

DelSiTech

The natural solution for drug delivery

Parenteral delivery of therapeutic proteins using biodegradable silica matrix

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LAll, La Jolla , February 6th, 2020.

A network diagram with several nodes (spheres) connected by lines, set against a blue gradient background. The nodes are arranged in a roughly circular pattern, with some lines extending from the top and bottom edges.

DelSiTech in brief

DelSiTech

DelSiTech in brief

- Private drug delivery & drug development company
- Located in Turku, Finland.
- Established in 2001
- Development collaborations and licensing agreements with biopharmaceutical and biotech companies



DelSiTech business model

Dual business model for proprietary drug delivery technology

- R&D services and technology licensing for partners
- In-house development of own super-generic drug products



DelSiTech

Our expertise

- Leading technology in biodegradable, amorphous, non-porous **silica-based drug delivery**.
- Silica microparticle encapsulation technology enabling truly **long-acting controlled release**.
- Parenteral (injectable, implantable) and topical delivery.
- Sustain release formulations from small molecule to biologics.
- Extensive formulation, analytical and manufacturing capabilities.
- From feasibility and preclinical up to clinical phases



Technology that promotes global health

- Long-lasting (> 12 months) subcutaneously injectable depot formulations for family planning
- Long-lasting (3-12 months) subcutaneously injectable depot formulations for HIV and Hepatitis B
- Improved thermostability of viral vector vaccines in countries with compromised cold chain
- Addresses issues in compliance, cost, safety and effectiveness of drug products



Published partnerships

Biologics:

- AstraZeneca/MedImmune
- C-Tri

Infectious diseases:

- Innovare
- Bill & Melinda Gates Foundation

Ophthalmology:

- Bayer

Animal Health:

- Solani Therapeutics

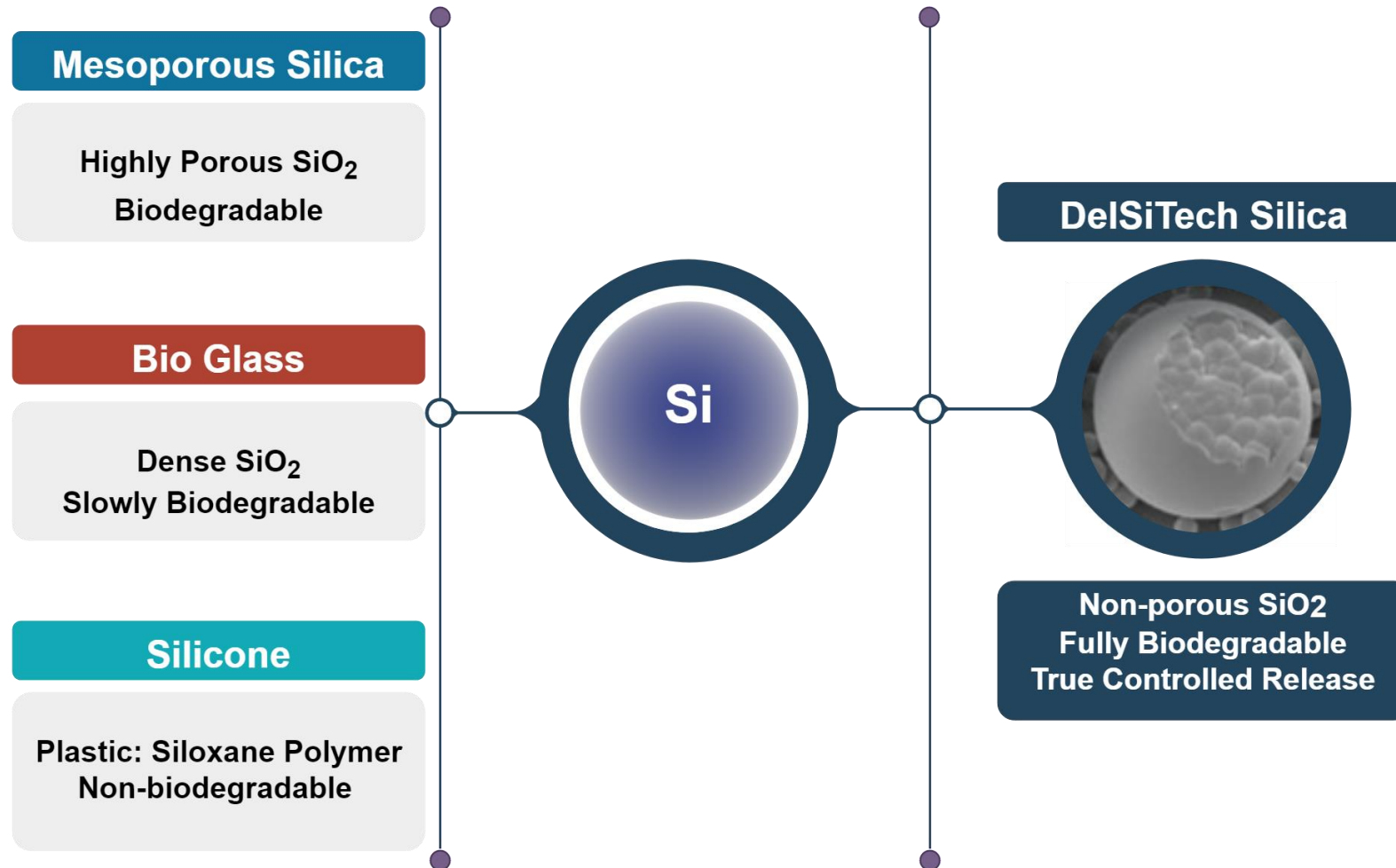




DelSiTech Silica Matrix Technology

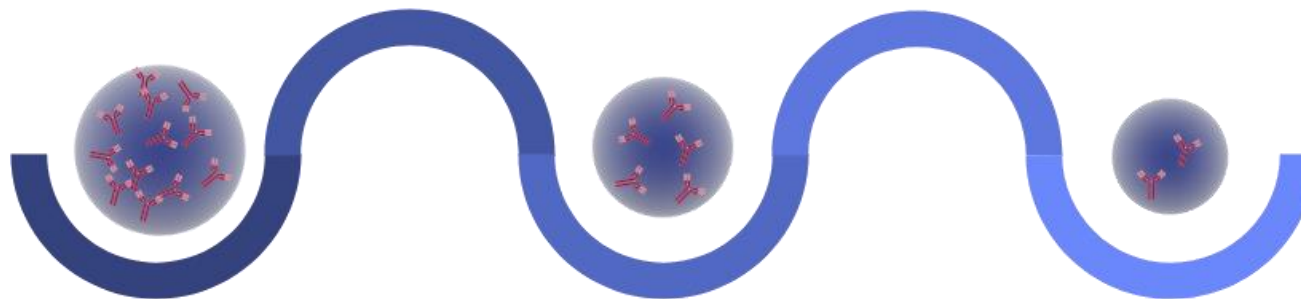
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Silicon based biomaterials and DelSiTech Silica Matrix



DelSiTech Silica Matrix: Biodegradation

- Fully biodegradable and bio-dissolvable in body tissues.
- Biodegrades into silicic acid [$\text{Si}(\text{OH})_4$] naturally present in body and excreted by kidneys.
- Biodegradation based on surface erosion by body fluids.
- Biodegradation adjustable from a day to many months.
- Drug release strictly controlled by matrix erosion (not API solubility).
- Initial burst controlled or eliminated.
- Well established in vitro-in vivo correlation for biodegradation rate.



