Administrarea transcutanata a medicamentelor: o abordare microtehnologica

Ciprian Iliescu,
Institute of Bioengineering and Nanotechnology

Cercetarea stiintifica in Singapore

- Tinta: Industrie condusa de R &D
- Economie bazata in principal pe: Industria petroliera, Banking, Santier naval, *Microelectronica*, *Biofarmaceutica*
- Nr personalului angajat in cercetare a crescut de la 12000 in 2001 la 25.000 in 2009 (si populatia a cresut de la 3.5 mil in 2001 la 5 mil in 2010)
- Investitile anuale in cercetare: 2 miliarde de Euro
- Agentia de stiinta divizata in doua ramuri: inginerie (microtechnologie) si biomedicala.
- Invatamintul universitar este axat pe dezvoltarea celor doua ramuri
- Modalitati de finanta:
  - Finatare directa de la agentie
  - Aplicatii Proiecte

Institute of Bioengineering and Nanotechnology

- Infintat in Martie 2003 (ED Prof Jackie Ying)
- Personal: 150 / inlusiv studenti
- No 7 in Asia
- Target : cercetare interdisciplinara cu aplicatii in Biologie si Medicina
- Arii de cercetare:
  - Cell and Tissue Engineering
  - Biosensors and Biodevices
  - Drug and gene Delivery
  - Pharmaceutical Synthesis & Green Chemistry

Outline

- General consideration regarding transdermal drug delivery
- Microneedles
- Microneedles with ultrasound enhancer (SEMA- method)
- Summary

Drug delivery- definition and methods

Definition:

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals.

Drug delivery methods:

- Invasive: injection (protein, peptides)
- Non-invasive:
  - Peroral (through the mouth),
  - transmucosal (nasal, sublingual, vaginal, ocular and rectal)
  - inhalation routes
  - **Transdermal** (skin).

Transdermal drug delivery enhancers

Transdermal drug delivery is more advantageous due to its better patient compliance than injection and oral delivery

Problem:

- drug release is limited by low skin permeability.

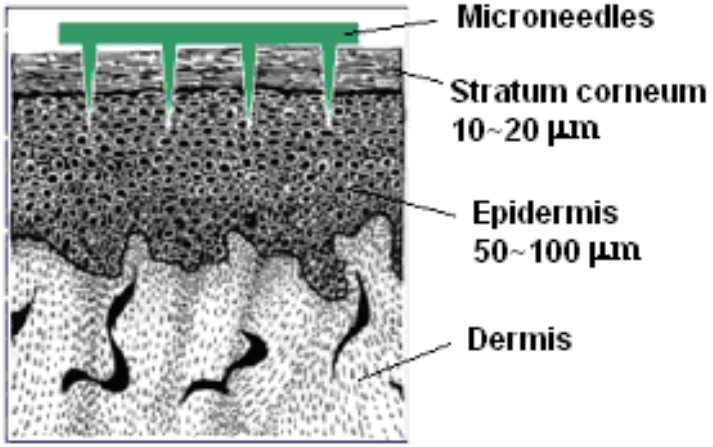
- No proteins /peptides can be administered transdermal.

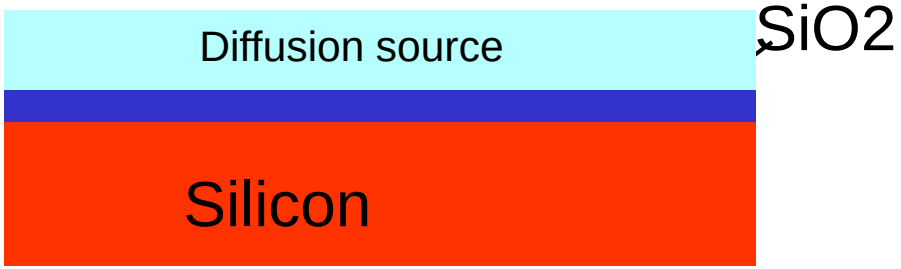
TDD methods:

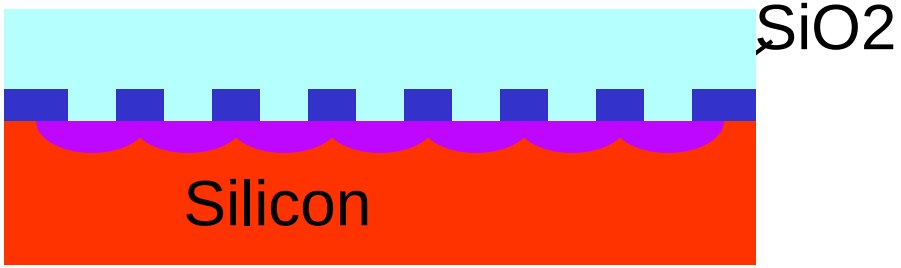
- mechanical (microneedles)
- chemical (improve the hydrophilicity of the skin)
- electroporation
- iontophoresis
- sonophoresis

