

FEASIBILITY OF SILICON AND SILICA BASED MESOPOROUS MATERIALS FOR ORAL DRUG DELIVERY APPLICATIONS

Jouni Hirvonen

Professor
Division of Pharmaceutical Technology, Faculty of Pharmacy,
University of Helsinki, Finland

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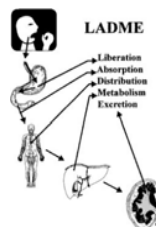
Outline and rationale for the Si and SiO₂ studies

- **Background**
 - Fabrication and properties of silicon and silica mesoporous microparticles
- **Aims of the study**
- **Experimental Results**
 - Cellular toxicity
 - Drug dissolution profiles
 - Drug absorption
- **Summary**



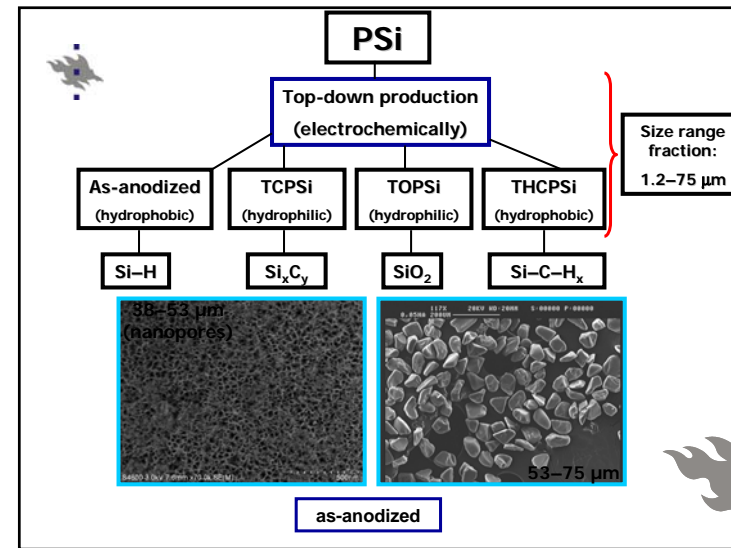
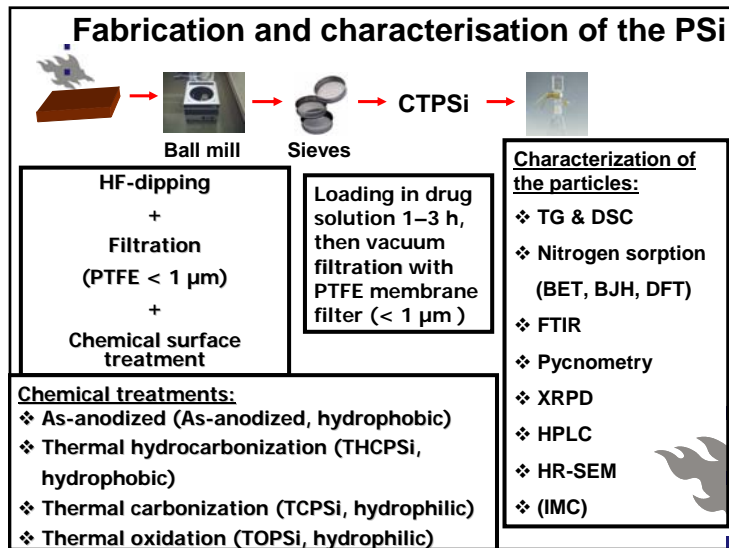
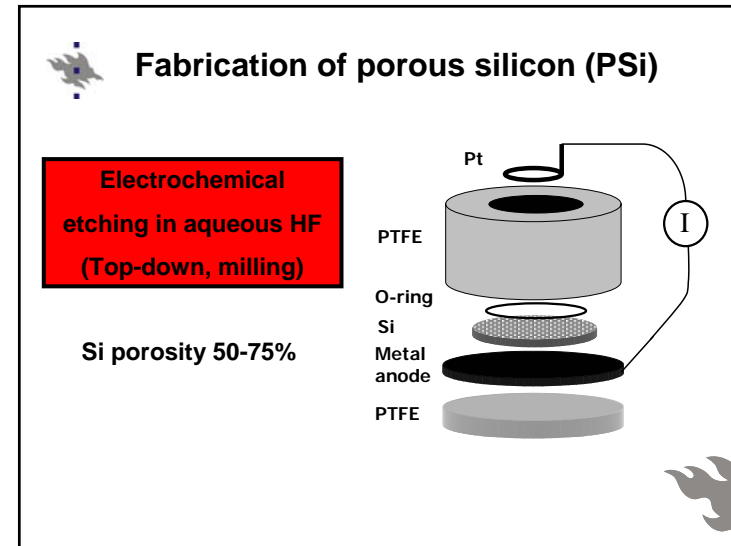
High demand for new oral drug formulation technologies

