Different Biodegradable Silica Structures In Drug Delivery

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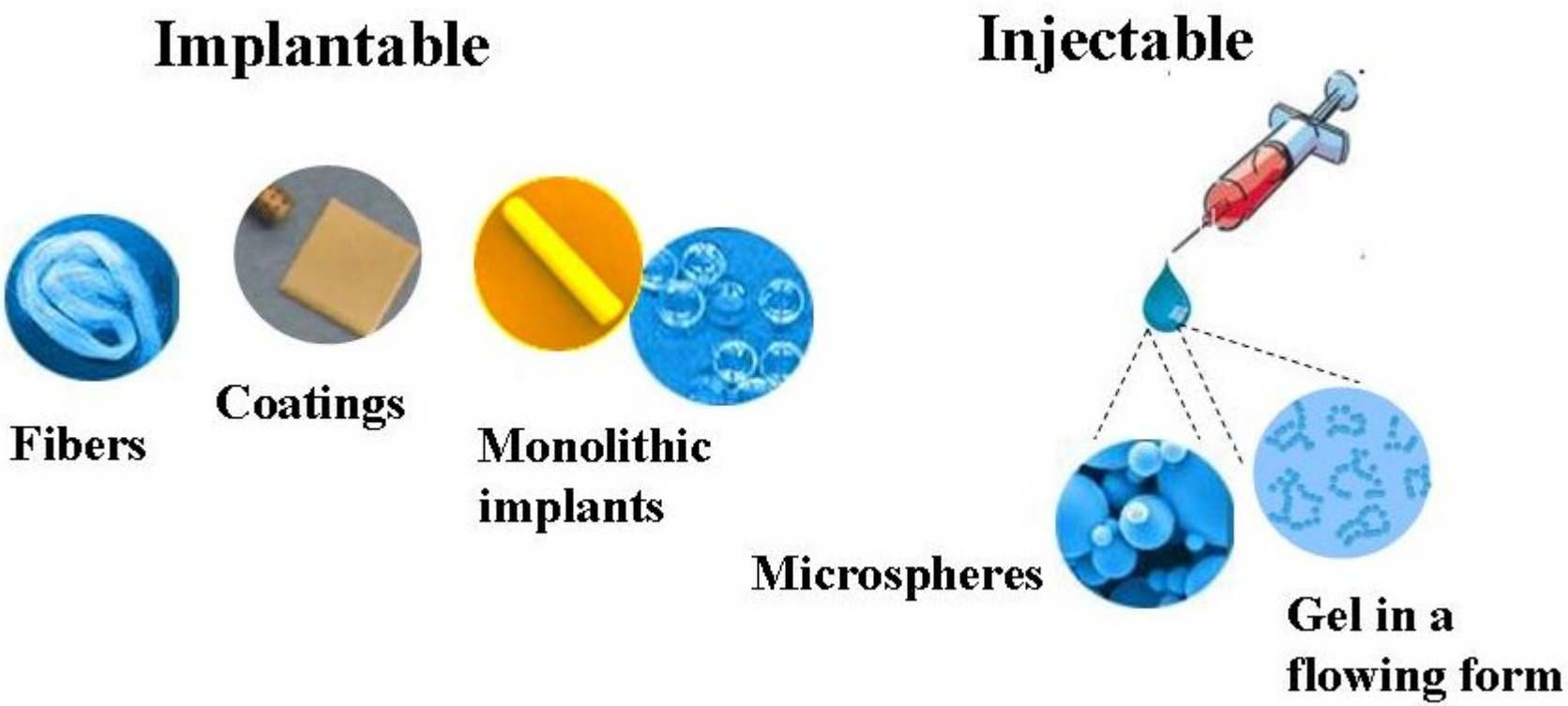
Different Morphologies of Biodegradable Silica

- ”Several levels of morphology”; different forms & structures
- monoliths, fibers, coatings, particles, nanoscale aggregates

- pore structure
-”chemical structure”; molecular level
- water (amount) in silica structures

} Can be varied on a large scale

Different Morphologies of Biodegradable Silica



…all used as biomaterials

Different Morphologies of Biodegradable Silica

- Silica can be prepared by **sol-gel technology**
  - mimics silica found in nature
  - variable amount of **H_2O** in resulting silica

- SiO_2 **hydrogels** (wet & soft)

↕

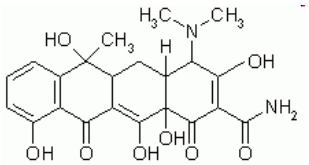
- SiO_2 **xerogels** (dry & hard)

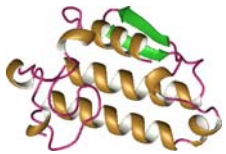
$SiO_2 \cdot nH_2O$

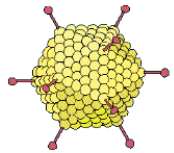
Different Morphologies of Biodegradable Silica

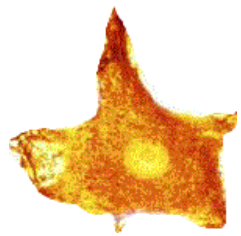
Why variation in morphology?