- General consideration regarding transdermal drug delivery
- Microneedles
  - µneedles for TDD
  - Why microneedles with biodegradable tips are needed?
  - Fabrication of silicon microneedles
  - Fabrication of the porous tip
  - Anodization process for the porous tips
- SEMA- method
- Summary

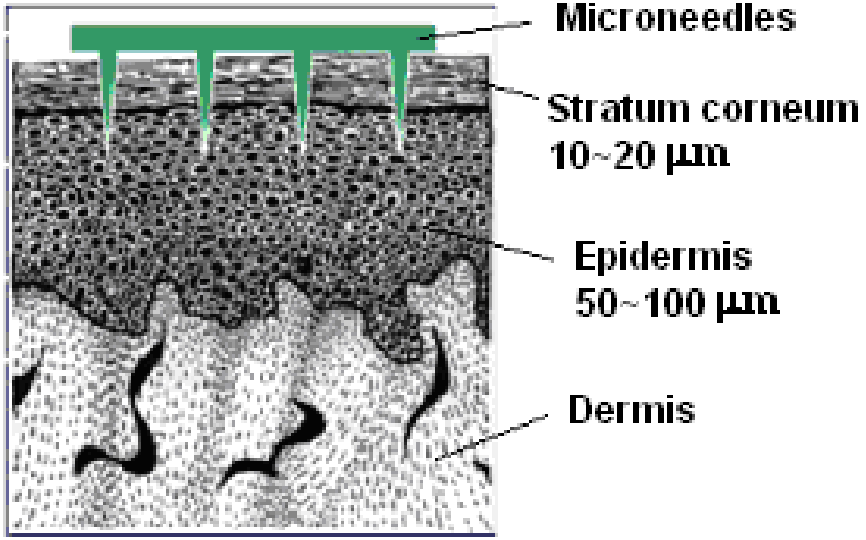
Skin structure and … its equivalent in microfabrication







Microneedles for TDD



Stratum corneum acts as a "masking layer" for the drug diffusion into the skin

Advantage:

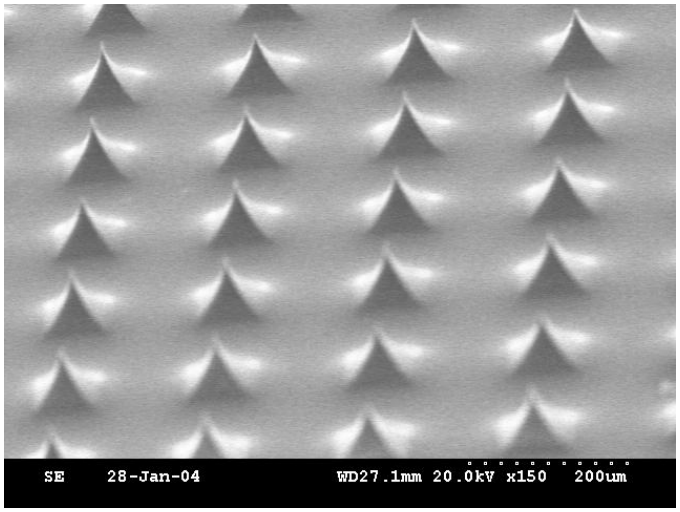
Microneedles penetrate the skin barrier of stratum corneum, provide very high permeability with minimal invasion and uniform delivery of drugs.

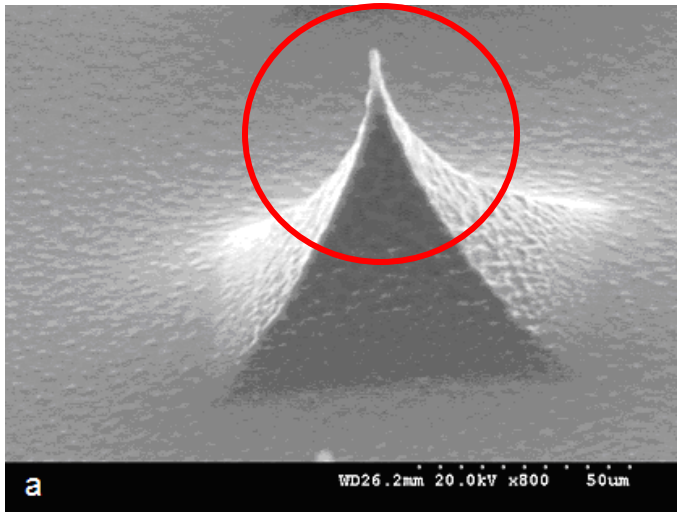
Disadvantages:

- still passive diffusion
- broking parts from the microneedle tip can cause infection
- limited quantity of drug delivery
- limited size of macromolecule drug

Why microneedles with biodegradable tips are needed?