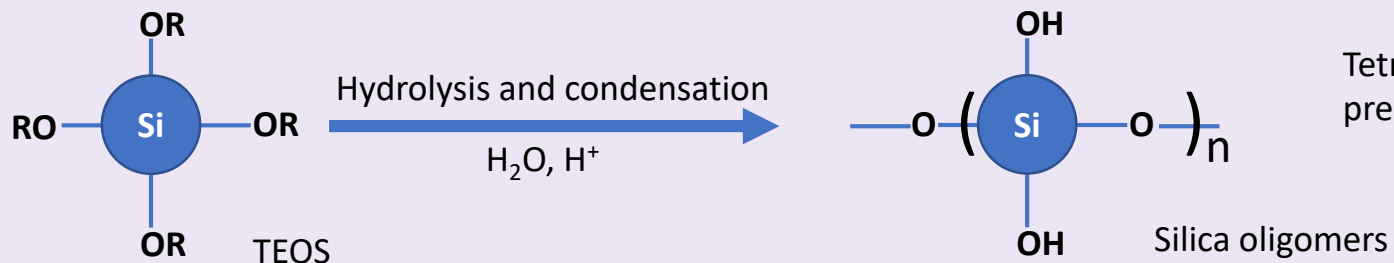
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DelSiTech Silica Matrix: Safety

- Silica is a compendial excipient for topical and oral drug products and an approved food additive (E511).
- FDA recognizes silica in all its forms safe (GRAS status)
- Human body contains several grams of silica mainly in the bone tissue
- Amorphous silica is non-mutagenic and non-carcinogenic
- Supported by extensive in-house toxicology data package

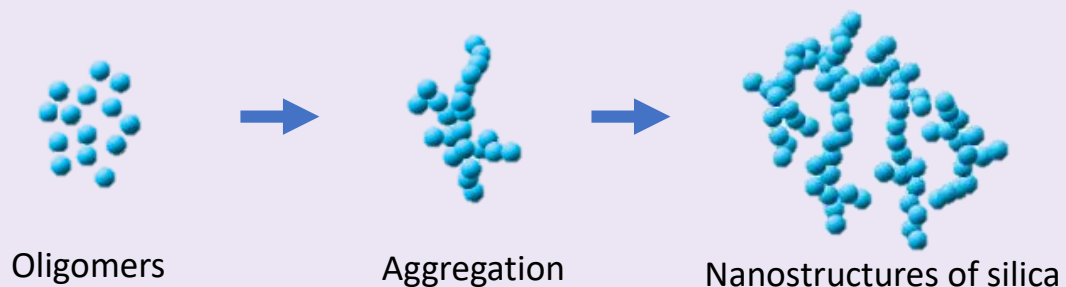
Silica Matrix Technology: API-loaded silica matrix formation

CHEMISTRY:
Polymerisation
of Silica



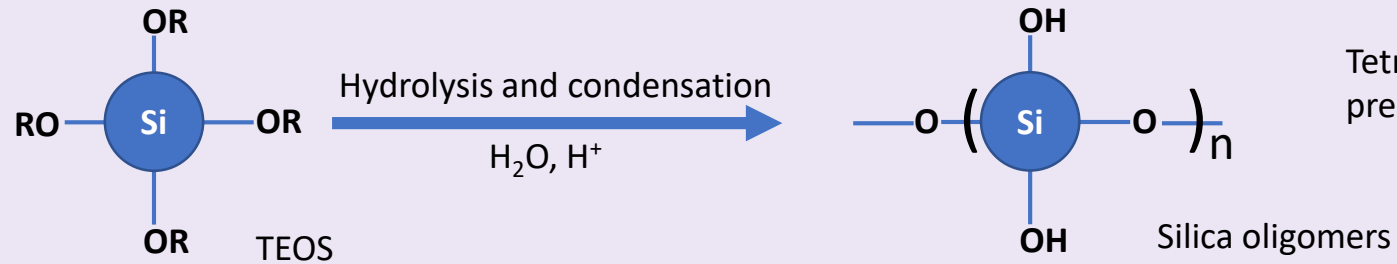
Tetraethyl orthosilicate (TEOS) is the precursor of silica oligomers

STRUCTURE:
Silica Oligomer
aggregation



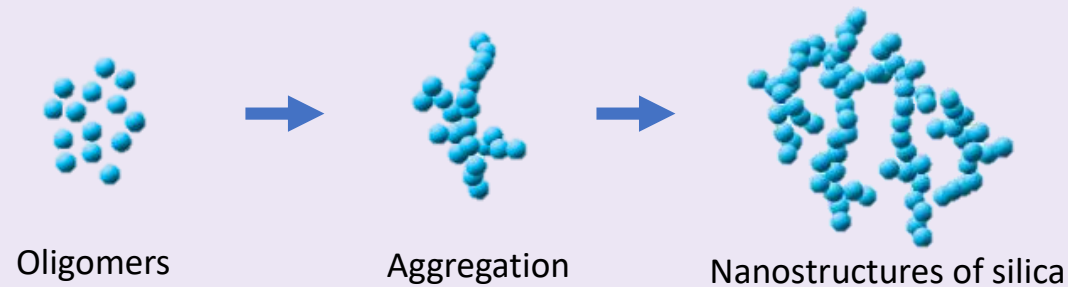
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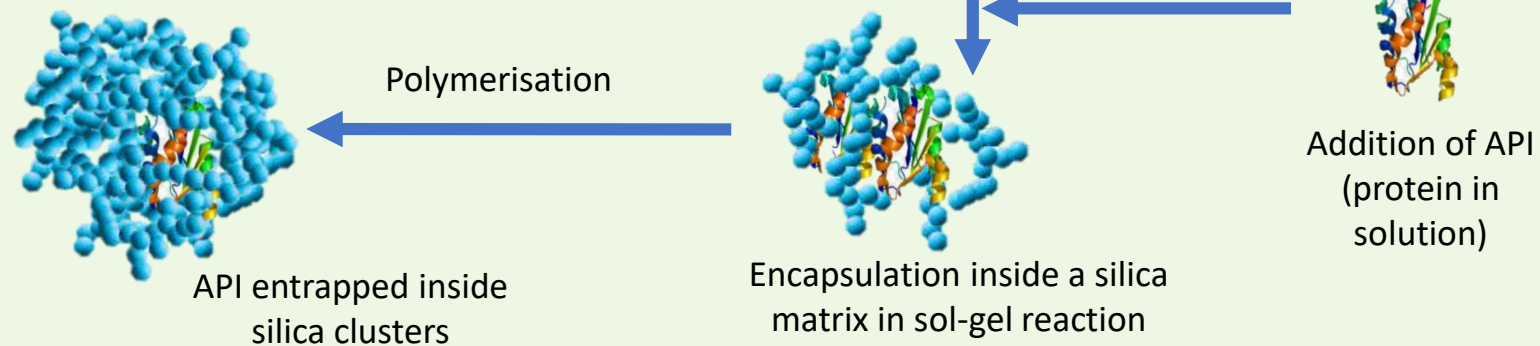
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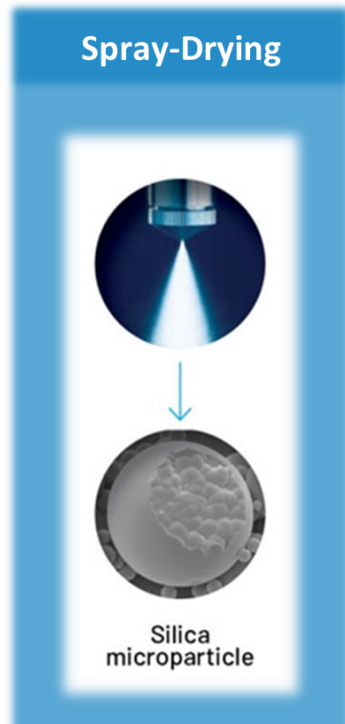
ENCAPSULATION:

Drug substance
encapsulation in
Silica Matrix



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Silica Matrix Technology: form giving and final products

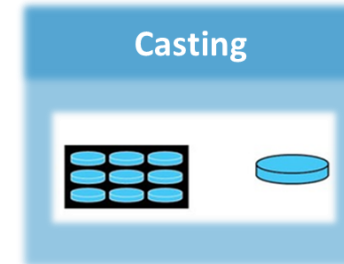


Silica Sol is combined with API and given form.

← Spray drying for production of silica microparticles.