- **Difficulties to develop successful drug candidates due to poor bioavailability when administered via the oral route**
 - Low solubility and dissolution rate in the stomach and intestinal lumen
 - Poor permeability properties in the GI tract
 - High intestinal and/or hepatic first pass metabolism
- **Dissolution and absorption enhancing drug delivery systems and materials regarded "key technologies" of drug formulation development today**



Why mesoporous particles?

- **Small size pores (2–50 nm) to confine space for drug molecules in an amorphous form**
 - disordered structure can be stabilized (reduced lattice energy)
- **Pore wall–drug molecule interactions**
 - small enough to avoid crystallization of drug molecules
 - prevent strong chemical interactions between the drug and the pores
- **Pore radius is large enough for fast release**
- **Wettability can be improved (hydrophilic particles)**
- **High drug load capacity (> 30%)**
- **Fabricated with desired surface chemistry, pore size, shape and morphology to achieve improved release kinetics**
 - resist the harsh conditions of stomach, GI lumen, and first pass metabolism maintaining their physicochemical properties unchanged
 - high local concentration due the drug loaded porous microparticles → improve the drug permeation across the GI wall



Mesoporous material as a drug delivery system

HR-TEM of actual mesoporous material

Mesopore \varnothing 2.5 nm
Ibu 1.0 x 0.5 nm

- Nanoscale pore prevents crystallization of loaded drug
- The drug is delivered in the amorphous/disordered form

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Mesoporous Material as a Drug Delivery System

HR-TEM of actual mesoporous material

% Drug loading:
 Antipyrine – 53
 Furosemide – 41
 Ranitidine – 40
 Ibuprofen – 39
 Indomethacin – 35
 Beclomethasone – 30

Fast release of drug with a dissolution and permeation enhancing effect!

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PSi and PSiO₂ in oral drug delivery applications (Dosis 24: 129-149)

Drug loading ("formulation")	Storage	Administration (dosing)
<ul style="list-style-type: none"> PSi/SiO₂ – solvent stability Drug – solvent stability PSi/SiO₂ – drug stability Loading degree Crystallinity of drug 	<ul style="list-style-type: none"> PSi/SiO₂ – drug stability Humidity Crystallinity of drug (Temperature) 	<ul style="list-style-type: none"> Toxicity Biocompatibility <ul style="list-style-type: none"> Biodegradation Dosing <ul style="list-style-type: none"> Crystallinity Surface interactions Hygroscopicity

Cell toxicity/viability tests (Dr. Helder Santos)

Three different viability assays

- CellTiter-Fluor[®] Cell Viability assay
- Luminescent Cell Viability Assay (CellTiter-Glo[®])
- Flow cytometer

