Parenteral sustained release of peptides and proteins – getting it right

Simon Bjerregaard
Who we are

Introduction

- Founded in Malmö, Sweden in 1950, privately owned research driven biopharmaceutical company headquartered in Switzerland.

- Global company with over 6,500 employees in 56 countries.

- Committed to helping people around the world build families and live better lives.

- Excellence in peptide and protein research combined with patient friendly drug delivery

- Leader in reproductive medicine and women’s health and in specialty areas within gastroenterology and urology.

- Corporate philosophy “People come first at Ferring”.
Why sustained release of peptides and proteins?

- Reducing drug burden (fewer injections)
- Increasing efficacy and safety by reducing fluctuations in plasma drug concentration
- Improved compliance
- Life cycle management of already approved drugs

<table>
<thead>
<tr>
<th>Protein</th>
<th>Nominal half-life (hours)</th>
<th>Molecular mass (kDa)</th>
<th>Ratio of half-life to mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSA</td>
<td>456</td>
<td>67</td>
<td>6.8</td>
</tr>
<tr>
<td>Transferrin</td>
<td>288</td>
<td>80</td>
<td>3.6</td>
</tr>
<tr>
<td>IgG1, IgG2, IgG4</td>
<td>480</td>
<td>146</td>
<td>3.3</td>
</tr>
<tr>
<td>IgG3</td>
<td>144</td>
<td>165</td>
<td>0.87</td>
</tr>
<tr>
<td>IgA monomer</td>
<td>120</td>
<td>160</td>
<td>0.75</td>
</tr>
<tr>
<td>Retinol-binding protein</td>
<td>12</td>
<td>21</td>
<td>0.57</td>
</tr>
<tr>
<td>Factor H</td>
<td>87</td>
<td>155</td>
<td>0.56</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>168</td>
<td>320</td>
<td>0.5</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>48</td>
<td>125</td>
<td>0.38</td>
</tr>
<tr>
<td>Factor IX</td>
<td>22</td>
<td>57</td>
<td>0.38</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>100</td>
<td>340</td>
<td>0.29</td>
</tr>
<tr>
<td>IFN-α</td>
<td>5</td>
<td>19</td>
<td>0.26</td>
</tr>
<tr>
<td>IgE</td>
<td>48</td>
<td>188</td>
<td>0.25</td>
</tr>
<tr>
<td>Pentameric IgM</td>
<td>144</td>
<td>970</td>
<td>0.15</td>
</tr>
<tr>
<td>IL-2</td>
<td>1.7</td>
<td>15</td>
<td>0.11</td>
</tr>
<tr>
<td>Thyroglobulin</td>
<td>65</td>
<td>660</td>
<td>0.1</td>
</tr>
<tr>
<td>G-CSF</td>
<td>2</td>
<td>20</td>
<td>0.1</td>
</tr>
<tr>
<td>Factor VIIa</td>
<td>3</td>
<td>50</td>
<td>0.06</td>
</tr>
<tr>
<td>PYY3-36</td>
<td>0.13</td>
<td>4</td>
<td>0.03</td>
</tr>
<tr>
<td>IGF-1</td>
<td>0.17</td>
<td>8</td>
<td>0.02</td>
</tr>
<tr>
<td>hGH</td>
<td>0.3</td>
<td>22</td>
<td>0.014</td>
</tr>
<tr>
<td>GLP-1</td>
<td>0.03</td>
<td>4</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Glucagon-Like Peptide-1 Infusion Must Be Maintained for 24 h/day to Obtain Acceptable Glycemia in Type 2 Diabetic Patients Who Are Poorly Controlled on Sulphonylurea Treatment

Jennifer Laskin, MD, Bradly Hillyer, MD, Kevin N., MD, Peter Damso, MD

Diabetes Care 24 (8) 2001

Human serum half-life of various human proteins

BioDrugs 29 (2015), 215–239
Main categories of parenteral long acting technologies

- Aqueous suspensions
  - Low soluble salts/crystals
  - Zinc complex

- Micro/nano-encapsulated
  - Non-PLGA
  - PLGA

- In situ forming depot
  - Biodegradable gel
  - Precipitating/self-assmebling

- Plasma half-life extension (conjugates)
  - Lipid conjugates
  - PEGylation
  - Peptide/protein extension