- Drug delivery device for many different kinds of biologically active agents (size, sensitivity etc.)









- Drug delivery device for different administration routes
  - also minimally invasive delivery

Silica by Sol-Gel Method – Why?

- The first sol-gel synthesis of silica was done already in 1860's
- in 1970's and 1980's studies on sol-gel silica in drug delivery
  → focus on pore structure (only)

→In general very much studied technology

- nanoparticle synthesis, controlled pore structures (with self-assembling polymers or other surface active agents), hybrids & composites etc.

… but what about the use as a biomaterial & toxicology?

→ We focused on biodegradation with plain silica

Silica by Sol-Gel Method – Why?

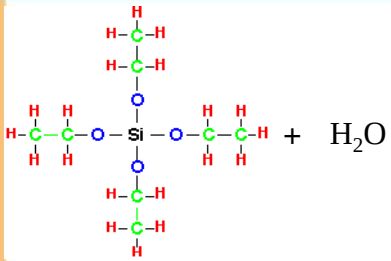
- In early 1990's Turku Biomaterials Research Group observed "weak signals" related to controlled release that was based on biodegradation of silica

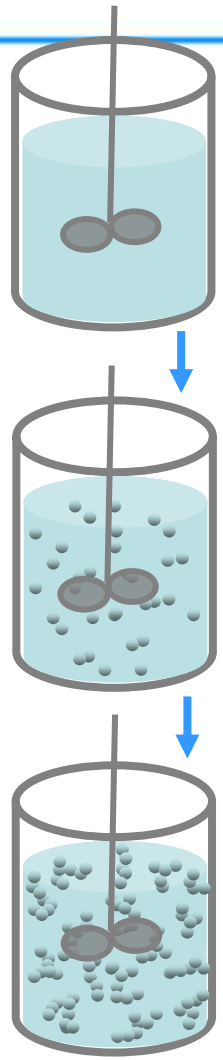
→ sol-gel technology

- good to combine with incorporation of drugs or active agents of any size by adding them into a liquid state during the process before a solid phase formation
→ effective encapsulation

→ sol-gel technology

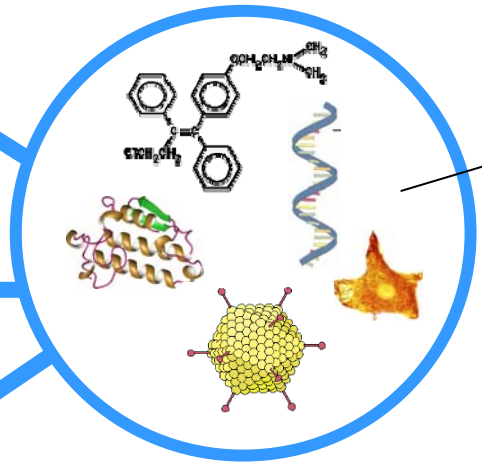
Encapsulaton of Drugs in Silica



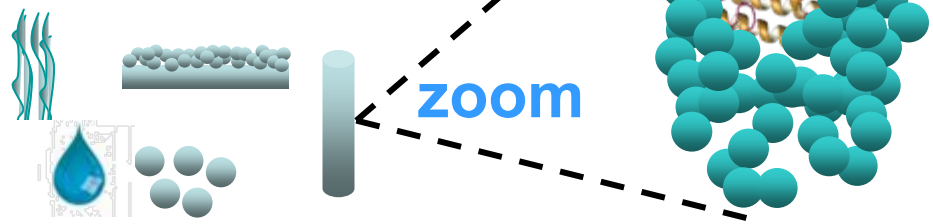


1. Reactions & nanoparticle formation and subsequent nanoparticle aggregation

2. Adjustment of properties (e.g., pH, temp.) prior to drug addition



Addition as longs as the system is flowing, i.e., when the liquid phase dominates



3. Form-giving to implantable or injectable form

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Biodegradation of Silica

- **Silica is biodegradable!**
  - even crystalline (e.g., quartz, but only few ppm)
  - amorphous silica about 130-150 ppm