GF-AFC substrate

GF-AFC substrate + Live-Cell substrate → AFC

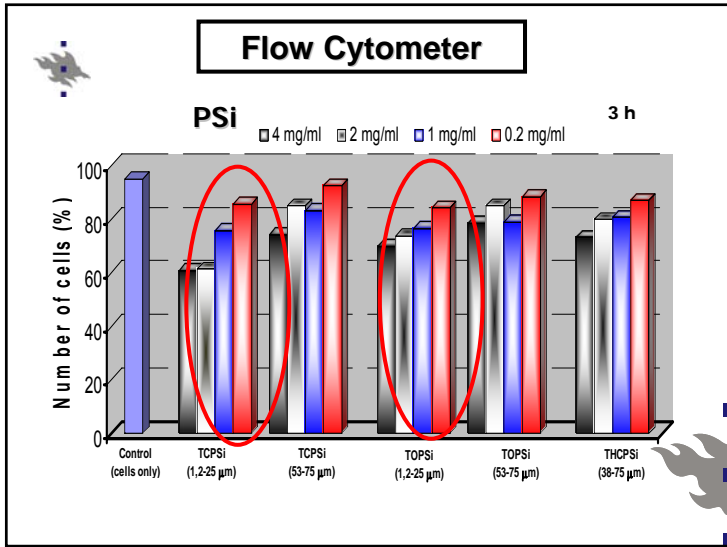
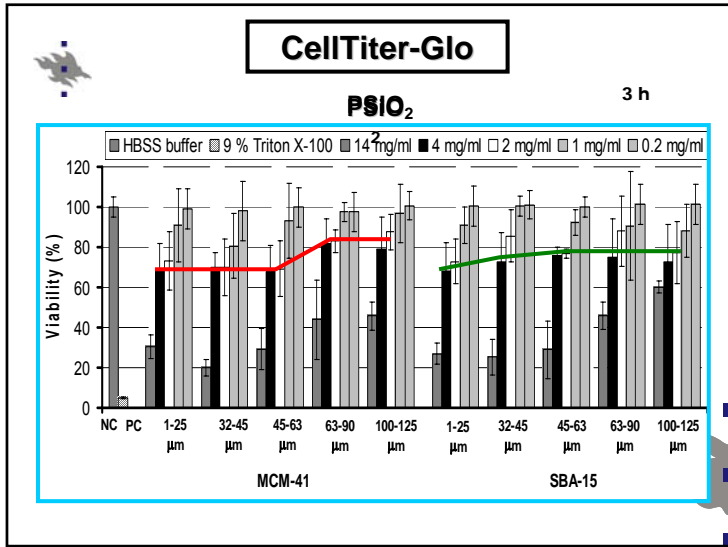
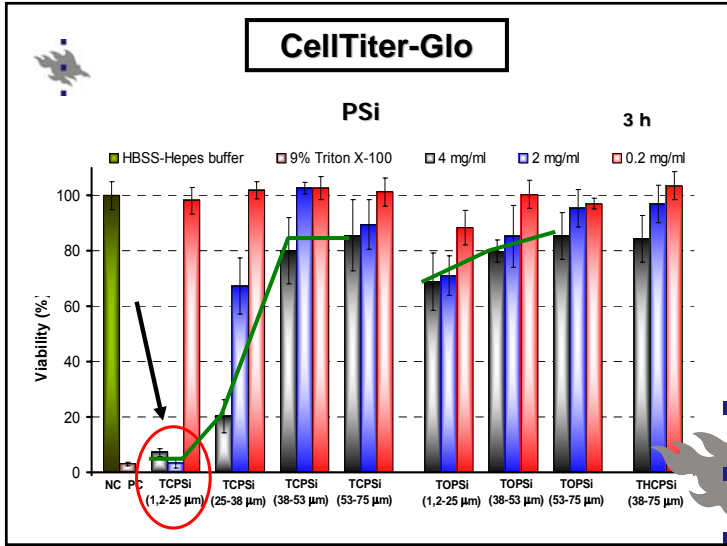
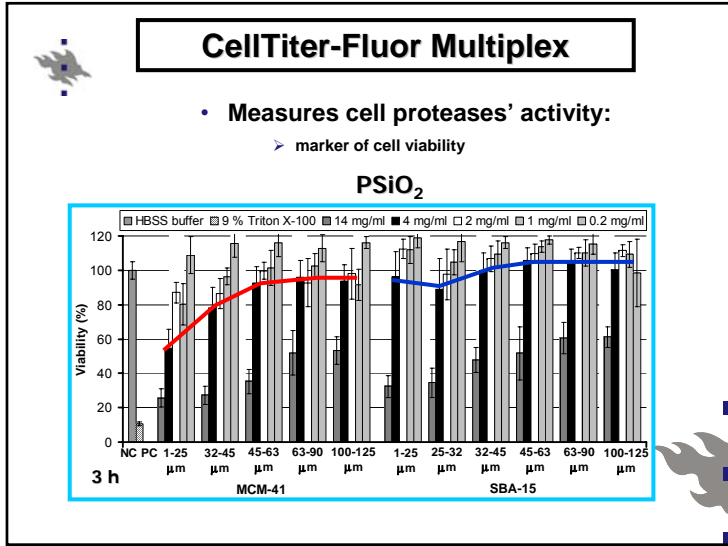
AFC + Luciferase → Light