Silicon microneedles are fragile, but with high aspect-ratio, easily broken in the skin and may cause infection.





Solution:

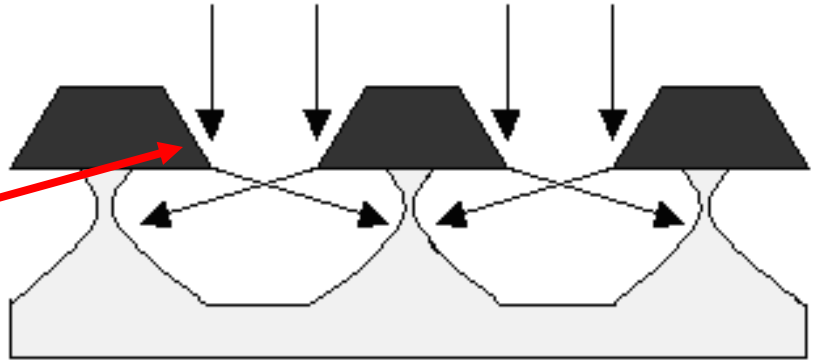
mesoporous silicon tips (biodegradable)

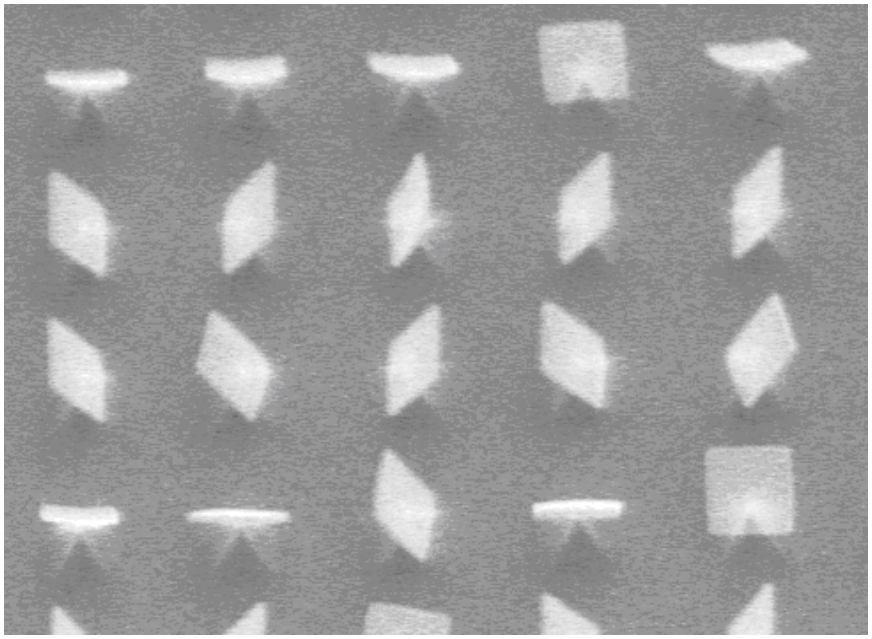
Fabrication of silicon microneedles

Isotropic deep RIE

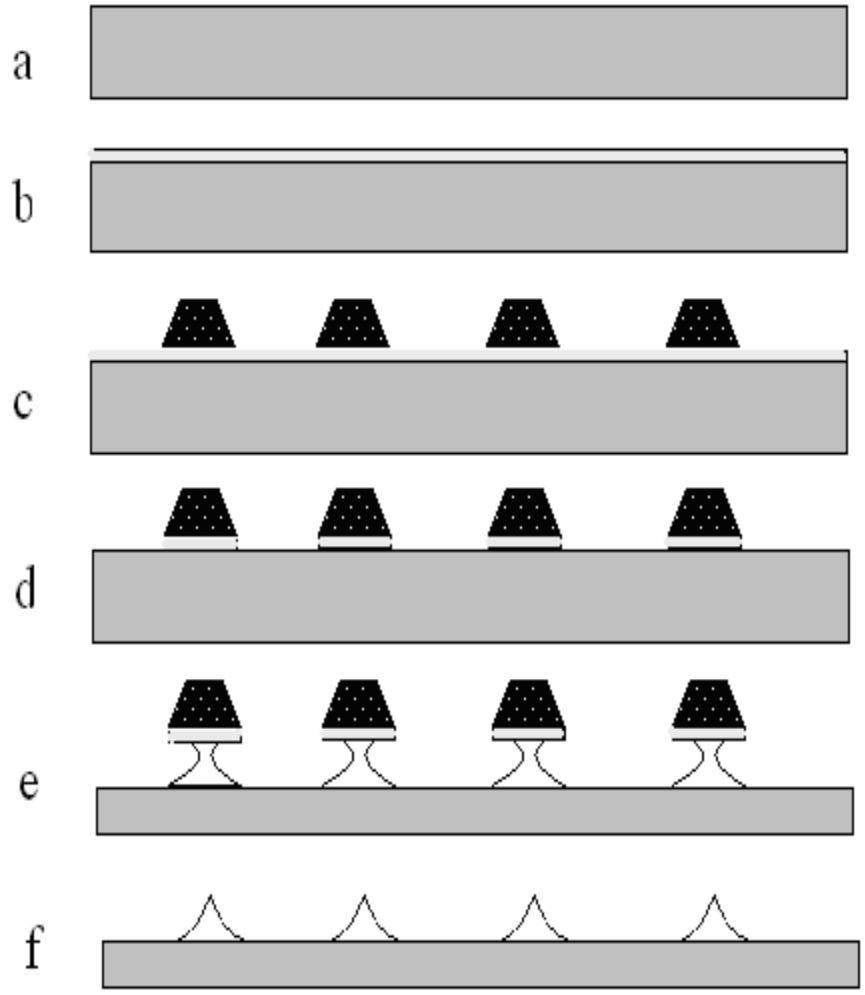