→In spite of the low solubility→ adjustable biodegradation

- Processing at 20-40°C → from few days to few months

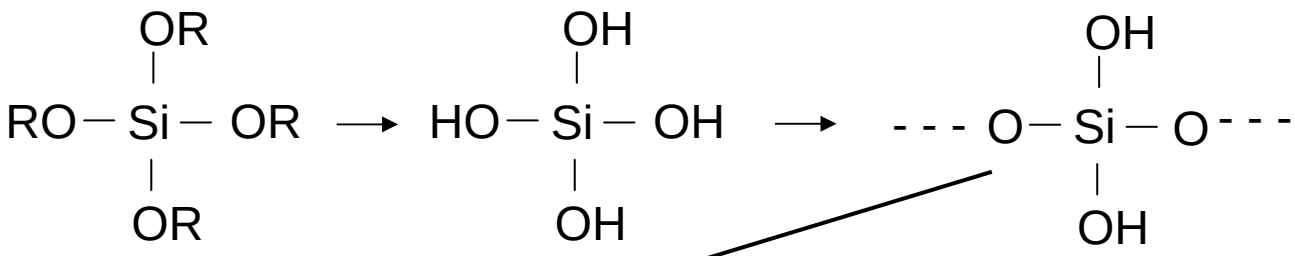
- low solubility → **dynamic system needed**
(liquid change & flow as it occurs in the body)

- low solubility → possible to store implants in water!

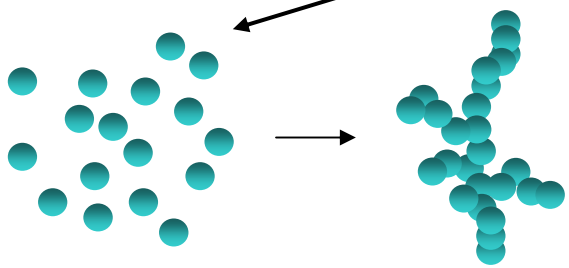
Biodegradation by dissolution only → No enzymatic degradation

Sol-Gel: Dual Nature of Silica Polymerisation

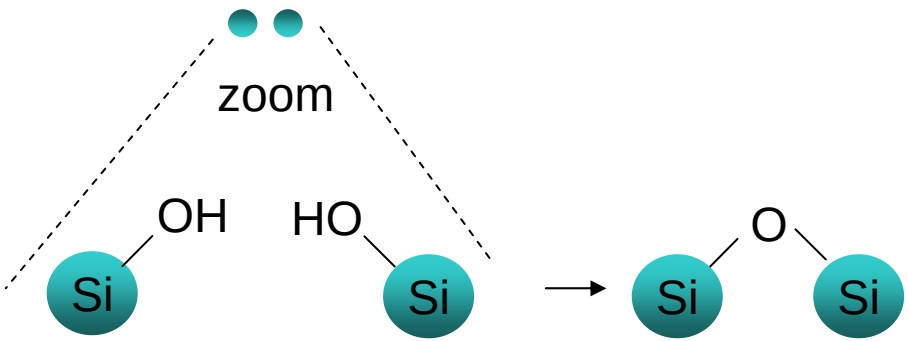
”molecular” polymerisation & aggregation