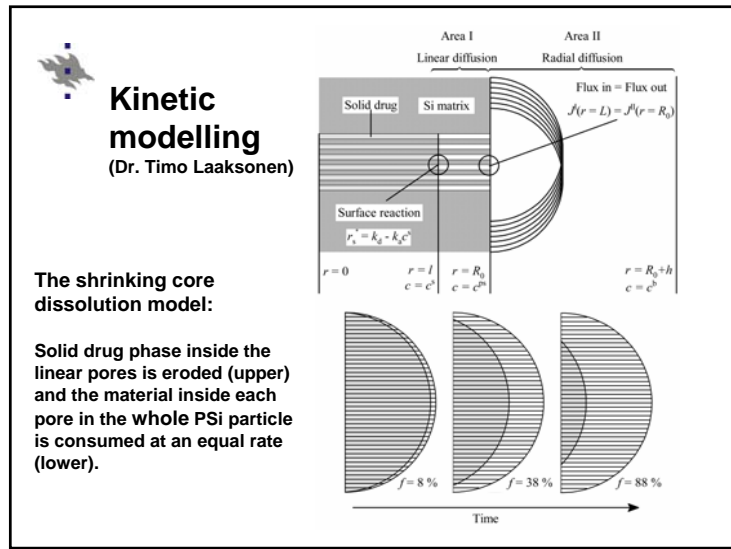
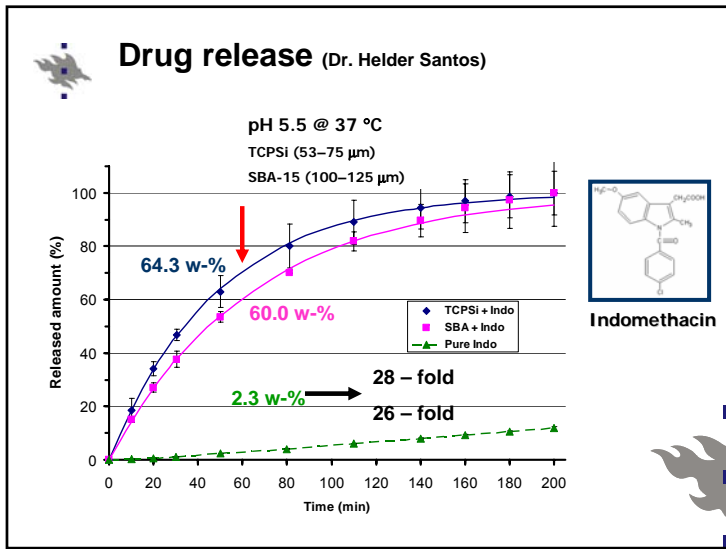
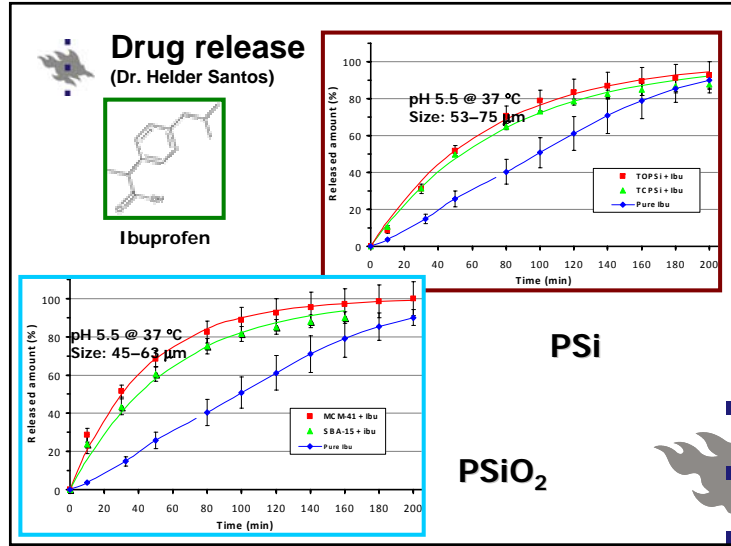
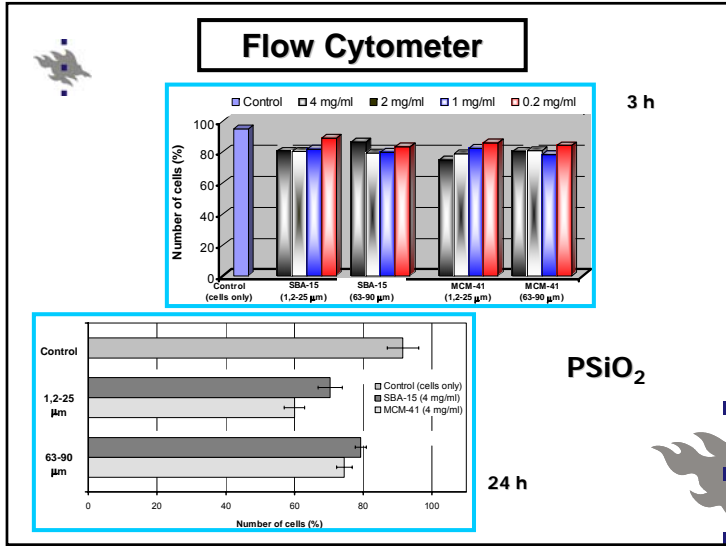
Oxyliclerin