+

notching effect of reflected charges on the masking layer





Fabrication of silicon microneedles



a) Silicon wafer

b) 1µm-thick SiO2 (PECVD)

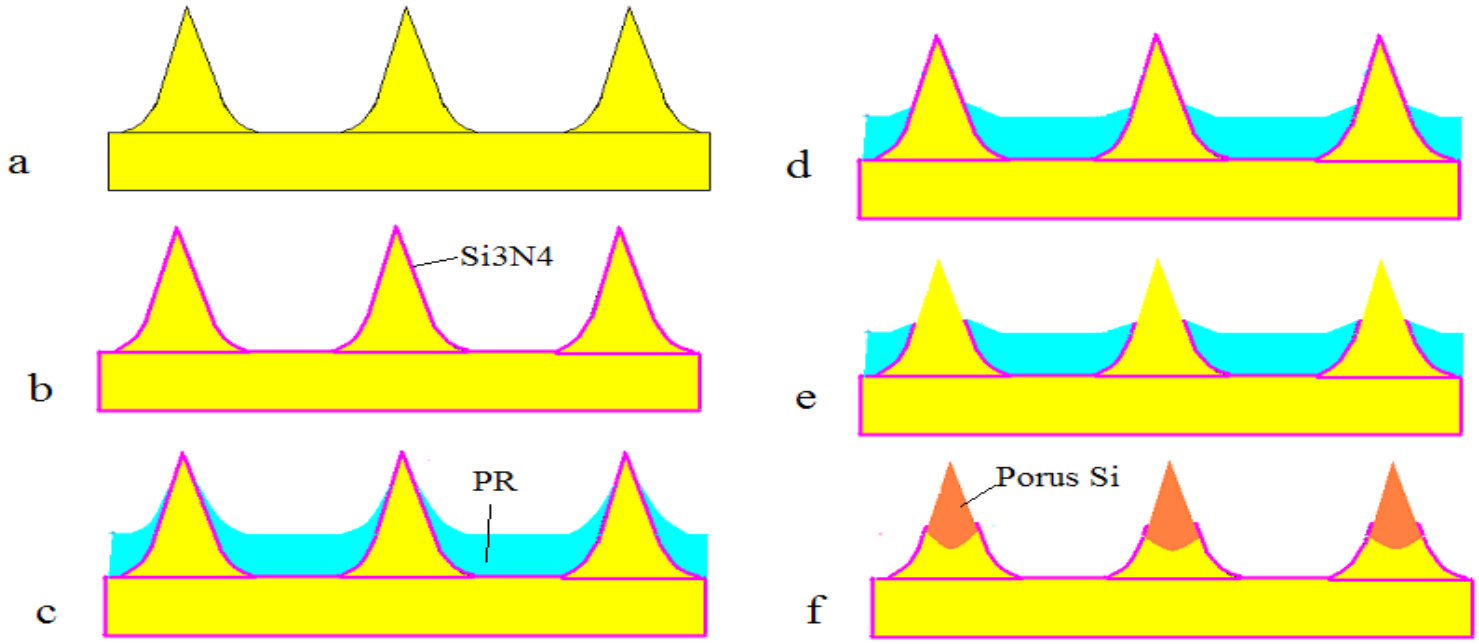
c) AZ 9620 photoresist mask (overheated)

d) RIE etch of the SiO2

e) Isotropic etching of silicon

f) (Removing of the mask)