”Molecular” polymerisation



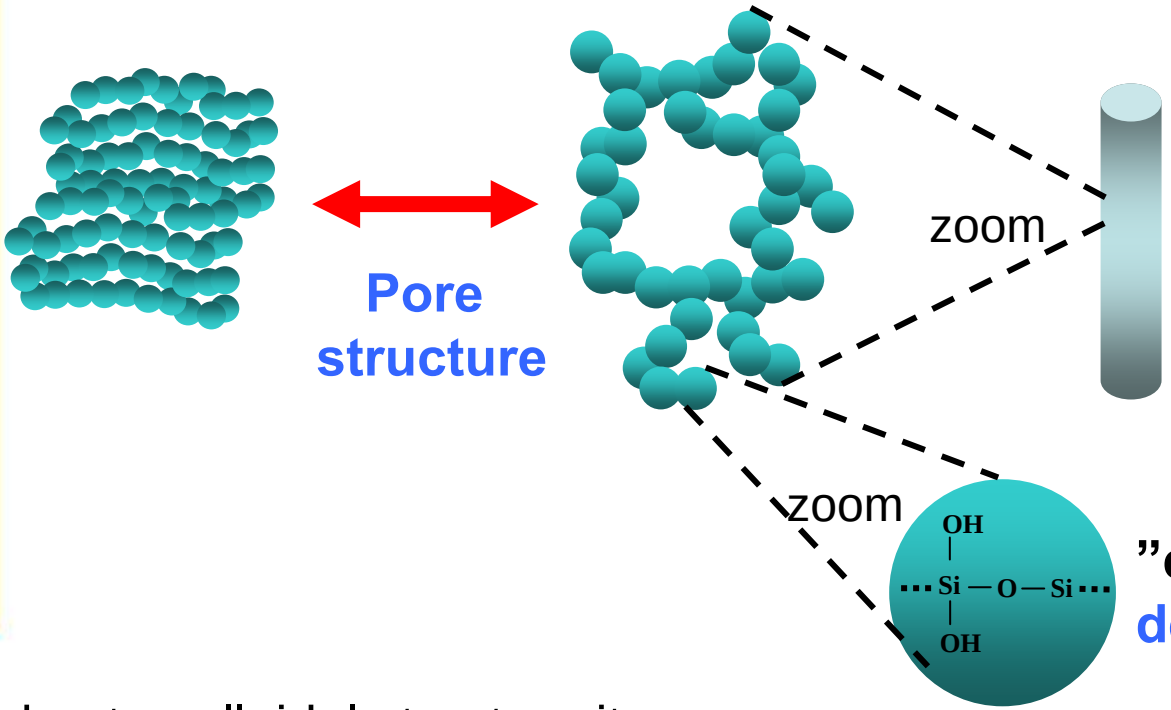
Aggregation by coagulation



”Chemical aggregation” of very small particles?

Sol-Gel: Dual Nature of Silica Polymerisation

…results in different structures

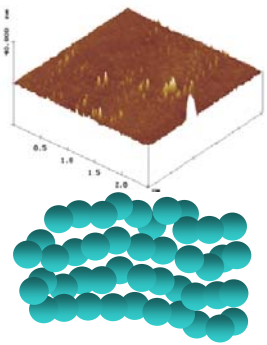


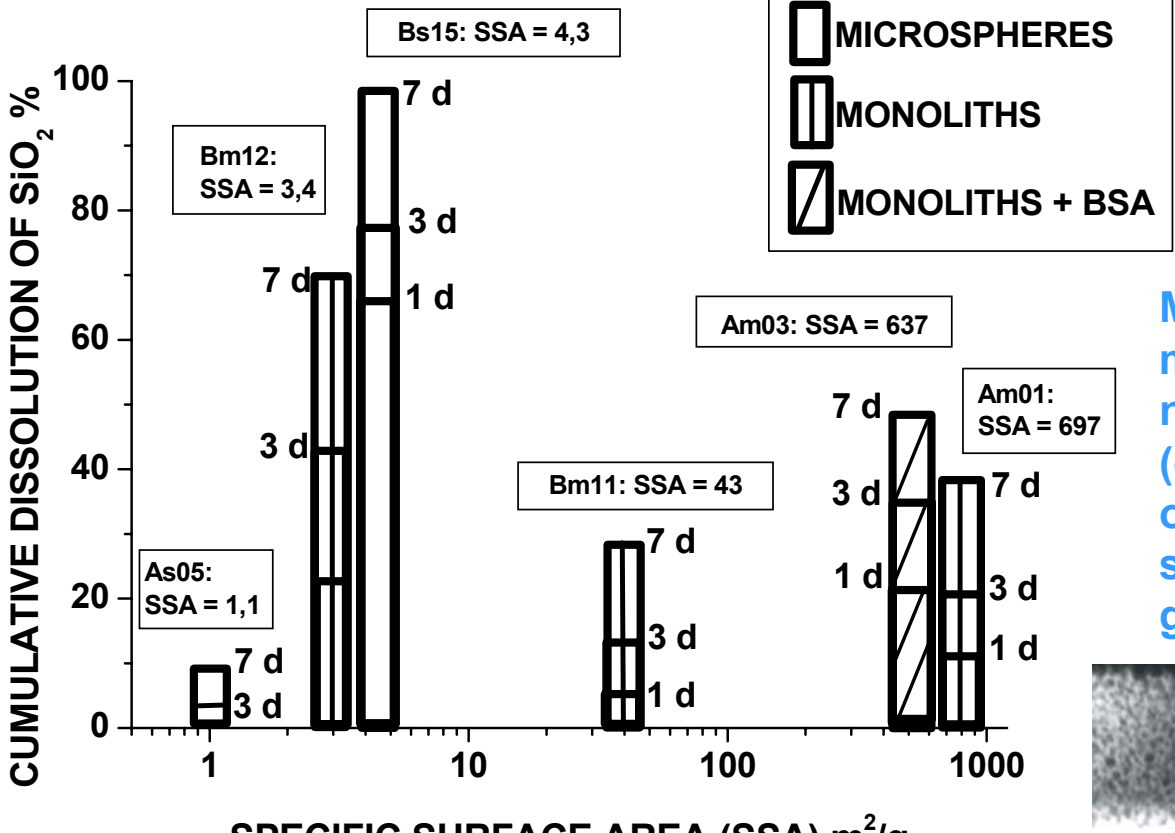
”chemical structure” :
degree of condensation

+ due to colloidal structure it
is possible to prepare silica structures,
even implants that contain >90% of water

