Biodegradable DelSiTech™ Silica Based Delivery of Therapeutic Peptides And Proteins

Dr. Lasse Leino, CEO
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Presentation Outline

• Company snap-shot

• Properties of DelSiTech™ Silica Matrix

• Encapsulation process

• Protein and peptide delivery case studies
DelSiTech Company Facts

• Private drug delivery & drug development company

• Head office and R&D in Turku, Finland

• Founded in 2001 based on biomaterial innovations made by academic research at local universities

• Leading company in advanced biodegradable silica-based, controlled release parenteral drug delivery
DelSiTech develops and commercializes its proprietary drug delivery technology

Business Model

- **R&D services and licensing of the technology**
- **In-house supergeneric/505(b)(2) drug products**

Silica Matrix
Recent News:
DelSiTech Licence Deal with Bayer AG

Bayer signs up DelSiTech ophthalmology drug delivery technology

by Angus Liu | Oct 3, 2016 11:44am
DelSiTech Services

• Formulation Development:
  • Development of controlled release formulations based on biodegradable silica matrix

• Analytical Support:
  • State of the art analytics to support pharmaceutical development

• Manufacture and Process Development:
  • Spray drying manufacture and process development with own bench top spray dryers
  • GMP manufacture at pilot scale
DelSiTech™ Silica Matrix
## Silicon (Si) based biomaterials

<table>
<thead>
<tr>
<th></th>
<th>Silicone</th>
<th>DelSiTech\textsuperscript{TM}Silica</th>
<th>Bioglass</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacture</strong></td>
<td>Polymerization</td>
<td>Sol-gel polymerization</td>
<td>Melt process at high temp.</td>
</tr>
<tr>
<td><strong>Si-structure</strong></td>
<td>Linear polysiloxane with organic side groups</td>
<td>Cross-linked SiO\textsubscript{2} with –OH groups</td>
<td>Cross-linked SiO\textsubscript{2} with inorganic ions</td>
</tr>
<tr>
<td><strong>Solid form</strong></td>
<td>Plastic</td>
<td>Amorphous/porous</td>
<td>Amorphous/dense</td>
</tr>
<tr>
<td><strong>Biodegradation</strong></td>
<td>Non-biodegradable</td>
<td>Biodegradable</td>
<td>Biodegradable</td>
</tr>
<tr>
<td><strong>Use in drug delivery</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

![Silicon structure](image1.png)

![DelSiTech structure](image2.png)

![Bioglass structure](image3.png)
DelSiTech™ Silica: Material Properties

- Physical state adjustable and can vary from liquid to solid depending on water content and form giving

- Nanoporous (not mesoporous) with active compound fully encapsulated during Sol-gel process and form giving

- Contains no toxic solvents or catalysts

- Can be sterilized e.g. by gamma-irradiation, heat & filtration
DelSiTech™ Silica: Safety

- Essentially non-toxic when given orally (LD$_{50}$ > 5g/kg)
- FDA recognizes silica in all its forms safe (GRAS status)
- Human body contains several grams of silica mainly in the bone tissue
- In the body, silica dissolves in silicic acid (SiO$_x$(OH)$_{4-2x}$) such as orthosilicic acid that is excreted in the urine
- Amorphous silica is non-mutagenic and non-carcinogenic
- Supported by extensive in-house toxicology data package
DelSiTech™ Silica: Biodegradation

- Fully biodegradable and dissolvable in body tissues
- Biodegradation based on surface erosion by body fluids
- Biodegradation adjustable from a day to many months
- Drug release strictly controlled by matrix erosion
- Well established in vitro-in vivo correlation for biodegradation rate (10-factor) after s.c./i.m. dosing
Effect of Water-to-TEOS Ratio in Sol-gel Process on DelSiTech™ Silica Dissolution* In Vitro

- Silica placebo microparticles with various R-values (R = molar water-to-TEOS ratio in Sol-gel reaction)
- No differences in particles size (D50 3-5 microns)
- Other process parameters (pH, temp., reaction time) identical

*In sink dissolution in TRIS buffer, pH 7.4/37 °C
DelSiTech™Silica: Stability improvement

• Encapsulation into silica matrix offers the possibility of increasing stability against elevated temperature

• For example, adenoviral vectors can be stored in silica matrix at 4 °C biologically active for more than 12 months - typical storage condition at -25 °C to -80 °C

• Silica matrix encapsulation provides also better thermostability for proteins and protects also from other external stability risk factors
DelSiTech™ Silica: Usability with APIs

- Various therapeutic agents ranging from small molecules to biological macromolecules and viruses can be encapsulated and delivered in silica matrix.

