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 + probenicid**
  - Important in prolonging action of penicillin at time of short supply
  - Probenicid 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
- **Polylactide/polyglycolide 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 attend 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)

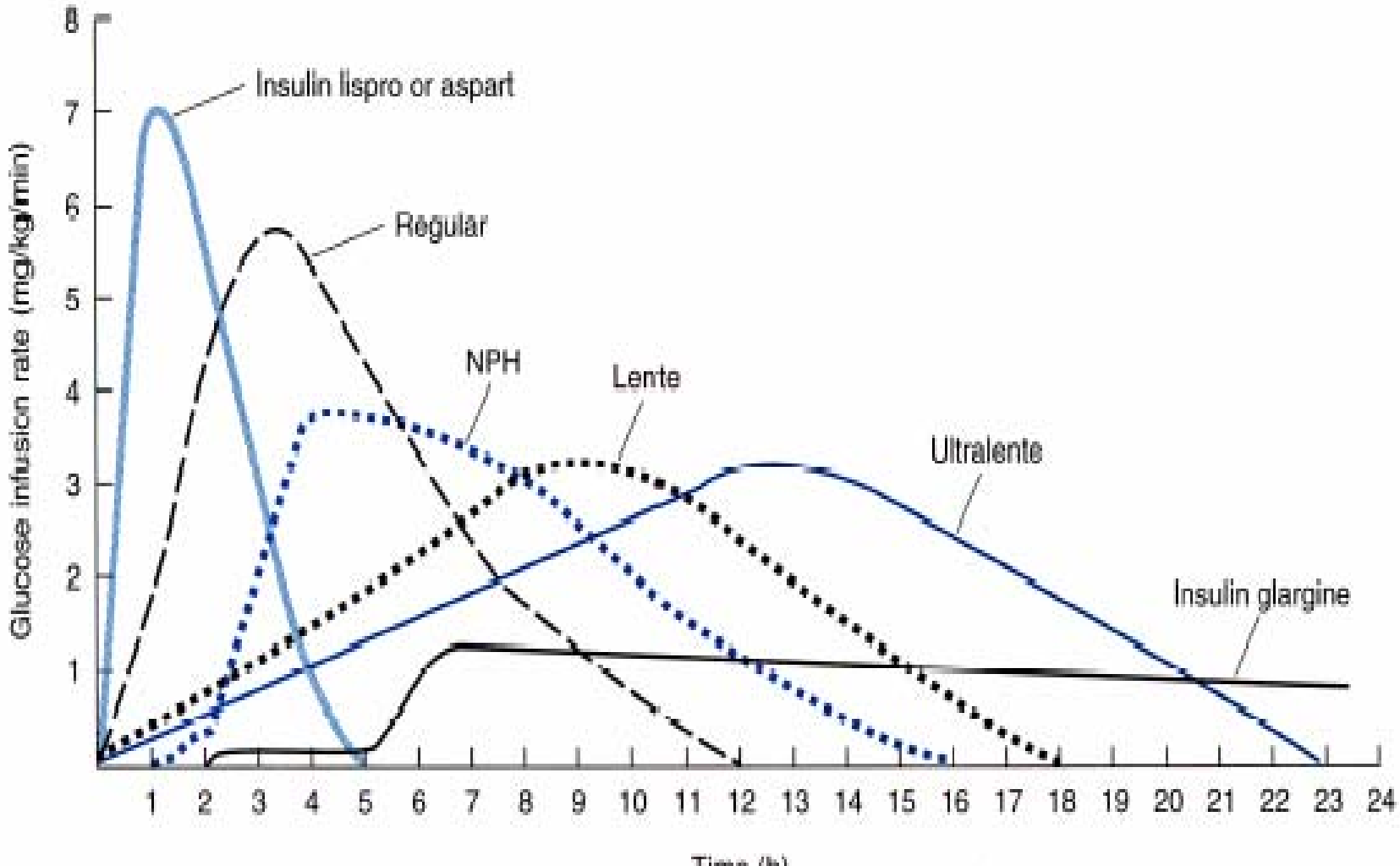
Approaches to development of long acting protein injections

- 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

Product	Polymer	Drug	Indication
Lupron depot	PLA	Leuprolide acetate	Prostate cancer, endometriosis
Nutropin depot	PLGA	Human growth hormone	Growth deficiencies
Sandosatin depot	PLGA-glucose	Octreotide	Acromegaly
Trelstar depot	PLGA	Triptorelin pamoate	Prostate cancer
Zoladex	PLA	Goserelin acetate	Prostate cancer, endometriosis

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 fomulated with N-methyl-2-pyrollidone
- 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 sulfydryl group on protein with ester, carbonate or aldehyde on the PEG


Standard-Interferon


Pegylated Interferon

Examples of pegylated products

Product	Generic name	Indication
Pegasys	**Pegylated α 2a interferon**	**Antiviral, antneoplastic, neutropenia**
Neulasta	**PEGfilgrastin**	**Neutropenia**
Adagen	**Pegadenosine**	**Enzyme replacement**
Oncospar	**Peg l-asparginase**	**Acute lymphocytic leukemia**
Somavert	**PEG growth hormone antagonist**	**acromegaly**