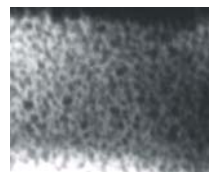
Controlled Biodegradation of Silica

t ≤ 40°C

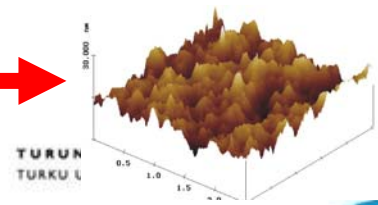


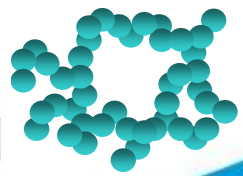


Match between molecular & nanoscale (overall impact of molecular structure is greater



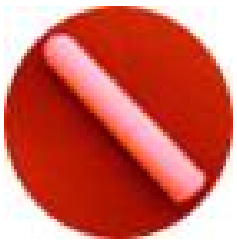
NMR	Q_2/%	Q_3/%	Q_4/%	$Q_4/(Q_2+Q_3)$
Am-	18,4	27,6	54,0	1,17
Bs-	0	79,6	20,4	0,26

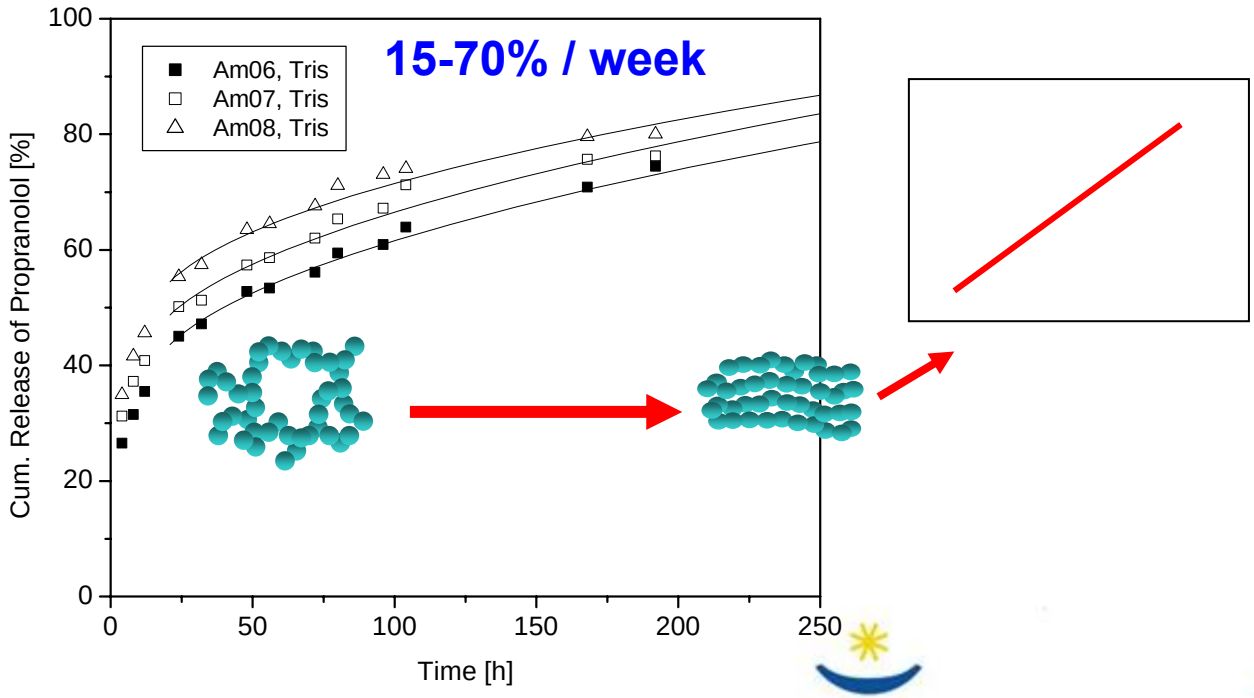




Release Mechanisms

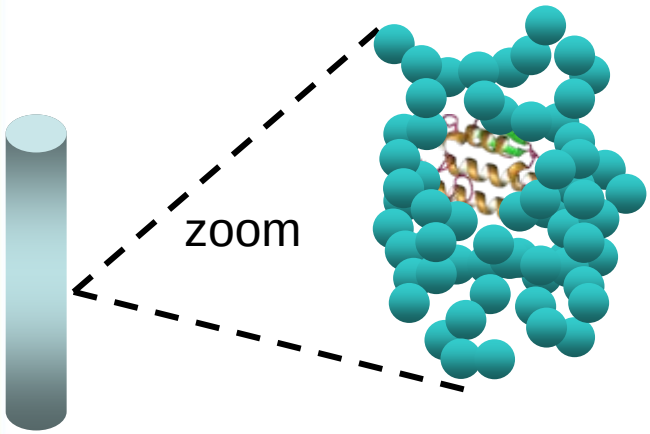
Monolithic rod + small drug molecule
with high water solubility:
diffusion-controlled release





Silica Degradation-based Release

- Monolithic rod + albumin: **matrix biodegradation-controlled** release; practically no release without the SiO_2 matrix dissolution!