Application:

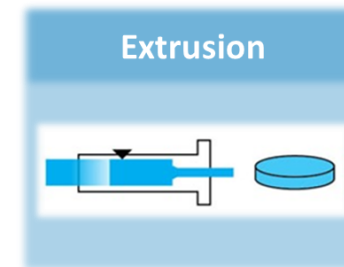
- prefilled syringes
- topical depot



Casting & extrusion technologies. →

Application:

- solid implants



Final products:

Topical sustained release hydrogel (eyedrop)

Long-acting injectable (prefilled syringe)

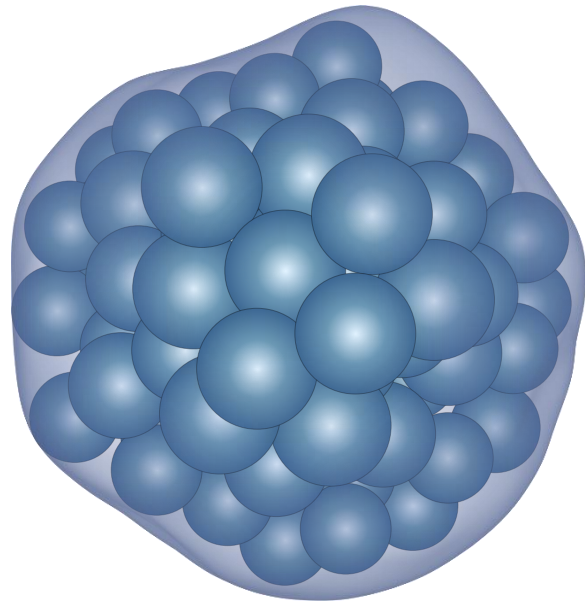
Long-acting implantable

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Key features of DelSiTech Silica Matrix technology:

- Silica sol-gel chemistry: water-based process, no solvents, no other chemicals needed
- Simple formulation: API + silica, no other excipients
- Microparticles formed by spray drying technique.
- Overall simple formulation and simple manufacturing process
- Works from nearly insoluble to highly water-soluble APIs
- Can be used with prefilled syringe, with 25G to 30G needles
- Can be sterilized e.g. by gamma-irradiation, E-beam, heat & filtration
- Protected by 10 patent families up to year 2036

DelSiTech Silica –Silica Matrix composite



Silica hydrogel

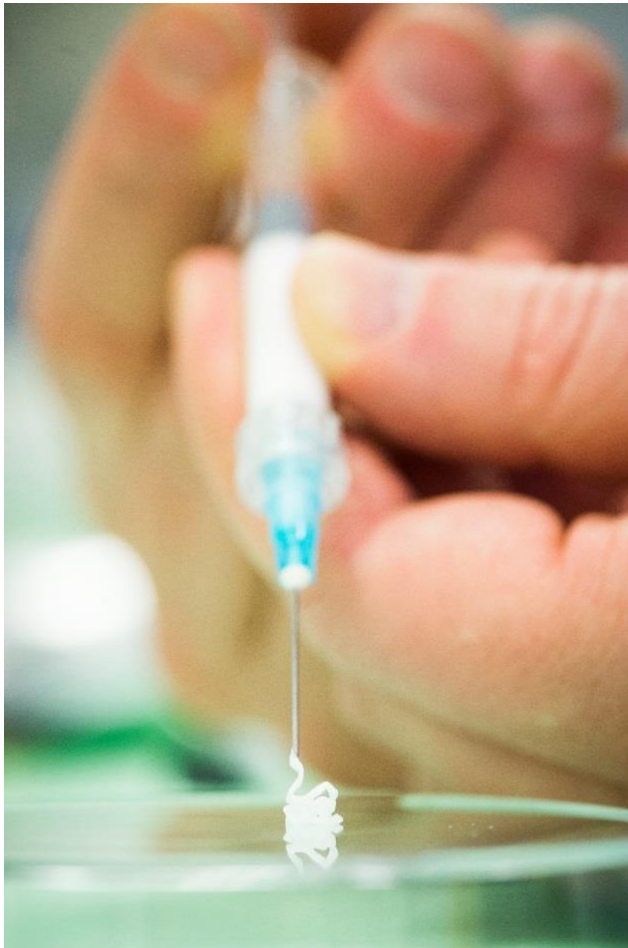


Silica-API microparticle

Silica microparticles – silica hydrogel composite is made of:

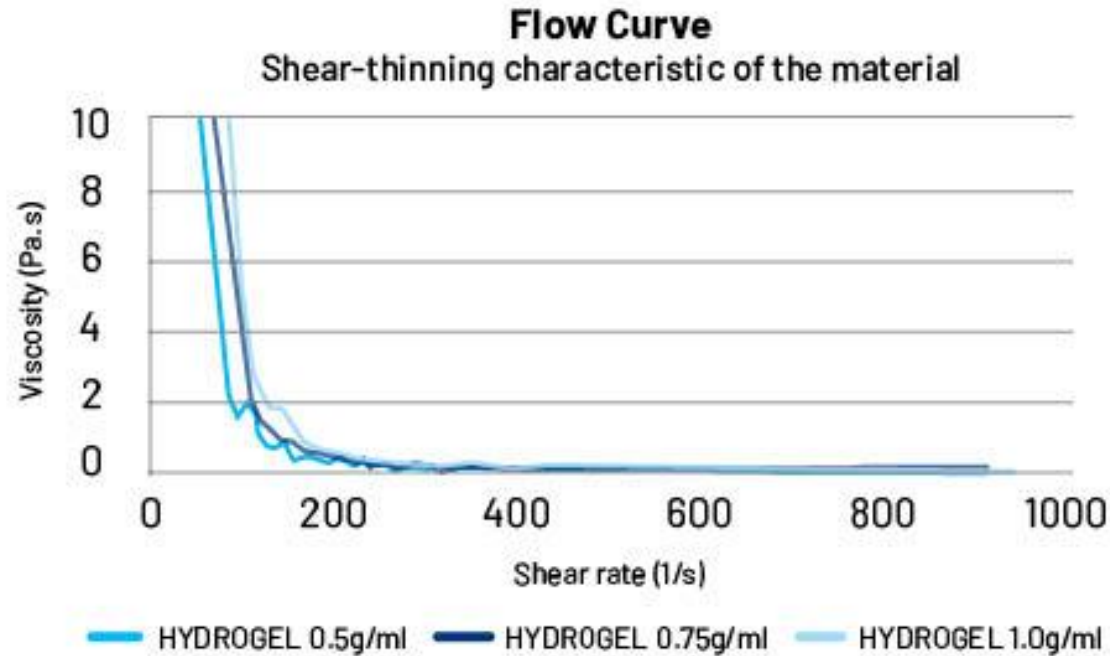
- Silica-API microparticles
 - loaded with API from 1% to 50% (compared to silica)
 - dictate the release kinetics of the API from the depot
- Silica hydrogel
 - maintains the particles together in one unit
 - guarantees the non sedimentation of the particles
 - guarantees the injectability of the microparticles

DelSiTech Silica Matrix dosage form #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 upon injection

Injectable silica-silica composite is shear-thinning material with easy injection

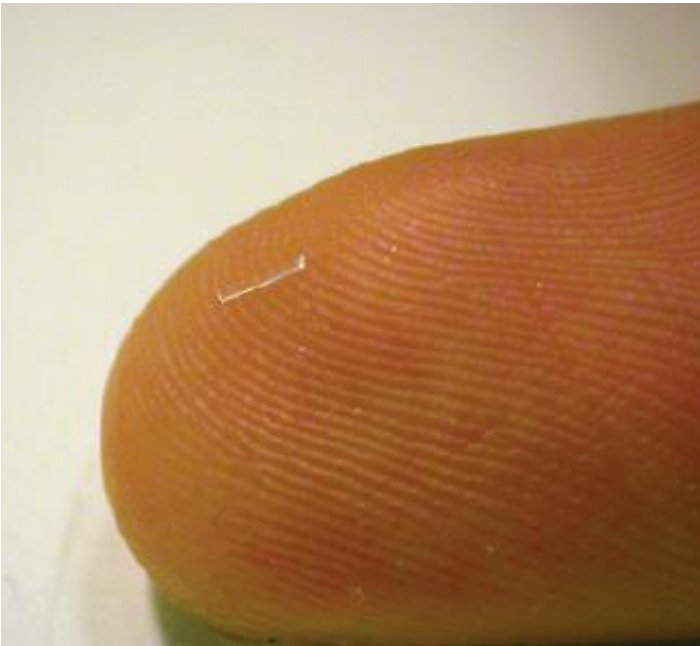


Silica-Silica composite depot after injection
→ reforms a gel

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

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DelSiTech Silica Matrix dosage form #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

