion Control needed throughout run (content uniformity)
What’s coming in our future?

Future Trends
Future Trends

- Reliance on established materials
- Some new materials
- More biopharmaceutical (peptides, proteins, nucleic acids)
- More highly potent drug substances
- Local drug delivery
- Implants with different shapes
- New manufacturing techniques (additive manufacturing, 3D printing)
- Drug delivery for immunotherapy
- Nanotechnology
- Continued attempts to develop generic, complex parenteral formulations
- On-demand drug delivery connected to sensors
Complex Parenteral Products
Patients

Better Outcomes