Fabrication of the porous tip



a) microneedles fabrication; b) Low stress PECVD Si3N4 deposition;

c) Photoresist deposition; d) O2 plasma etch of PR

e) Si3N4 etch in plasma; f) Porous Si process

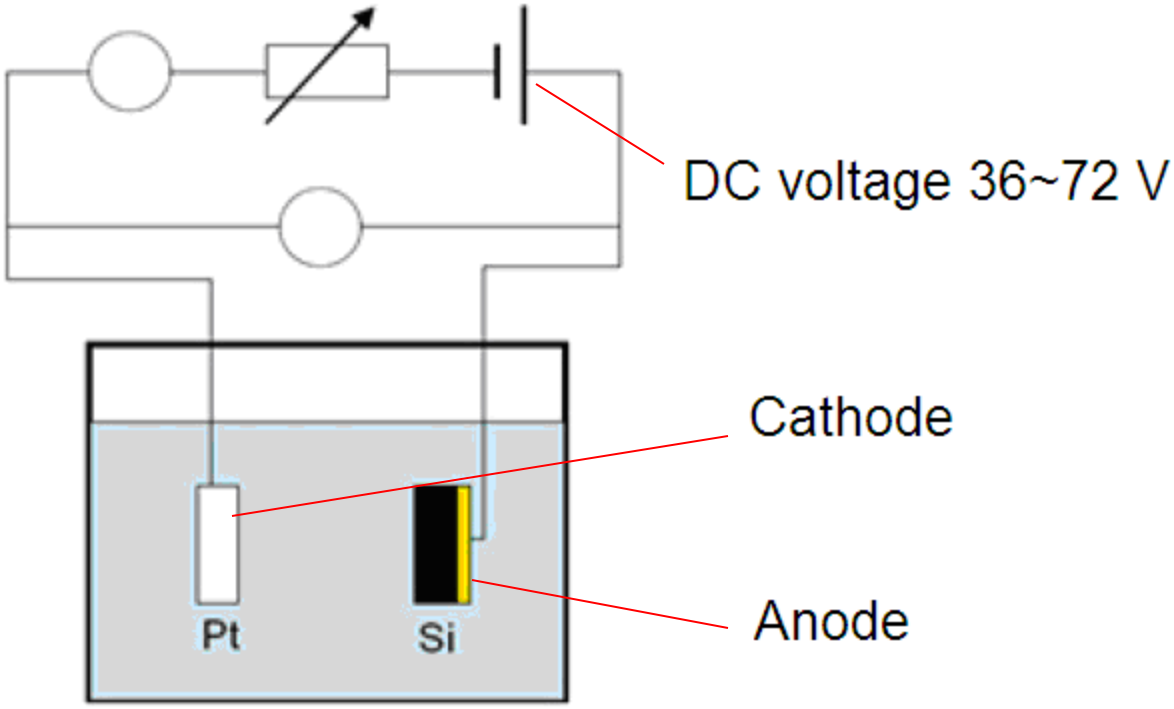
Anodization process for the porous tip

Method: anodic electrochemical etching process

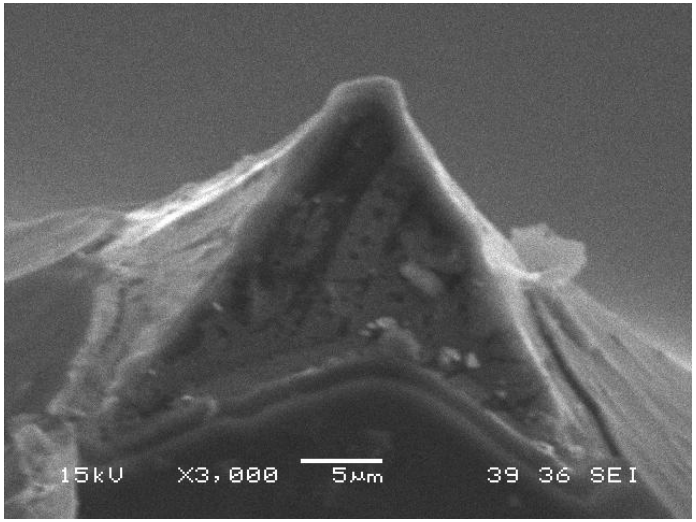
Chemical Solution:

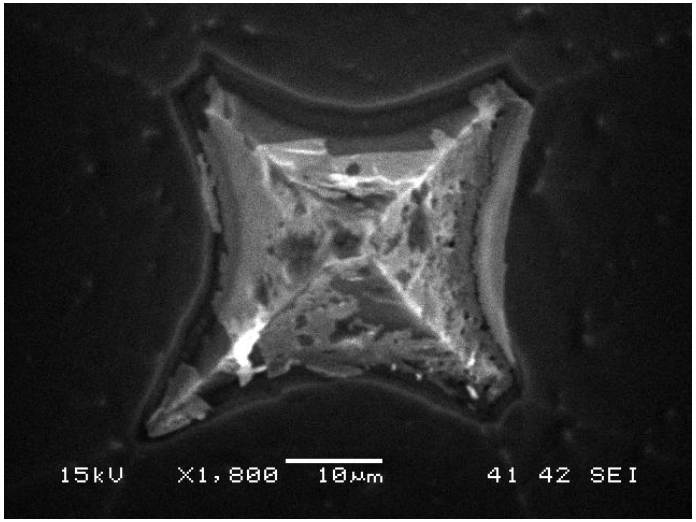
MeCN : HF : H_2O = 92% : 4% : 4% by weight

Electrical power: DC 36~72 V, current intensity 10 mA·cm^2



Results

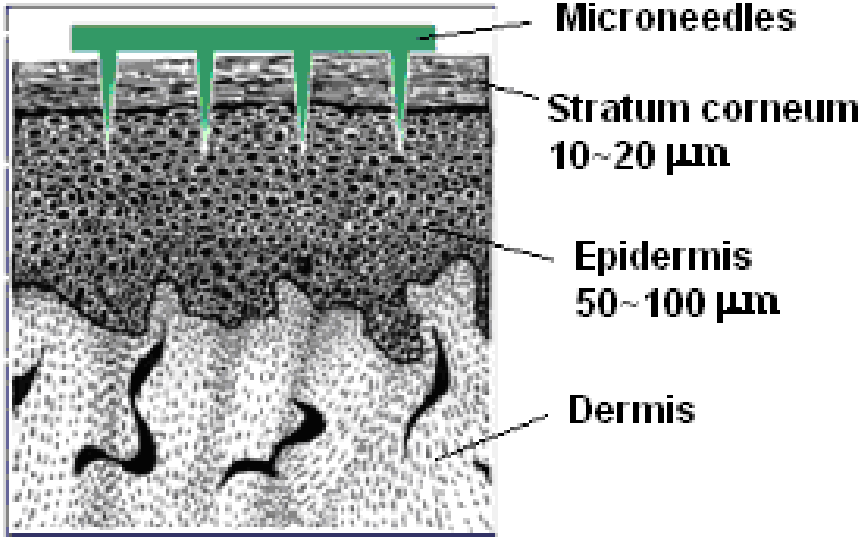




Microneedle with biodegradable tip

- General consideration regarding transdermal drug delivery
- Microneedles
- *Microneedles with ultrasound enhancer (SEMA- method)*
  - General considerations
  - SEMA method
  - Process flow of the TDD using SEMA
  - Fabrication of hollow microneedles array
  - Low frequency sonophoresis
  - Testing
  - Considerations regarding thermal effect
- Summary

General considerations



Stratum corneum acts as a "masking layer" for the drug diffusion into the skin

Advantage:

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Disadvantages:

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- broking parts from the microneedle tip can cause infection

Target: insulin

Drug diffusion

The **drug flux *F*** through the skin is proportional with the concentration gradient as given by the Fick's first law:

$$F = -D\frac{\partial C}{\partial x}$$

where ***D* is the diffusion coefficient** while ***∂C/∂x* is the concentration** gradient.

The flux gradient $\partial F/\partial x$ is proportional with the change of concentration in time and is approximated by the Fick's second law of diffusion:

$$\frac{\partial C(x,t)}{\partial t} = -\frac{\partial F}{\partial x} = D\frac{\partial^2 C}{\partial x^2}$$

where the concentration *C* is a function of position *x* and time *t*, while *D* is assumed to be constant.

Drug diffusion

Under these conditions eqn. can be simplified to:

$$\frac{dm}{dt} = D\frac{C_0}{h}$$

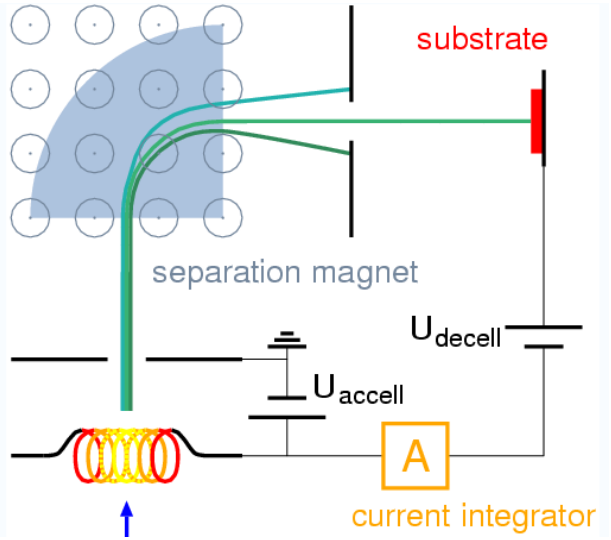
where *m* is the mass of permeant that passes per unit area through membrane in the time *t*, *Co* is the concentration of the source and *h* is the membrane thickness.