DelSiTech Silica Matrix dosage form #3: Ophthalmic silica composite eye drops



- API encapsulated either in silica microparticles or silica hydrogel, or both
- Packing in ready-to-use Single Dose Units
- One drop applied in conjunctiva cul-de-sac, where it stays for 24 hours maintaining therapeutic drug concentration in the eye



DelSiTech Silica Matrix Technology Applications

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A proven range of applications

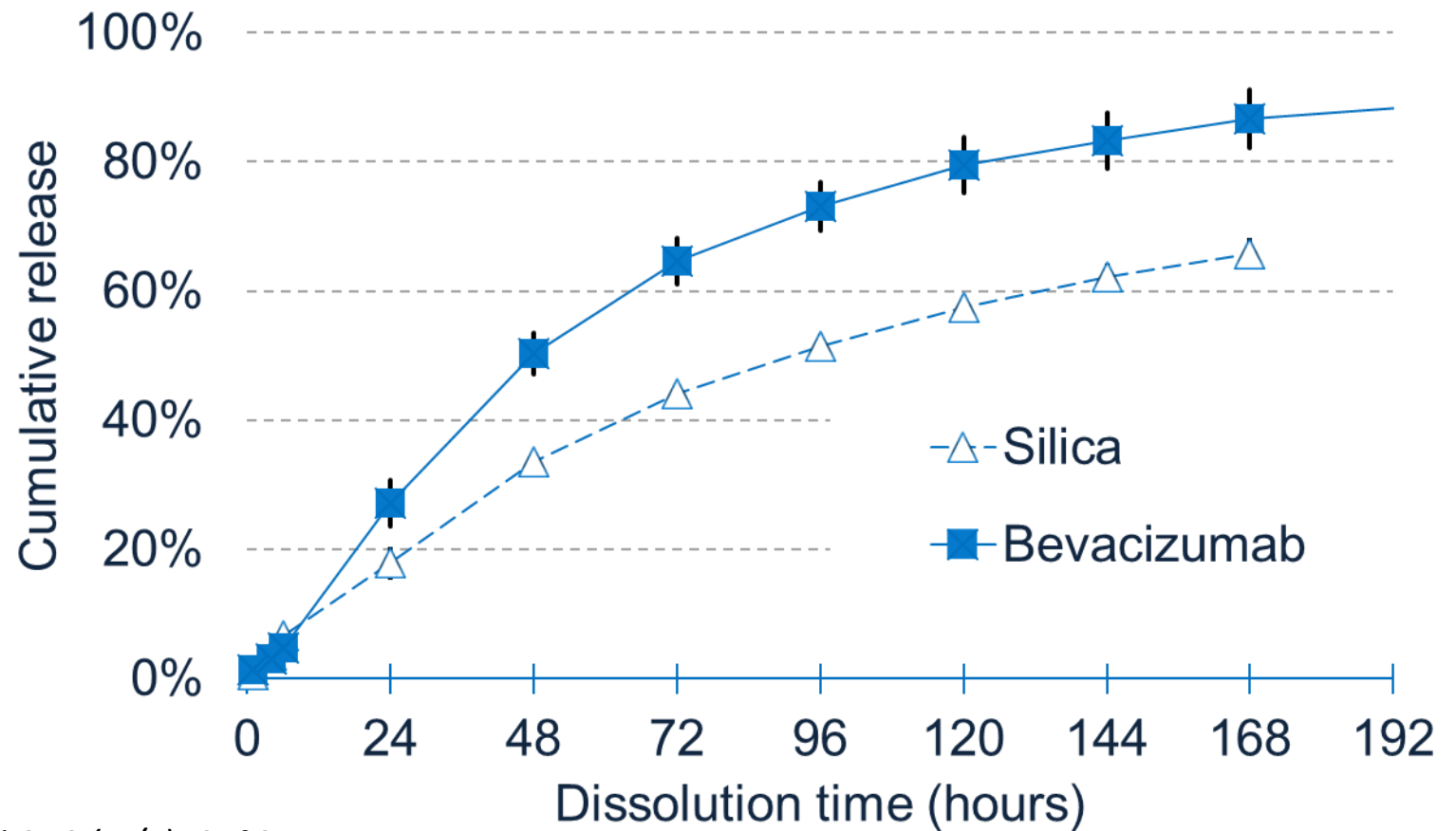
- **Large Molecules:** Delivery of peptides, proteins & antibodies, nucleic acids.
- **Ophthalmology:** Delivery to front and back of the eye
- **Infectious diseases:** Treatment of chronic parasitic diseases, viral diseases
- **Family Planning:** Long-acting contraceptives
- **Viral vaccines:** Thermostability improvement
- **Animal Health:** Companion and production animals
- **Pain medication:** Slow-release pain treatment in post-operative pain
- **Oncology:** Long-acting administration of anticancer drugs
- **Metabolic disease:** Long acting drugs with controlled burst
- **CNS:** Long acting drugs and improved compliance in severe CNS disorders
- **Abuse Deterrence:** oral and injectable opioids



Example 1: Release mechanism of large proteins

The protein payload is released by controlled dissolution of silica (1)

- The release of the API follows the dissolution of silica
- The release rate of the API is adjusted by tuning the Silica dissolution kinetics