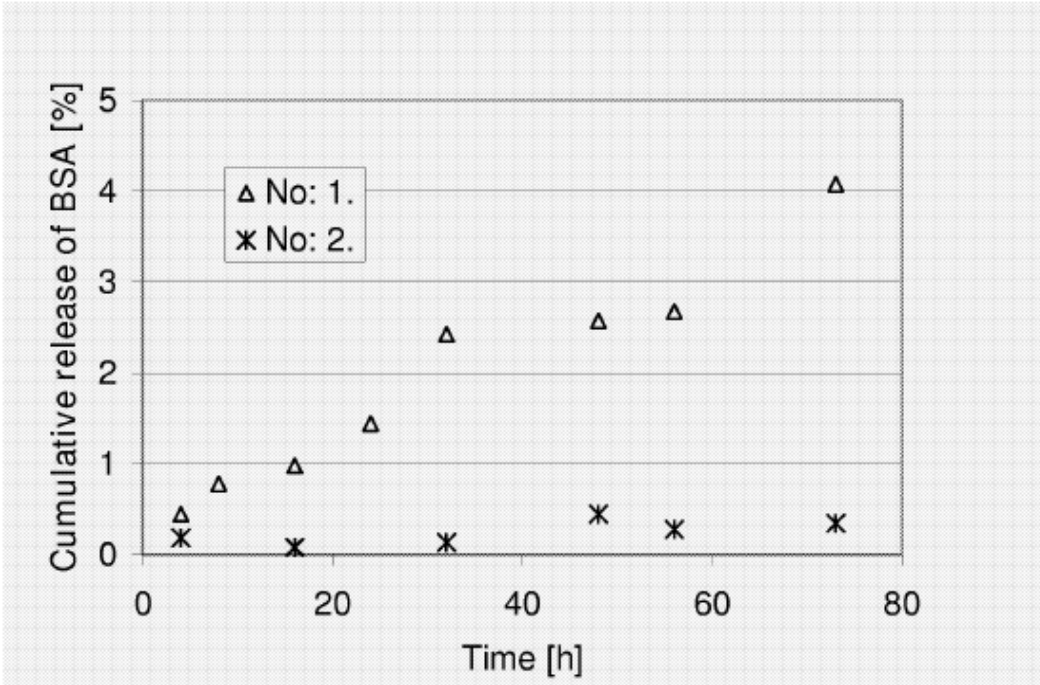
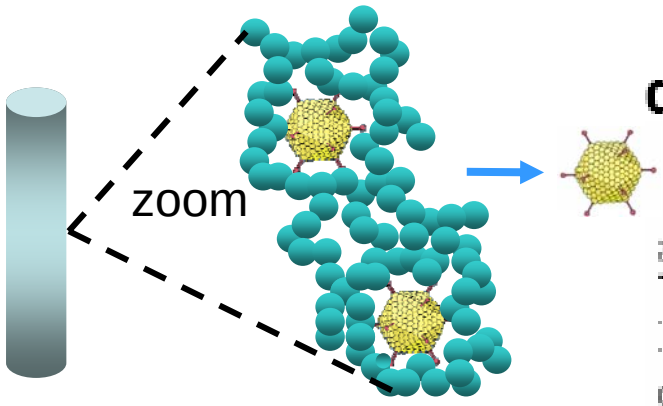