+AMP+PPi+CO₂+Light

- FSC (forward scatter channel):
 - Info on particle/cell size
 - distinguish between debris, clumps and living cells
- SSC (side scatter channel):
 - Info about granular content of the sample
- Cells stained with a fluorescent dye: Propidium Iodide (PI)

Source: Promega[®]

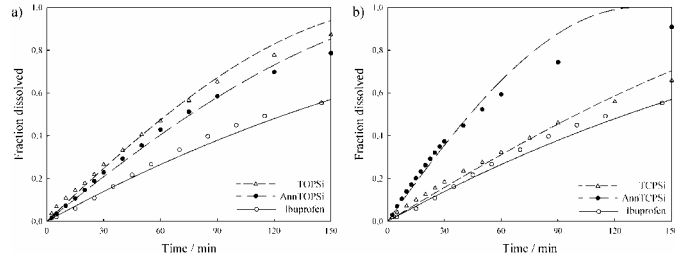






Kinetic modelling

(Dr. Timo Laaksonen)

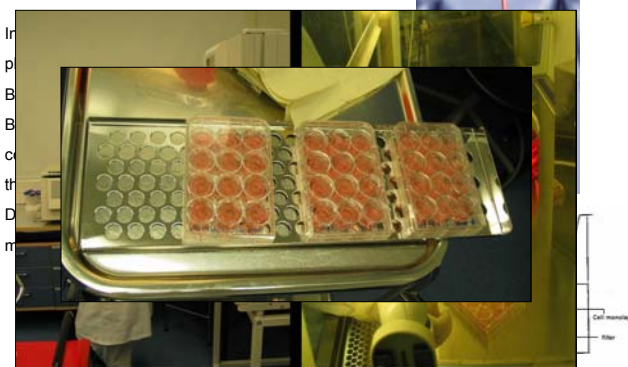


Dissolution profiles for ibuprofen and ibuprofen loaded PSI-particles. Symbols mark the measured dissolution curves and lines are calculated values fitted to the data by adjusting the rate of the surface reaction.