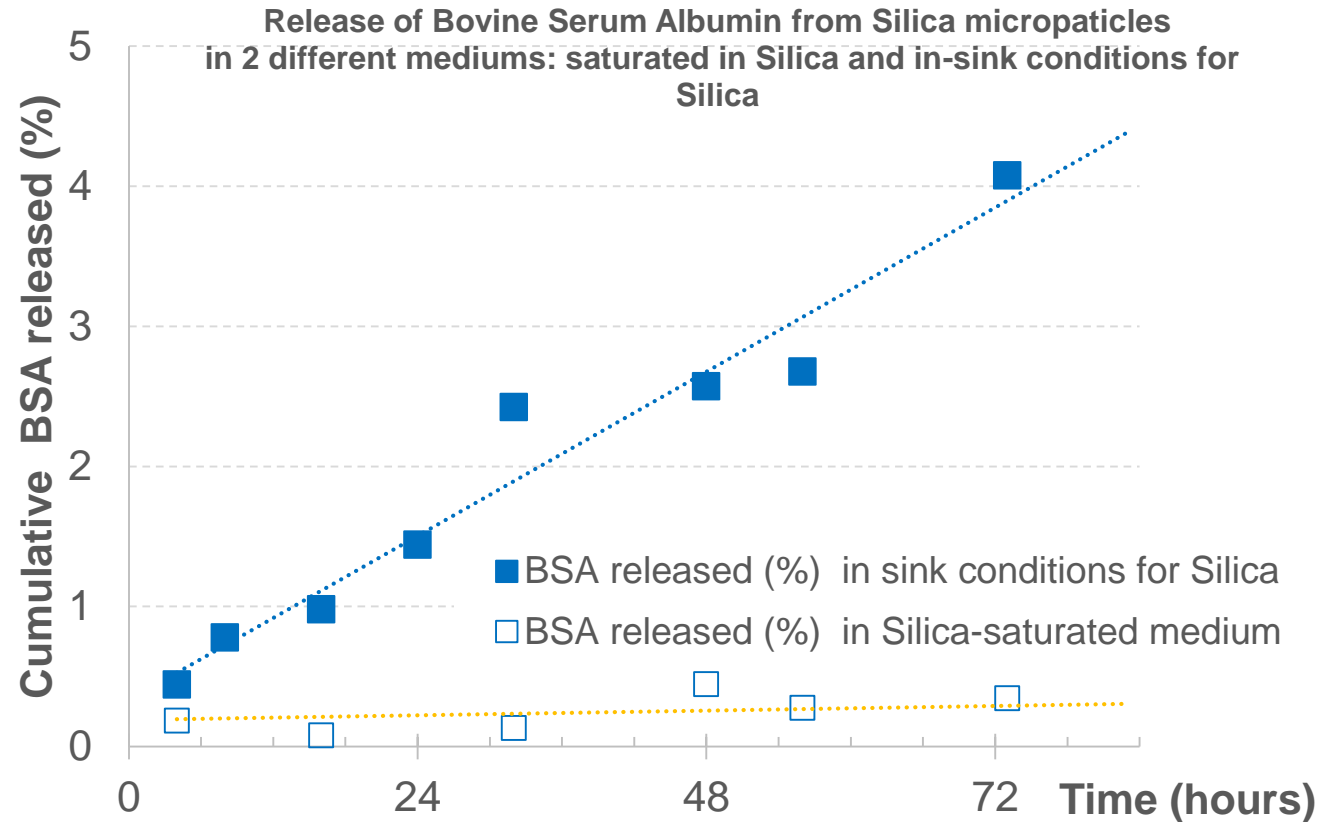


Conditions: 50mM TRIS, Tween 80 0.05% (v/v) + 0.5% SDS (w/v), 37°C
- In-sink dissolution of silica-silica microparticle – hydrogel composite depot

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The protein payload is released by controlled dissolution of silica (2)

- Bovine serum albumin (BSA) as a model of large protein (~66kDa)
- Dissolution test has been performed with
 - in sink conditions for the silica and
 - in silica saturated dissolution medium.
- Release is not based on diffusion
- No burst release is seen
- BSA is released from the depot only when the silica can dissolve (in-sink conditions for Silica)



DeSI Tech



Example 2: Sustained release of Bevacizumab

Long-acting release of Bevacizumab

- Goal: long-acting injectable of Bevacizumab for ocular delivery
- Bevacizumab
 - Anti-VEGF humanized antibody
 - Mass: 149 kDa
- Bevacizumab encapsulated with DelSiTech Silica Matrix technology.
- Microparticles dispersed in silica hydrogel
- Testing of in-vitro release and biological activity

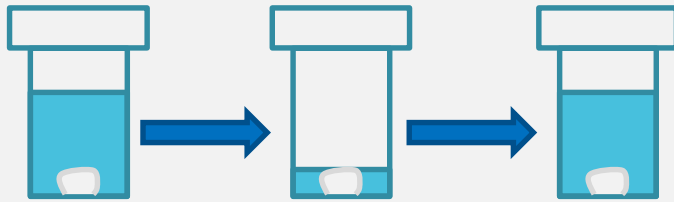
"Sustained in vitro release of bevacizumab from biodegradable silica microparticle-silica hydrogel composite formulations", P. Noppari , L. Puskala, M. Lagström, M. Päiviö, J. Mikkola, L. Leino ; ARVO 2019.



Dissolution: in-sink and flow through

In sink

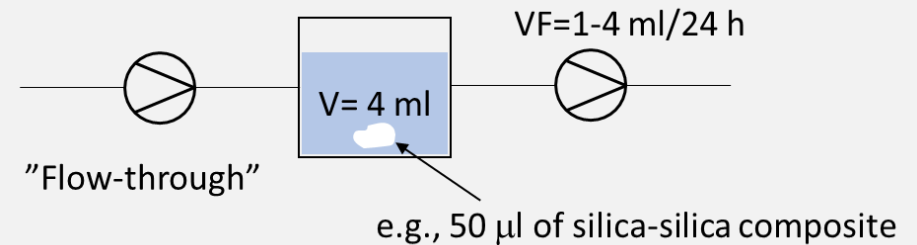
- Performed in TRIS buffer @ 37°C
50mM TRIS, Tween 80 0.05% (v/v)



- The buffer is exchanged regularly to keep the in-sink conditions of the silica
- In sink condition the dissolution is accelerated compared to in vivo

Flow through

- Performed in TRIS buffer @ 37°C [50mM TRIS, Tween 80 0.05% (v/v)]
- Mimic the in-vivo conditions. Not in-sink conditions



- The silica dissolution is limited by the flow of the liquid
 - The silica dissolution is the limiting factor for the API release
- ➔ Slower release used for prediction of the API release in-vivo

Adjustment of the Bevacizumab release rate

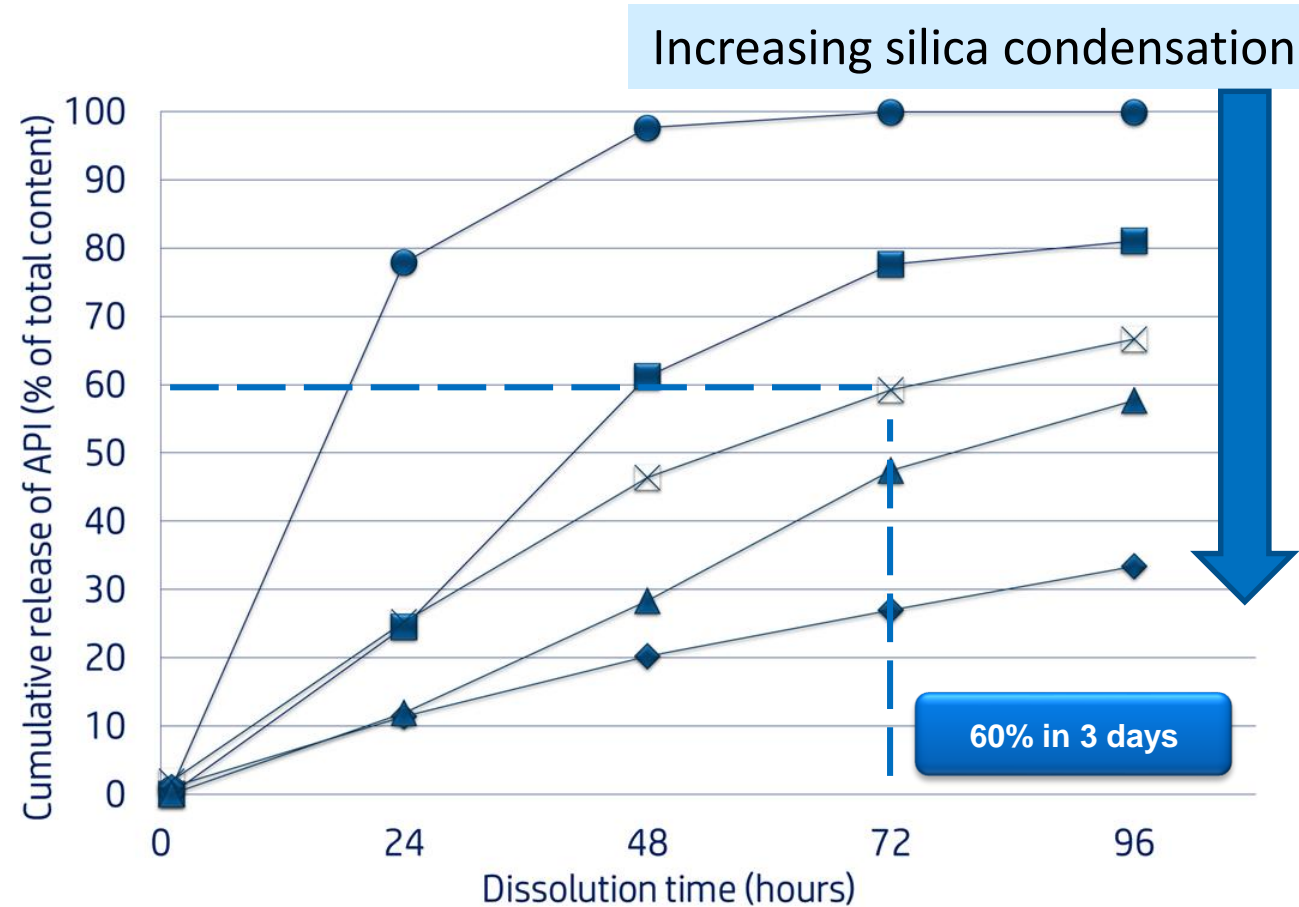
The release rate of the Bevacizumab is adjusted by adjusting the silica

The higher the water/silica precursor ratio is the higher the silica matrix condensation (less hydroxyl groups)

Increasing the condensation of the silica,
→ slows down the dissolution kinetics of silica
→ slows down the release rate of Bevacizumab

Other parameters can be left constant (particle size, temperature, pH, API loading...)