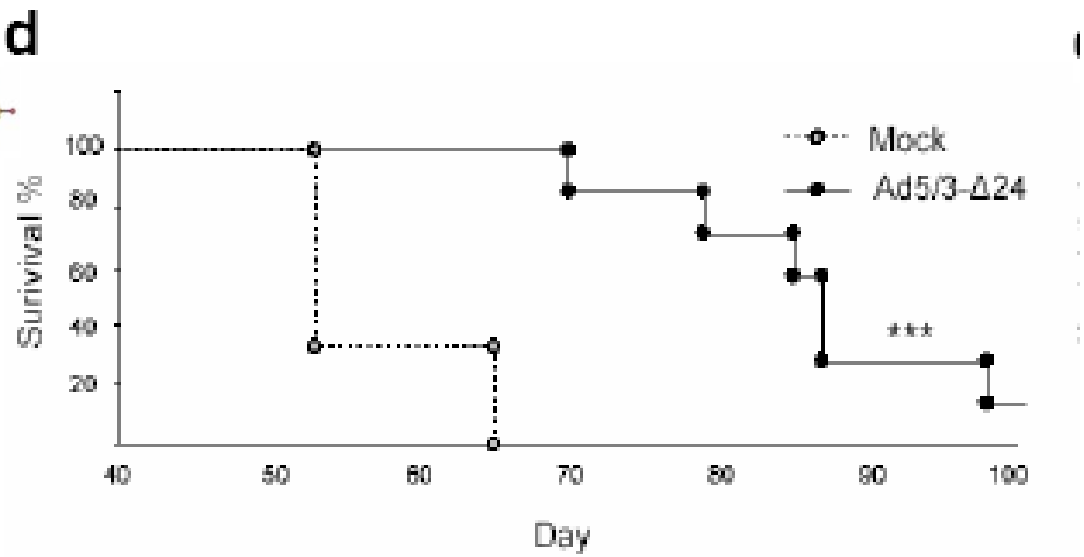
Figure 6

- The same observed for viral vectors and low water-soluble small-molecule drugs

In vivo Study on Therapeutic Viral Vector

- Survival of mice with pancreatic cancer treated with therapeutic viruses encapsulated in DelSiTech's silica





- **COLLABORATION WITH:**

UNIVERSITY OF HELSINKI
RATIONAL DRUG DESIGN / CANCER THERAPY GROUP

From L. Kangasniemi, M. Koskinen, M. Jokinen, H. Jalonen, A. Hemminki et al., Extended Release of Adenovirus from Silica Implants *In vitro* and *In Vivo* (Gene Therapy 16, 2009)

Mock = silica implant without viruses

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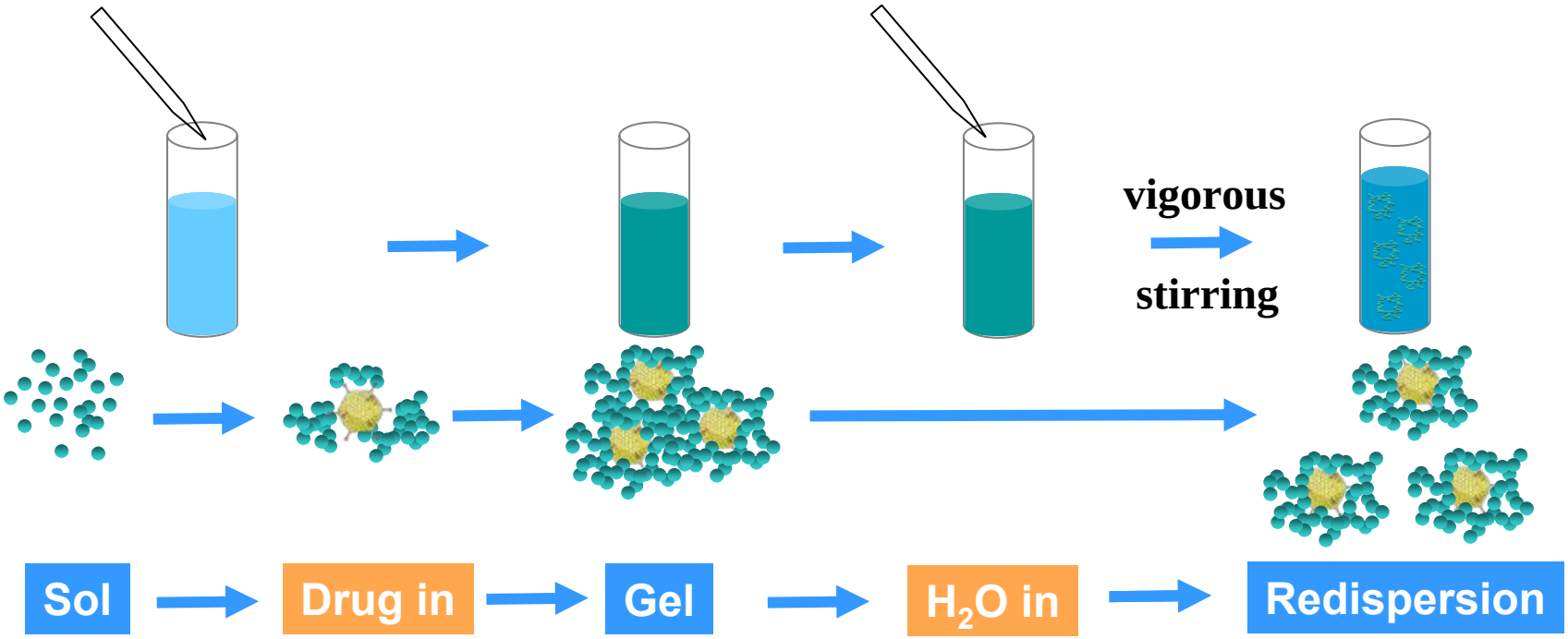
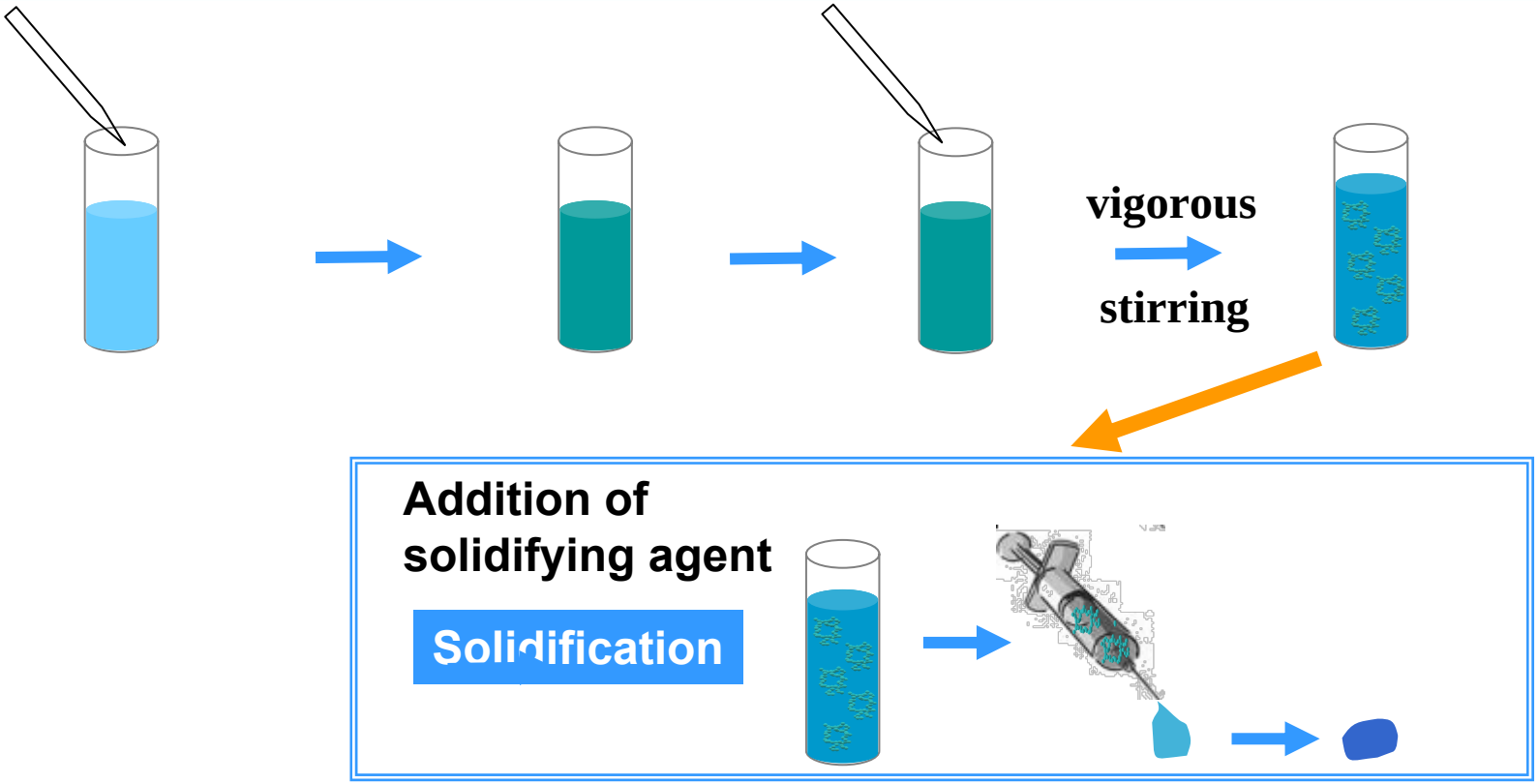
One-pot Synthesis of Injectable Silica



Possible to inject with very thin needles, e.g., 31G (Ø =ca. 0.25 mm) → suitable also for intraocular delivery

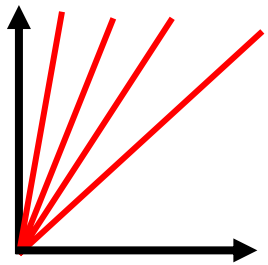
Regelling / Solidification of Injectable Silica



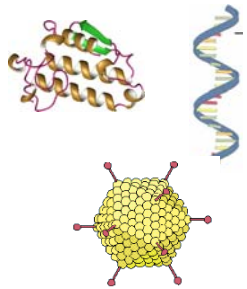
After injection a semi-solid, implant-like structure

Benefits of Biodegradable Silica

- **Steady & sustained release;** days to months
  - large molecules & other agents
  - small molecules with low water solubility



- **Labile drugs retain their activity** in silica
  - high H_2O content =mild conditions
  - proof of concept for several labile drugs, **only solution to viruses** to our knowledge



- **Effective encapsulation**
  - injectable, implantable

- **Options for delivery, also minimally invasive**
  - implants & injectable formulations (26-31G)

Thank you for your attention!

Morphologies from nature: diatoms with a silica shell

”the jewels of the sea”

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