Approaches to Development of Long Acting Injection Formulations – Challenges and Solutions

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Introduction

- Approximately 15% of the current drug delivery market are injectable products
- Increasing potential requirements with products from biotechnology revolution
- Short acting injections have limitations for chronic care products
Outline

- General rationale for long acting formulations
- Therapeutic opportunities
- Overview of current technologies
- Specific formulations examples
- Future developments
- Summary and conclusions
Rationale for long acting formulations

- Improved safety and/or efficacy
- Improved patient compliance and outcomes
- Cost reduction
- Life cycle optimization
- Allows bolus delivery for some drugs that otherwise could require slow IV administration
Idealized characteristics of long acting injection

- Controlled delivery over from 1 week to 6 months from single injection
- Biodegradable/ biocompatible carrier materials
- Easy to manufacture, store and administer product
- Compatible with sensitive molecules (e.g. proteins)
- Compatible with conventional drugs
- Low or high loading capability
- Can deliver water soluble or insoluble products
- Provides proprietary protection
- Low toxicity
- All GRAS excipients
- Does not require drug modification
Typical opportunities/benefits for long-acting products

- Treatment of resistant patients
  - Antipsychotics
- Improving convenience of chronic care products
  - Insulins
  - Enbrel ®
- Improvement in safety profiles
  - Pegylated interferons
History of long acting injectable formulations

- **Penicillin + probenecid**
  - Important in prolonging action of penicillin at time of short supply
  - Probenecid blocks renal tubular secretion of penicillin
- **NPH (Neutral protamine Hagedorn) insulin - 1946**
  - Insulin formulated with protamine derived from herring or salmon milt
  - Protamine binds and precipitates proteins
- **Benzathine penicillin**
  - IM prodrug that releases benzyl penicillin over a 2-4 week period
- **Depot neuroleptics - 1960’s**
  - Haloperidol dodecanoate formulated in sesame oil and benzyl alcohol
- **Poly lactide/ poly glycolide depots**
  - First patents for depot delivery issued in 1973
  - First clinical trials with steroid depots in late 1970’s
  - First product launch with Decapeptyl LP (LHRH analog) in 1986
Potential challenges for long-acting formulations

- Creating zero order kinetics
- Chemical modification of parent drug
  - Creates new API with attendant requirements to support approval for marketing
- Use of non-GRAS excipients
  - Requires demonstration of safety for new materials
- Consistent quality of polymeric materials
- Poor drug stability
- Burst effect and dose dumping
Challenges with injectable particulate systems

- Limited array of acceptable polymeric or carrier materials
- Particles attract macrophages of the RES and tend to localization in certain organs (liver, spleen)
Approaches to development of long acting protein injections

- Protein engineering of native protein
- Changes in primary structure
- Formulations that modify circulating half-life
  - Glycosylation
  - Pegylation
  - Polymer conjugation
- Formulation with excipients that delay uptake from injection site
  - Depot formulations
History of insulin formulations
a model for the future?

- Regular animal sourced insulin 1920’s
- NPH insulin 1940’s
- Lente and Ultralente insulins – longer acting formulations – 1953
- Human rDNA insulin 1980’s
- Insulin lispro – genetically modified short acting insulin 1990’s
- Insulin glargine – genetically modified long acting insulin 2000’s
- Non-injectable insulin e.g. inhaled
Insulin product profiles
Insulin glargine

- Designed to have low aqueous solubility at neutral pH
- Completely soluble at pH4 in the injection formulation
- Neutralized after injection to form microprecipitates
- Insulin glargine released relatively constantly over 24 hours
Polylactide/polyglycolide copolymers for depot use

- Typically produced through melt polymerization
- Primarily linear structures
- Racemic DL and L-polymers available commercially
- L-polymers resorb more slowly than DL
- Polymer ratios typically from 50:50 to 100% lactide. High glycolide limits solubility
- Resorption curves impacted by molecular weight, changing particle size, and changing L-polymer ratio
## Examples of depot proteins

<table>
<thead>
<tr>
<th>Product</th>
<th>Polymer</th>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupron depot</td>
<td>PLA</td>
<td>Leuprolide acetate</td>
<td>Prostate cancer, endometriosis</td>
</tr>
<tr>
<td>Nutropin depot</td>
<td>PLGA</td>
<td>Human growth hormone</td>
<td>Growth deficiencies</td>
</tr>
<tr>
<td>Sandosatin depot</td>
<td>PLGA-glucose</td>
<td>Octreotide</td>
<td>Acromegaly</td>
</tr>
<tr>
<td>Trelstar depot</td>
<td>PLGA</td>
<td>Triptorelin pamoate</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>Zoladex</td>
<td>PLA</td>
<td>Goserelin acetate</td>
<td>Prostate cancer, endometriosis</td>
</tr>
</tbody>
</table>
Lupron depot

- Monthly IM injection of leuprolide acetate in a pre-filled dual chamber syringe
- Formulation contains leuprolide acetate, gelatin, DL-lactic and glycolic acid copolymer, and D-mannitol
Eligard ®

- Sustained release formulation of leuprolide acetate using Atrigel ™ (QLT Inc) technology
- Available in one-, three-, four- and six-month dosage forms
- Uses PLGA formulated with N-methyl-2-pyrolidone
- Solidifies after injection to provide sustained payout
Pegylation of Proteins