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

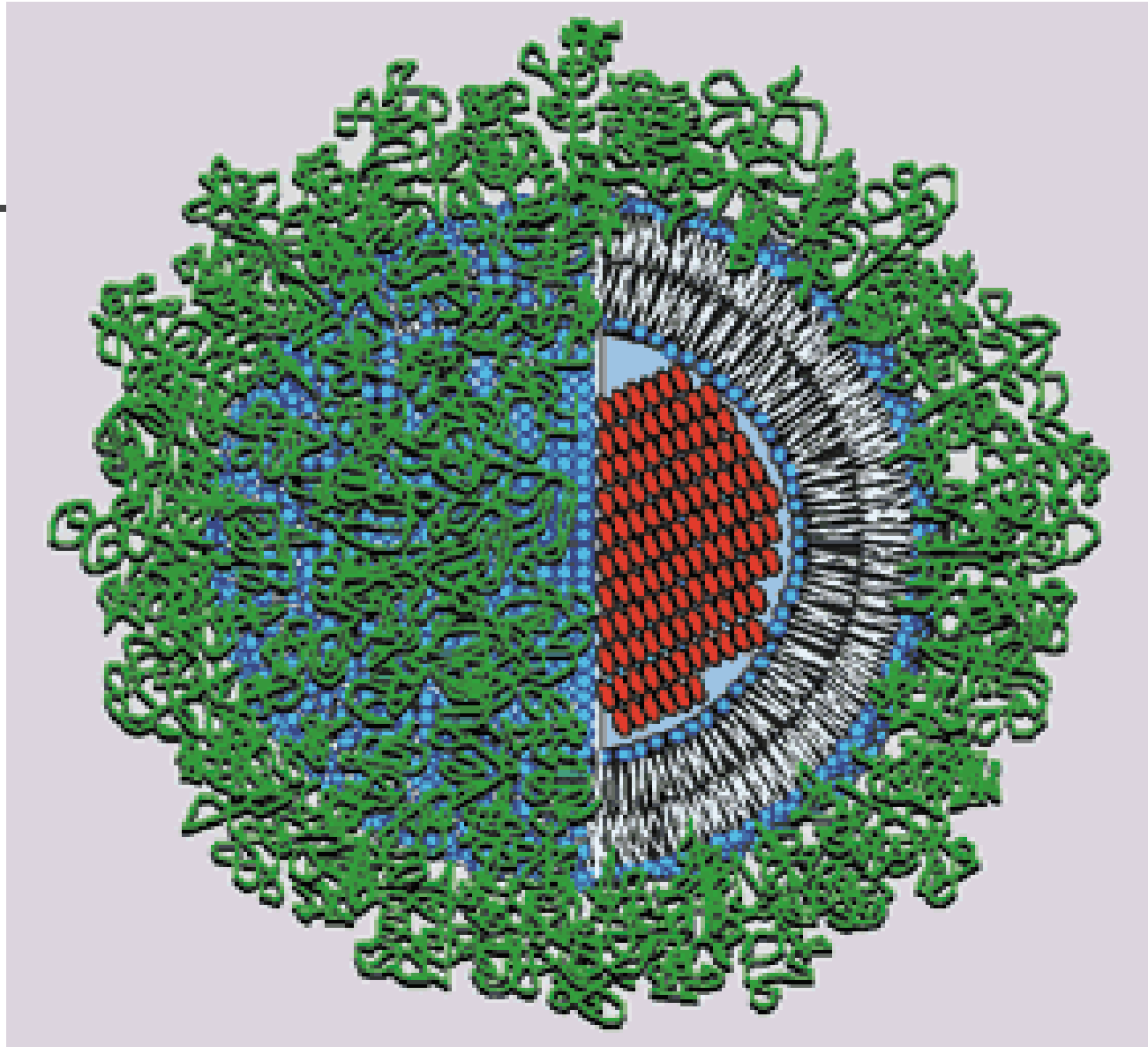
- Liposomes
- Microspheres and nanoparticles
- Polymeric Gels
- Implants
- Prodrugs

Examples of liposomal products

Product	Generic name	Route	Indication
Ambisome	**Amphotericin B**	**IV**	**Antifungal**
DepoCyt	**cytarabine**	**intrathecal**	**Antineoplastic**
DaunoXome	**daunorubicin**	**IV**	**Antineoplastic**
Doxil	**doxorubicin**	**IV**	**Antineoplastic**
Liprostin	**Prostoglandin E2**	**IV**	**Peripheral vascular disease**

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

Product name	**Company**	**Ingredient**	**Formulation**
Arestin	OraPharma	minocycline	microparticles
Atridox	Collagenex	Doxycycline	microparticles
Risperdal Consta	J&J	risperidone	microparticles

Some specialty companies providing long acting injection technology

Company	Technology	Name	Applications
Flamel	**Aminoacid polymers**	**Medusa**	**Long acting insulin, INF α-2b, IL-2**
Macromed	**Thermosetting gels**	**ReGel**	**Oncogel ® (PhaseII)**
Alkermes	**Cryogenically processed PLGA**	**Prolease, Medisorb**	**hGH**
SkyePharma	**Non-concentric aqueous core lipid chambers**	**Depofoam**	**Depocyt ®, Peptides, DNA, proteins**
QLT	**PLGA in N-methyl-2-pyrollidone thermosetting gel**	**Atrigel**	**Eligard®**
Alza	**PEG coated liposomes**	**Stealth**	**Doxil®**
Durect	**Sucrose acetate isobutyrate**	**SABER**	**SABER-bupivacaine**

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?