In vitro in sink dissolution release results for Bevacizumab from different injectable silica-silica composite hydrogel formulations



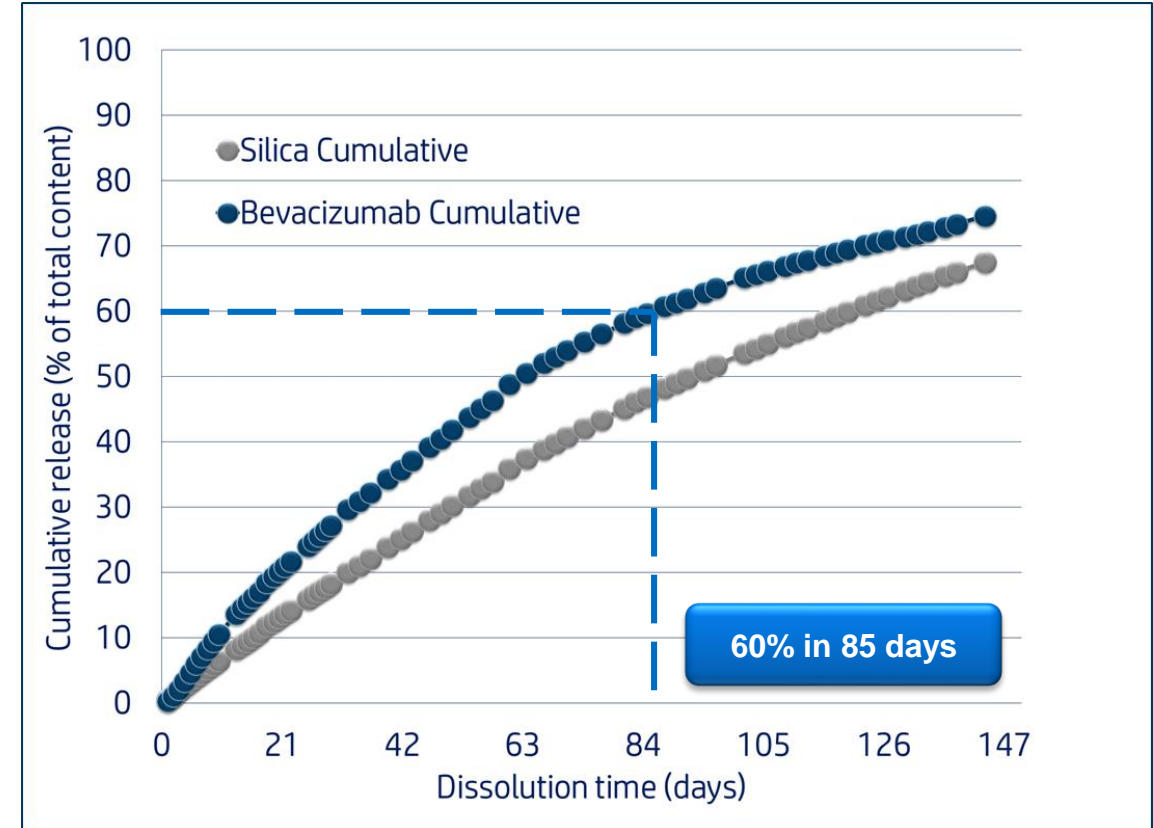
Flow through dissolution

- Flow through used to mimic/ in-vivo conditions
- The non-sink dissolution confirms the in sink dissolution
- Based on previous cases the in sink dissolution is about 20-30 times faster than in-vivo, same range for flow through.

- ➔ In sink is also a predictive model for animal studies.
- ➔ In sink can be used for in-vitro in-vivo correlation

Conditions: 50mM TRIS, Tween 80 0.05% (v/v) + 0.5% SDS (w/v), 37 C - In-sink dissolution of silica-silica microparticle – hydrogel composite depot

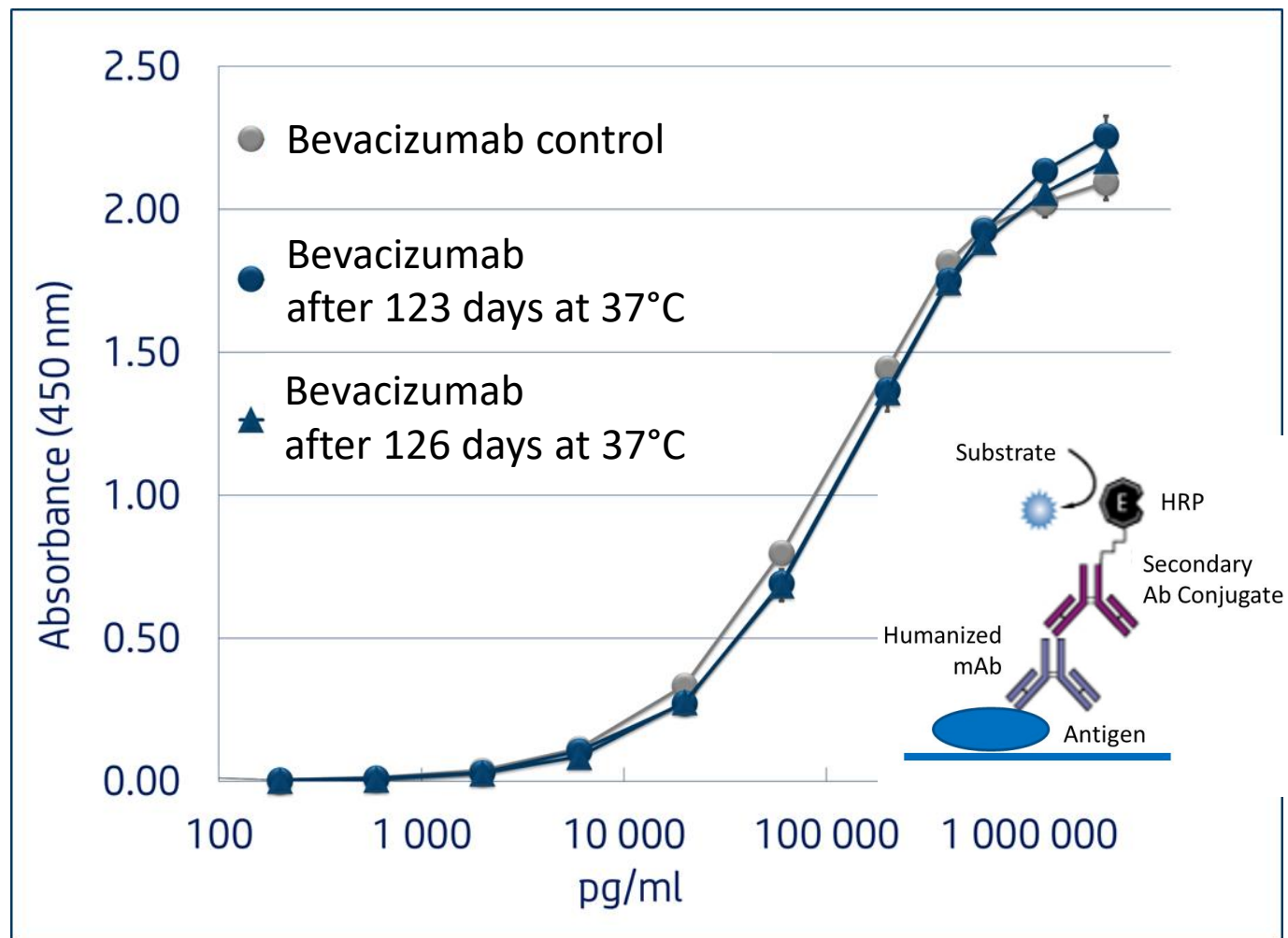
Flow-through dissolution in vitro results (simulating intravitreal conditions) for dissolution of silica and release of Bevacizumab from injectable silica-silica composite hydrogel.