Speaking in general terms, the diffusion coefficient *D* is a function of the activating energy *Ea* and temperature *T*:

$$D = f\,(Ea, T)$$

Drug diffusion- “drug implantation”

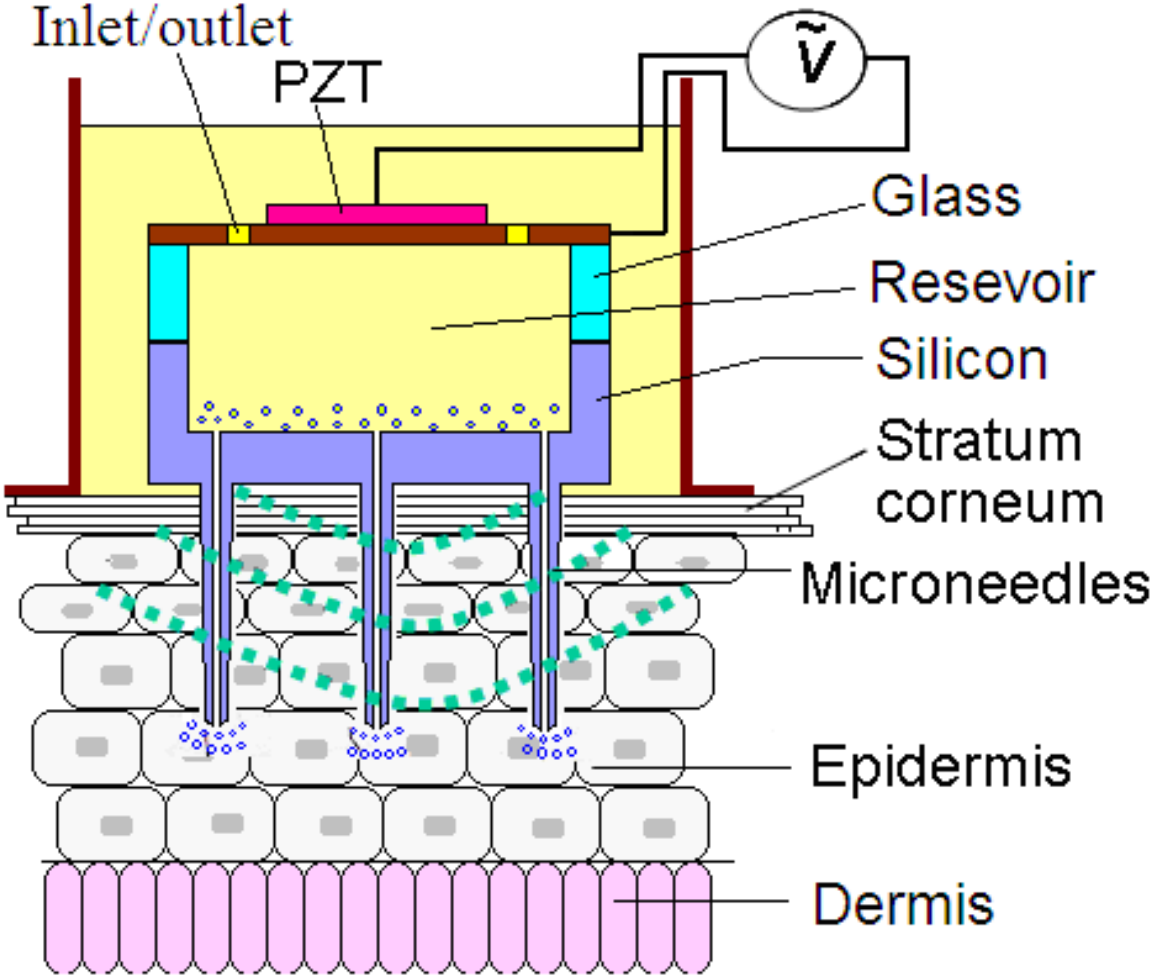
- Temperature can not b sensitively modify in transdermal drug delivery
- Only solution can be improving the activation energy