- Decreased proteolysis
- Decreased immunogenicity
- Enhanced solubility
- Increased half-life
- Altered distribution
- Enhanced stability in storage
- Enhanced solubility
Pegylation of Proteins

- PEGs are amphophilic molecules and generally non-toxic
- Increases molecule size to limit kidney secretion
- Limits enzyme recognition to avoid breakdown
- Pegylation reaction controlled by PEG/protein type, reaction time, temperature, pH, etc
- Covalent bonds between an amino or sulphydryl group on protein with ester, carbonate or aldehyde on the PEG
# Examples of pegylated products

<table>
<thead>
<tr>
<th>Product</th>
<th>Generic name</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegasys</td>
<td>Pegylated $\alpha_2$a interferon</td>
<td>Antiviral, antineoplastic, neutropenia</td>
</tr>
<tr>
<td>Neulasta</td>
<td>PEGfilgrastin</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Adagen</td>
<td>Pegadenosine</td>
<td>Enzyme replacement</td>
</tr>
<tr>
<td>Oncospar</td>
<td>Peg l-asparaginase</td>
<td>Acute lymphocytic leukemia</td>
</tr>
<tr>
<td>Somavert</td>
<td>PEG growth hormone antagonist</td>
<td>acromegaly</td>
</tr>
</tbody>
</table>
Polymeric gels

- Usually free flowing liquids at ambient conditions
- Gel following injection to create an IM depot of drug
- Typically formulated from PLGA polyesters
- Examples include:
  - Eligard®; leuprolide acetate for injection
  - Atridox®; doxycycline gel for periodontal disease
  - H.P. Acthar Gel, ACTH formulated with 16% gelatin for IM or SC use in management of MS
Approaches to development of long acting formulations for conventional molecules

- Liposomes
- Microspheres and nanoparticles
- Polymeric Gels
- Implants
- Prodrugs
Examples of liposomal products

<table>
<thead>
<tr>
<th>Product</th>
<th>Generic name</th>
<th>Route</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambisome</td>
<td>Amphotericin B</td>
<td>IV</td>
<td>Antifungal</td>
</tr>
<tr>
<td>DepoCyt</td>
<td>cytarabine</td>
<td>intrathecal</td>
<td>Antineoplastic</td>
</tr>
<tr>
<td>DaunoXome</td>
<td>daunorubicin</td>
<td>IV</td>
<td>Antineoplastic</td>
</tr>
<tr>
<td>Doxil</td>
<td>doxorubicin</td>
<td>IV</td>
<td>Antineoplastic</td>
</tr>
<tr>
<td>Liprostin</td>
<td>Prostaglandin E2</td>
<td>IV</td>
<td>Peripheral vascular disease</td>
</tr>
</tbody>
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Stealth Liposomes

- Lipid nanoparticles with PEG coating
- Avoid recognition by RES system
- Dororubicin (Doxil®) liposome
Representation of a Stealth liposome
### Polylactide/Glycolide small molecule formulations

<table>
<thead>
<tr>
<th>Product name</th>
<th>Company</th>
<th>Ingredient</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arestin</td>
<td>OraPharma</td>
<td>minocycline</td>
<td>microparticles</td>
</tr>
<tr>
<td>Atridox</td>
<td>Collagenex</td>
<td>Doxycycline</td>
<td>microparticles</td>
</tr>
<tr>
<td>Risperdal Consta</td>
<td>J &amp;J</td>
<td>risperidone</td>
<td>microparticles</td>
</tr>
</tbody>
</table>
Some specialty companies providing long acting injection technology

<table>
<thead>
<tr>
<th>Company</th>
<th>Technology</th>
<th>Name</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flamel</td>
<td>Aminoacid polymers</td>
<td>Medusa</td>
<td>Long acting insulin, INF α-2b, IL-2</td>
</tr>
<tr>
<td>Macromed</td>
<td>Thermosetting gels</td>
<td>ReGel</td>
<td>Oncogel ® (PhaseI)</td>
</tr>
<tr>
<td>Alkermes</td>
<td>Cryogenically processed PLGA</td>
<td>Prolease, Medisorb</td>
<td>hGH</td>
</tr>
<tr>
<td>SkyePharma</td>
<td>Non-concentric aqueous core lipid chambers</td>
<td>Depofoam</td>
<td>Depocyt ®, Peptides, DNA, proteins</td>
</tr>
<tr>
<td>QLT</td>
<td>PLGA in N-methyl-2-pyrolidone thermosetting gel</td>
<td>Atrigel</td>
<td>Eligard®</td>
</tr>
<tr>
<td>Alza</td>
<td>PEG coated liposomes</td>
<td>Stealth</td>
<td>Doxil®</td>
</tr>
<tr>
<td>Durect</td>
<td>Sucrose acetate isobutyrate</td>
<td>SABER</td>
<td>SABER-bupivacaine</td>
</tr>
</tbody>
</table>
The Future?

- Greater willingness to build optimized drug delivery into initial product entry
- Responsive drug delivery systems (e.g. pH sensitive liposomes)
- Wider use of modified proteins (pegylated, glycosylated, etc.)
- Nanotechnology devices delivering high potency drugs?
- Miniscule particles that can travel through the body to detect and cure disease?