Retained binding activity at 37 °C

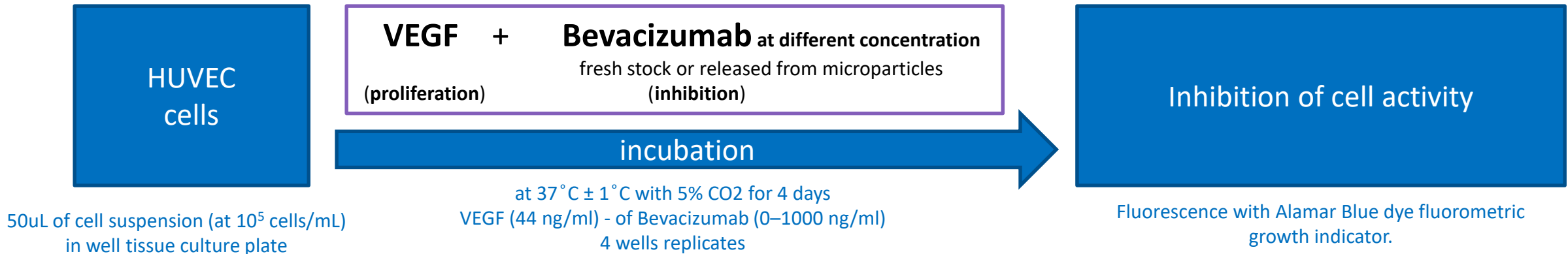
- Antigen-binding curves of Bevacizumab released from microparticles in flow-trough dissolution and a control sample made from fresh mAb stock.
- Storage at 37°C for 4 months.
- Dissolution for 48h followed by ELISA binding assay.

Binding activity is maintained for Bevacizumab released from the silica depot even after 4mo at 37 °C



Biological activity of Bevacizumab released from microparticles (1)

Biological activity of released Bevacizumab was analyzed by measuring inhibition of the VEGF induced proliferation of human umbilical vein endothelial cells (HUVECs)



- The growth of HUVEC cells is depending on VEGF activity.
- The anti-VEGF biological activity of Bevacizumab can be followed in verifying the inhibition of cell growth.
- Bevacizumab i) control and ii) released from microparticles were compared.

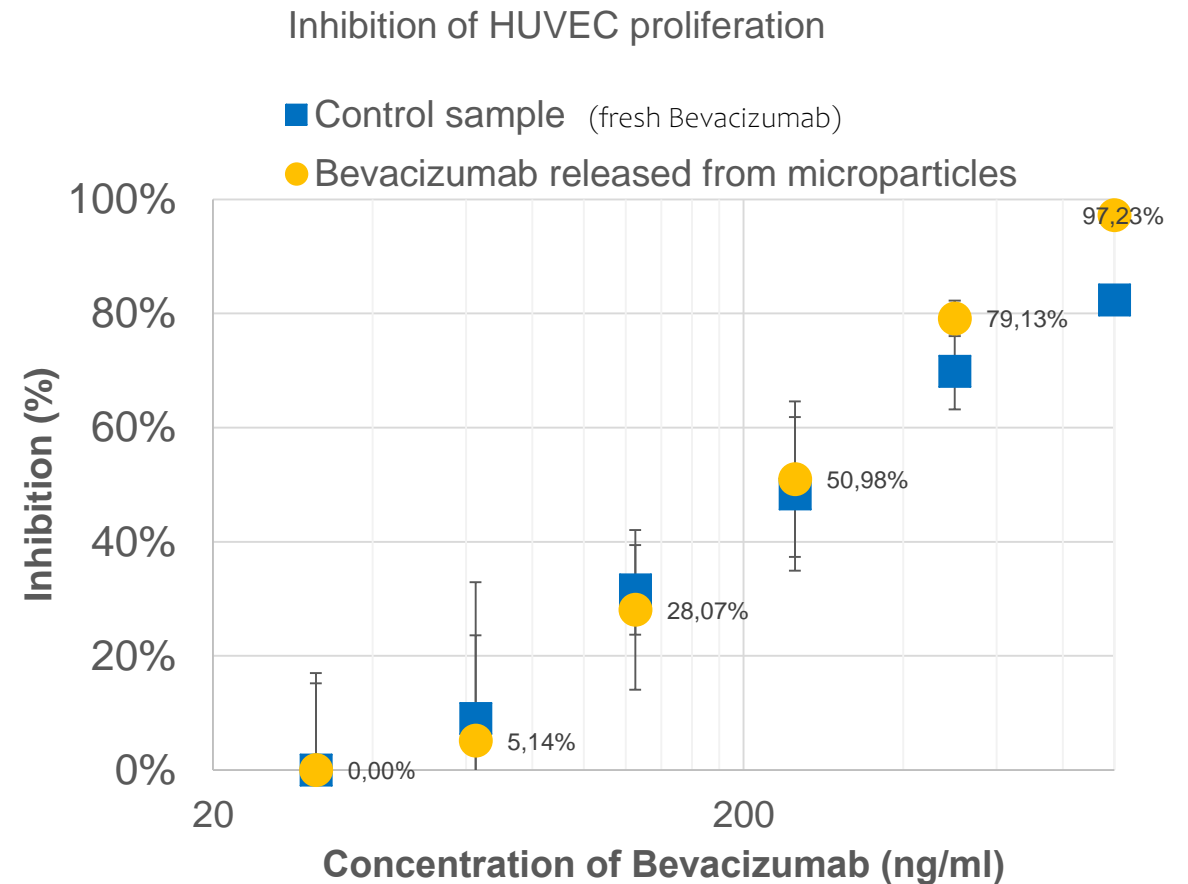
Reference of method: :Biological activity of bevacizumab, a humanized anti-VEGF antibody in vitro. Yaning Wang, David Fei, Martin Vanderlaan & An Song
Angiogenesis (2004) 7: 335–345 Springer 2005

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Biological activity of Bevacizumab released from microparticles (2)

- Inhibition of HUVEC cell proliferation was seen in both samples of fresh Bevacizumab and Bevacizumab released from the microparticles.

- The anti-VEGF biological activity of Bevacizumab is maintained after encapsulation and release from the microparticles





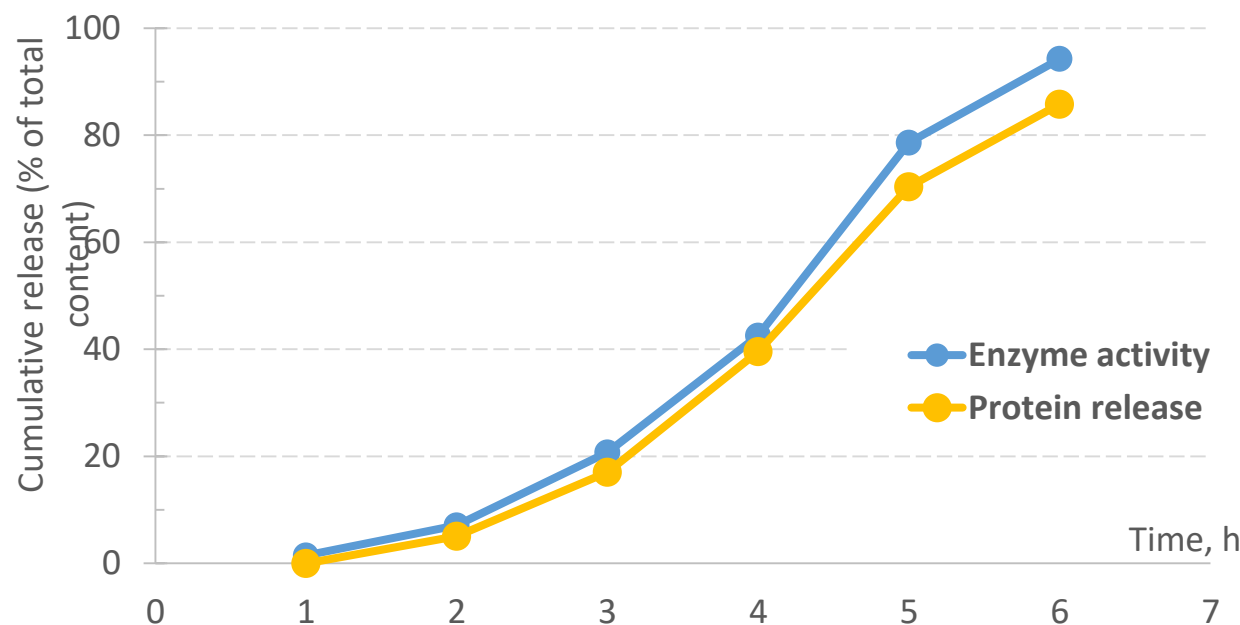
**Example 3:
Stability of biological activity (enzyme)**