- Implants
  - Biodegradable
  - Non-biodegradable

Depot duration of marketed products:
- 1 day
- 6 months
- 6 months
- Few weeks
- 1 year
Aqueous suspensions
- Low soluble salts/crystals
  - Zinc complex
    - NPH insulin
    - Tretracosactide zinc phosphate
    - GLP-1 analogs-protamine-zinc

Micro/nano-encapsulated
- Non-PLGA
  - PLGA
    - Sandostatin LAR® (Novartis)
      - Nutropin Depot® 1999-2004 (Genentech/Alkermes)
    - Lupron Depot® (Takeda)
    - Decapeptyl® Depot (Ferring)
    - Trelstar® (Debiopharm)
    - ImSus® (Alrise)
    - FormEze™ (Evonik)
    - Bydureon® (Amylin/Alkermes)
    - Somatuline® LA (Ipsen)
    - Luphere® (Peptron)
    - Lutrate® Depot (GP-Pharm)
    - Spherotide (Xbrane)
    - Decapeptyl™ SR (Ipsen)
    - Q-Sphera™ (Midatech)

In situ forming depot
- Biodegradable gel
  - Eligard® (Tolmar)
  - SIF™ (Foresee)
  - BEPO® MedinCell
  - HexPLA (Evonik)
  - FluidCrystal® (Camurus)
  - InGell® Gamma (InnoCore)
  - ReGel®
  - Hyasis (Albumedix)
  - InGell Gamma (InnoCore)

Marketed products w. peptides/proteins
- Double emulsion, solvent evaporation/extraction
- Coacervation
- Hot melt extrusion/micronization
- Spray drying
- Degradation pattern of PLGA microparticles

Degarelix nanofibers

Key:
- Marketed products w. peptides/proteins

Marketed depot formulations
Program Count vs Molecule/API Name

- Majority of products are GnRH agonists
- Few/no drug products with proteins

Spray dried hGH, hyaluronate, lecithin microparticles
J. Pharm. Sci. 105, 2016, 613-622
Key factors driving selection of formulation design

- Depot duration in relation to potency and plasma half-life of active
- Therapeutic window vs PK variability
- Stability (process, storage and in vivo)
- Controlling/understanding release rate and mechanism
  - Predictive in vitro release rate (mode/duration) and/or animal experiments
- CMC risk/proven technology
- Presentation of drug product (e.g. needle size, ready to use, autoinjector)
- Manufacturing capabilities (highly potent API, GMP, aseptic)
Matching API with sustained delivery technology

Importance of potency and plasma half-life of API:

<table>
<thead>
<tr>
<th>API</th>
<th>Maximum strength (dose per day)</th>
<th>Plasma half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>2 mg (300 µg/day)</td>
<td>2.4 hours</td>
</tr>
<tr>
<td>Leuprolide</td>
<td>45 mg (250 µg/day)</td>
<td>3 hours</td>
</tr>
<tr>
<td>Triptorelin</td>
<td>22.5 mg (125 µg/day)</td>
<td>3 hours</td>
</tr>
<tr>
<td>Degarelix</td>
<td>80 mg (3 mg/day)</td>
<td></td>
</tr>
<tr>
<td>Lanreotide</td>
<td>120 mg (4 mg/day)</td>
<td>2 hours</td>
</tr>
</tbody>
</table>

Injection volume limitations:
SC: 1-2 ml
IM: 1-5 ml

Solid dose limitations for microparticles: 20-30% v/v

\[ C_p = \frac{J}{CL} \]

Organs, receptors, enzymes clear peptide from circulation

Peptide soluble in s.c. space

Formulation

Blood
Drug delivery considerations for user-friendly microparticulate formulations

- Various user segments (e.g., self-administration/HCP)
- Comparison with competitors
- COGS constraints
- Flexible dosing requirements

**Suspension medium**
- Physiological acceptance
- Viscosity
- Stabilizers (may impact PK)

**Device/container**
- Particle size and particle size distribution
- Particle amount/volume
- Physical stability/Agglomeration
- Terminal sterilization
- Chemical stability (storage)

**Microparticles**
- Resuspendibility
- Stability of suspension until injection
- Syringeability / injectability
- Local tolerability