Drug permeation studies

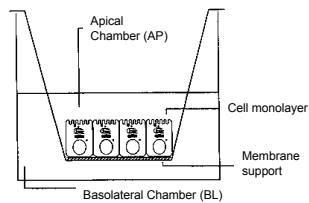
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Permeability experiments across Caco-2 cell monolayers

Permeation from apical to basolateral chamber (absorptive direction)

Caco-2 cells (ATCC), P31-42, grown on 12-well Transwells, monolayer age 21-28 days



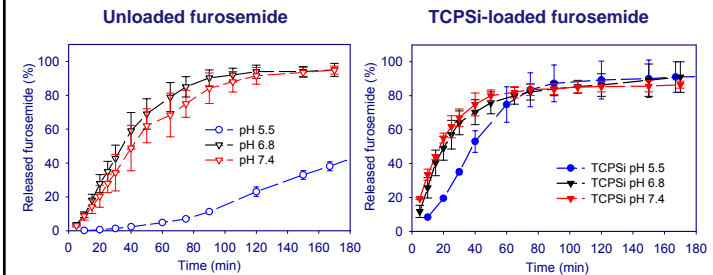
- apical pH 5.5, 6.8 and 7.4
- basolateral pH 7.4
- furosemide solutions
- suspensions of furosemide-TCPSi
 - about 1.5 mg per monolayer
- apical chamber transferred to fresh basolateral chamber every 25-30 min up to 180 min
- TEER determined before and after
- mannitol permeability checked after