Enzymatic activity maintained after encapsulation and dissolution

- The cumulative protein mass dissolution profile of the API release overlap the cumulative enzymatic activity.

- The specific activity of the enzyme remains intact after encapsulation process (spray drying).

Release of an enzyme from spray-dried microparticles during in sink dissolution test



Formulation spray dried at 100 °C inlet, outlet 57 °C.
Dissolution in 50 mM Tris pH 7.4 0.01 % Tween 80

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**Example 4:
In-vivo release of large proteins (mAb)**

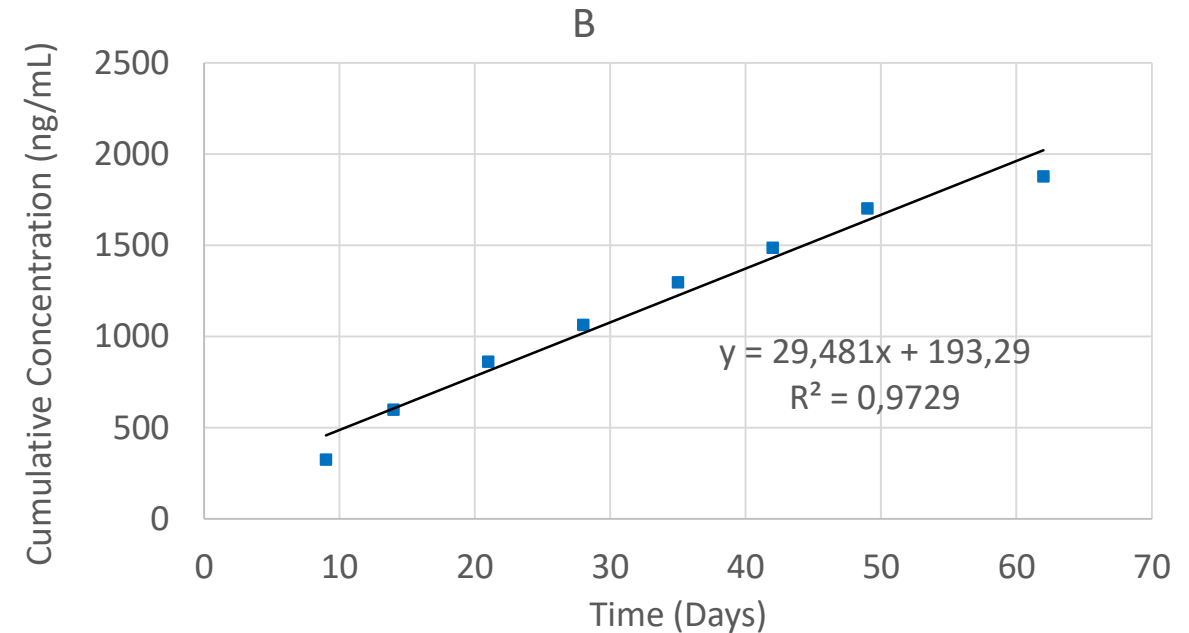
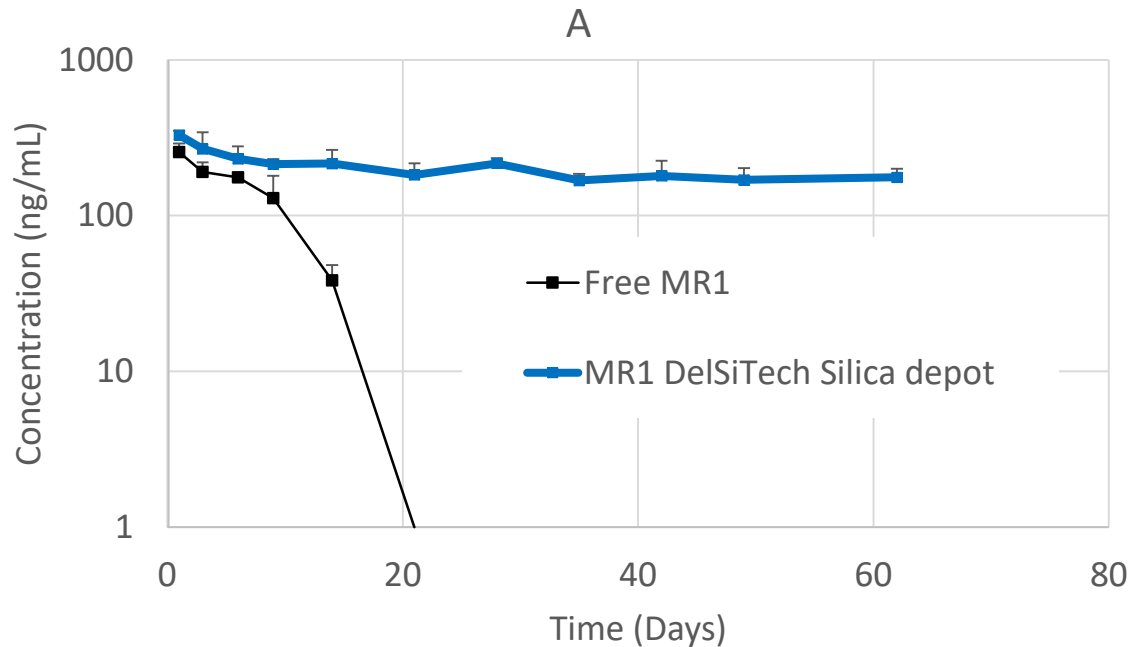
Example: 6-month protein controlled release

- Humanized anti-CD40L MR1 antibody
- Molecule properties :
 - MW ca. 150 kDa
 - Sparingly water soluble
- Target: 6 months release after subcutaneous injection
- Formulation strategy:
 - Encapsulation of MR1 in silica microparticles
 - Mixing MR1-silica microparticles with silica hydrogel
 - Protein load ca. 2.8 mass-% in the microparticles (8.4 mg in 1 ml injection)

Tyagi, P., Koskinen, M., Mikkola, J., Leino, L. & Schwarz, A. Silica microparticles for sustained zero-order release of an anti-CD40L antibody. *Drug Deliv. Transl. Res.* **8**, 368–374 (2018).

Example: 6-month protein controlled release

- In vivo results in mouse model after single s.c. injection: plasma profiles (A) and cumulative concentration (B)



Results (mouse model):

- Sustained stable plasma concentration for > 65 days
- Zero order release profile

DelSiTech

Long-Acting injectables with DelSiTech Silica Matrix:

- **Unique technology: biodegradable silica matrix composite of microparticles and hydrogel**
- **True control of API release based on silica erosion and not on API solubility**
- **Versatility: can encapsulate small molecules to large proteins**
- **Stabilization of the API in dry microparticles**
- **Retained chemical and biological activity**
- **Validated technology with several licensing agreements and developments**

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Contact Details

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