**Reconstituted suspension**

- Terumo needles

**MixJect™**

**Terumo needles**
Example of development timeline for Bydureon using an established microparticle platform (Medisorb)

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>Amylin-Alkermes Contract</td>
</tr>
<tr>
<td>2002</td>
<td>AC2993 Phase II 2 doses</td>
</tr>
<tr>
<td>2003</td>
<td>Phase II Multidose Once weekly</td>
</tr>
<tr>
<td>2004</td>
<td>Phase III</td>
</tr>
<tr>
<td>2005</td>
<td>Pre NDA Meeting with FDA</td>
</tr>
<tr>
<td>2006</td>
<td>Complete response letter</td>
</tr>
<tr>
<td>2008</td>
<td>FDA approval</td>
</tr>
</tbody>
</table>

Source: PharmaCircle

US Patent 6,331,317*)

Scale up by parallelization

Human PK of pilot scale and commercial scale batch

Short timeline for going into p - but overall timeline not impr

*) S. Freitas et al., J. Cont. Rel. 102 (2005) 313–332
The back up strategy: Complementary technologies

- Consider 2-3 complementary technologies as fall back strategy in early phases of development e.g. PLGA microparticles and in situ forming depot.
- Different risk profiles regarding PK, scale up potential, cost of goods, contractual obligations, timelines, manufacturing/technology transfer, user acceptability, etc.
- Select primary technology platform after confirmatory technical pilot scale batch.
Typical manufacturing of PLGA microparticles

S. Freitas et al., J. Cont. Rel. 102 (2005) 313–332
Various morphologies of Triptorelin PLGA microparticles

Reference + 5 % NaCl + 2% Poloxamer 407

Source: Mahboubian A et al., IJPR (2010), 9 (4): 369-378
Drying equally important as formation of microparticles

Critical effect of freezing/freeze-drying on sustained release of FITC-dextran encapsulated within PLGA microspheres

Different possible process flows for FD

- Wet microparticles
- Supension with excipients (cake former, stabilizer etc.)
- Suspension in water
- Quick freeze of vials
- Filling suspension in vials
- Lyophilization in vials
- Lyophilization in bulk
- Filling of powder + capping
- Dry blending with excipients

15
Importance of interpretation of data

Shear rate sweep for two suspension media

Shear rate range related to suspension stability

Shear rate range related to syringeability
Syringeability

Importance of testing under non-ideal conditions

SEM of Decapeptyl Depot PLGA microparticles

Light microscopy of PLGA mp after a freeze-thaw cycle

Sedimentation of microparticles

Needle clogging is a stochastic phenomenon

<table>
<thead>
<tr>
<th>Syringeability test setup</th>
<th>Texture analyzer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant injection speed</td>
<td>2.5 m/sec</td>
</tr>
<tr>
<td>Time after reconstitution for the dose force test</td>
<td>3 min</td>
</tr>
</tbody>
</table>
Impact on gamma-irradiation on purity

Purity 99.65 %

Purity 96.17 %
Impact of gamma irradiation on visual appearance of glass

> 25 kGy
Non-irradiated

> 25 kGy
> 15 kGy

Corning C-51 tubing

Standard Borosilicate hydrolyte class I tubing
Summary

Key points

▶ Parenteral depot formulations are easy to make in lab scale, but difficult to manufacture in commercial format.
▶ Not all peptides and proteins are amendable to sustained release principles.
▶ Large potential within sustained release of peptides and proteins which could be realized with novel technologies.
Future directions

- Smarter manufacturing processes
  - Continuous (real) production
  - Modulisation
  - Automatisation
  - Process intensification (microfluidics)

- Peptide and protein engineering (designing peptides for optimised SR formulation – e.g. increased stability, higher potency, longer plasma half-lifes, self-assembling properties)

- Filling the innovation gap
  - Commercial viable depot formulations for proteins
  - Hybrid technologies with longer duration of action (e.g. plasma half-life extension in combination with microencapsulation or in situ forming depot)
  - Products with alternative polymers e.g. polycaprolactones
Acknowledgements

- Ferring LCM organisation
  - Ann Svensson
- Ferring Global Pharmaceutical R&D
  - Georg Schmies
  - Helena Nicklasson
  - Camilla Borglin
  - Wolfgang Koechling
  - Kasper Lind Hoffmann
  - Pernille Rosted
- Centre For Industrial Rheology
  - Joshua Marsh