$$P_{app} \text{ (cm/s)} = \Delta Q / (\Delta t \cdot 60 \cdot A \cdot C_0)$$

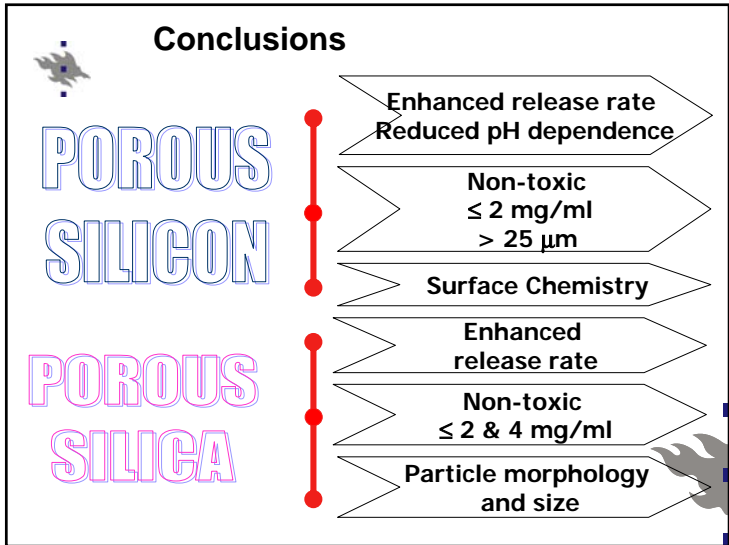
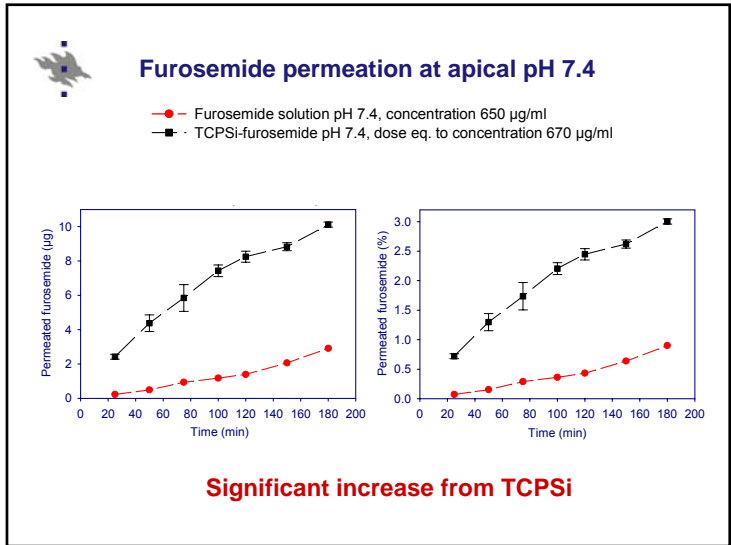
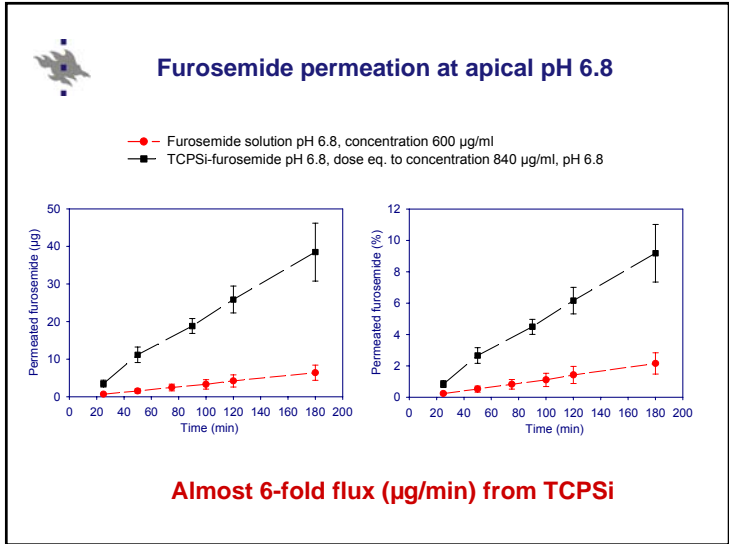
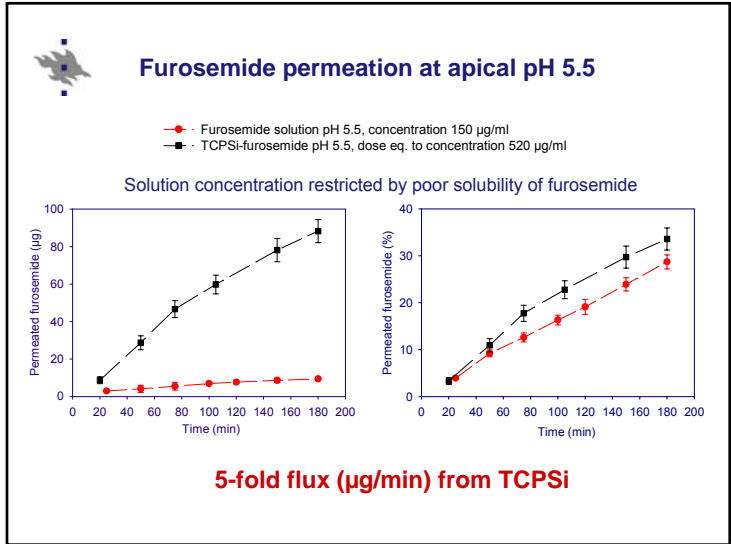
$$\Delta Q / \Delta t = \text{flux across monolayer (}\mu\text{g/min)}$$



Dissolution of unloaded furosemide and from TCPSi microparticles



Marked difference at pH 5.5



Acknowledgements

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M. Kemell & M. Ritala



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N. Kumar, D. Yu. Murzin, T. Salmi



ACADEMY of FINLAND

Articles

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Thank you for coming!