Small drug molecules: $d < 2\ \text{nm}$

Proteins, DNA, RNA, polysaccharides: $d = 2-20...100\ \text{nm}$

Viruses: $d = 20-300\ \text{nm}$

Adenovirus/lentivirus/poxvirus

Cells and bacteria: $d = 1-100\ \mu\text{m}$
DelSiTech™ Silica Dosage Forms #1: Injectable Silica-Silica Composite Depots

- API encapsulated in silica sol gel, followed by form giving in spray drying to produce microparticles
- Mixing microparticles with silica hydrogel to produce an injectable depot formulation
- Packing in prefilled syringe, ready-to-use
- Stable at rest, flowing in injection
Injectable Silica-Silica Composites Are Shear-Thinning Material with Easy Injection

- Viscosity flow curves of silica microparticle-silica hydrogel depot formulations
- Microparticles mixed in at concentrations 0.5, 0.75 and 1.0 mg/ml

- Silica-silica composite depot after injection into gelatin gel
DelSiTech™ Silica Dosage Forms #2: Silica Monolithic Implants

- API encapsulated in silica sol gel, followed by form giving to produce an implant
- Form giving by casting in molds or extrusion
- Variable sizes and shapes, including micro-implants for e.g. intra-ocular use
Encapsulation in DelSiTech™ Silica
Overview on Encapsulation Process

- Sol-gel reaction
- Encapsulation of API
- Form giving
Step #1: Production of Silica in Sol-gel Reaction

- Tetraethyl orthosilicate i.e. TEOS reacts with water in a hydrolysis reaction, catalyzed by acidic pH:

  $$\text{Si(OC}_2\text{H}_5\text{)}_4 + 2 \text{H}_2\text{O} \rightarrow \text{SiO}_2 + 4 \text{HOCH}_2\text{CH}_3$$

- Hydrolysis is accompanied with polymerization via siloxane (Si-O-Si) bonds and incorporation of hydroxyl (OH-) groups in the polymer structure

- Polymerization degree, branching and condensation of silica sol-gel depends on water to TEOS precursor ratio (= R), pH and reaction time → impacts on silica dissolution rate in water solution
Step #1: Triple Polymerisation of Silica in Sol-gel

Molecular polymerisation

Oligomer aggregation by coagulation

Formation of nanoporous structure

TEOS

Oligomers with siloxane bond structure

Nanosize silica aggregates and particles

Silica polymer network

DelSiTech
Steps #1 & #2: Sol-gel Reaction and Encapsulation

Mixing liquid precursors TEOS, $\text{H}_2\text{O}$ and $\text{HCl}$

Addition of API

Sol-gel formation and silica polymerisation

All-liquid system

Silica nanoparticle formation

API entrapped inside silica clusters

$T = 0\text{–}40^\circ\text{C}$
Step #3: Form Giving of Drug Delivery Matrices

- Casting
- Spray drying
- Extrusion

Silica sol with API

Implant

Silica microparticle
Protein & Peptide Delivery
Early Studies: In Vitro Release of Bovine Serum Albumin*

- BSA (mw 68 kDa) encapsulated in monolithic silica sticks (3x25 mm, 2% payload)
- Cm20 R15 based formulation
- Cm23 R30 based formulation
- In vitro dissolution test run in 50 mM TRIS at pH 7.4 and 37 °C in sink

Case Study #1

Delivery of MR1 humanized antibody
Development of Injectable Silica Depot Formulation for MR1 antibody

- Humanized anti-CD40L antibody
- Potential use e.g. in autoimmune diseases by blocking CD40L, the receptor for CD40
- Molecule properties:
  - MW ca. 150 kDa
  - Sparingly water soluble
- Target release time 6 months after s.c. injection
- Formulation strategy:
  - Encapsulation of the peptide in high R silica sol (high condensation level -> slowly dissolving silica matrix) and form giving by spray drying
  - Mixing peptide-silica microparticles with R400 silica hydrogel to maintain injectability
In Vitro Dissolution of Injectable Silica Depot Formulation for MR1*

- R150 silica microparticle with 3% payload, mixed with R400 silica hydrogel
- In vitro dissolution test run in 50 mM TRIS/PBS-Tween at pH 7.4 and 37 °C in sink

Mean, n=3, SD > 2.5% for each mean value

*P. Tyagi et al., Silica Microparticles for Sustained Delivery of MR1 Antibody, 2016 AAPS meeting, Denver, CO, Poster #17R1130
In vivo release MR1 from silica microparticle-silica hydrogel formulation in the rat after single s.c. injection*

In vivo serum concentration of MR1 in the rat after s.c. depot and s.c. bolus injections (n=3 rats), measured by ELISA

Cumulative concentration vs. time showing zero order release.

*P. Tyagi et al., Silica Microparticles for Sustained Delivery of MR1 Antibody, 2016 AAPS meeting, Denver, CO, Poster #17R1130
Conclusions

• DelSiTech™Silica is unique, versatile drug delivery vehicle that has proven safety, biocompatibility and material characteristics

• Combination of Sol-gel technology with spray drying is a powerful tool to produce controlled release formulations for all types of active substances

• DelSiTech™Silica is especially well suited for sustained release of large molecules such as proteins and peptides
Aknowledgements

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