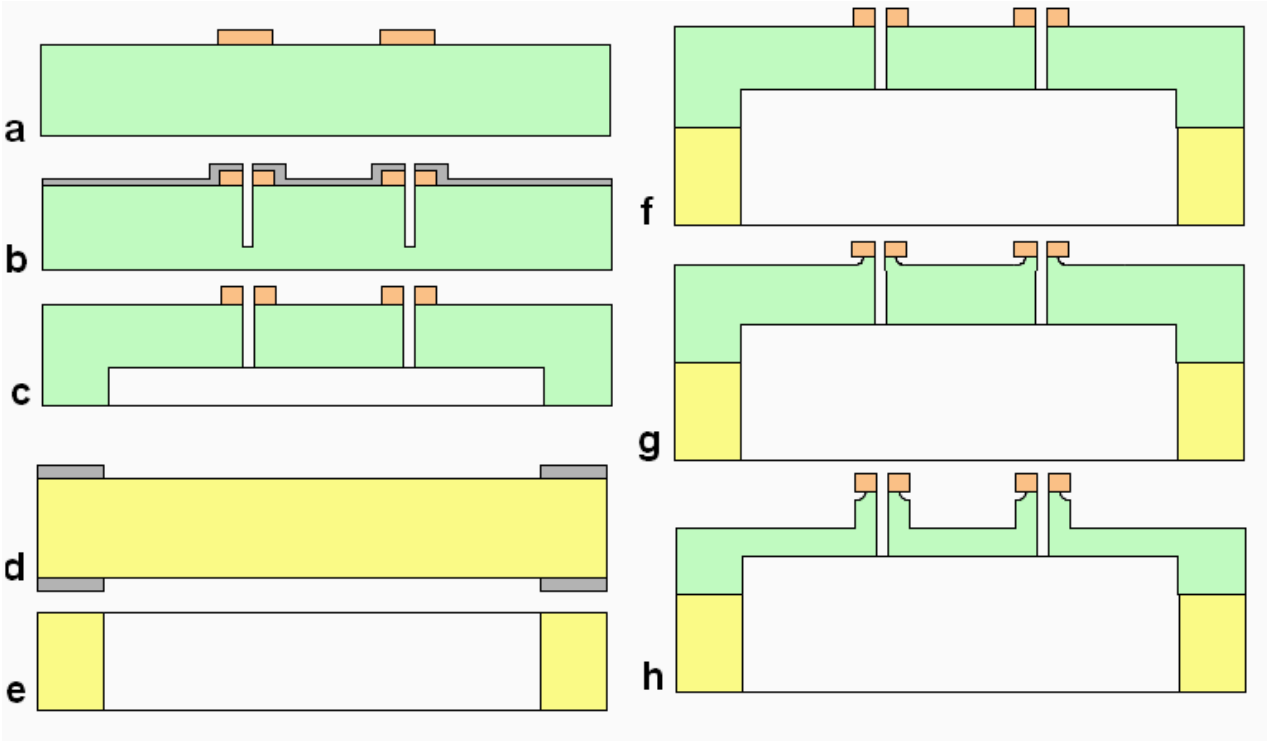
Schematic view of an ion implanter

Ultrasonic energy

SEMA method


Inlet/outlet
PZT
$\tilde{V}$
Glass
Resevoir
Silicon
Stratum corneum
Microneedles
Epidermis
Dermis

Fabrication of hollow microneedles array



Typical process for silicon microneedles

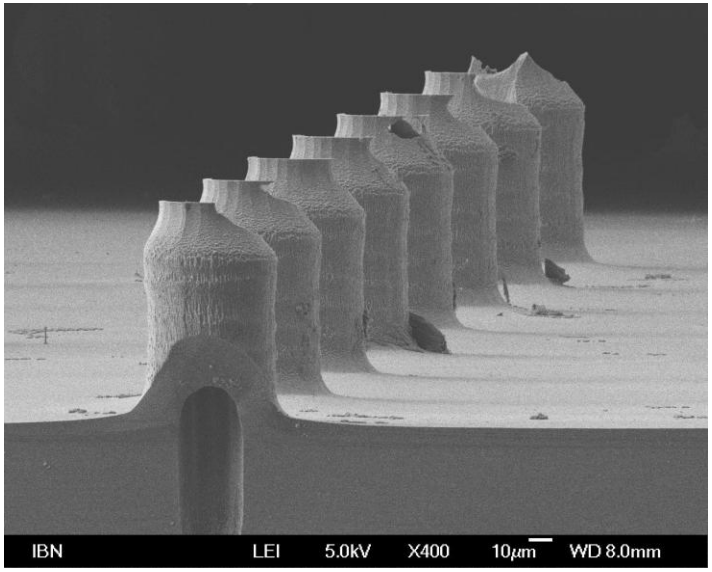
a) patterning of SiO2 layer; b) etching and oxidation of the holes;

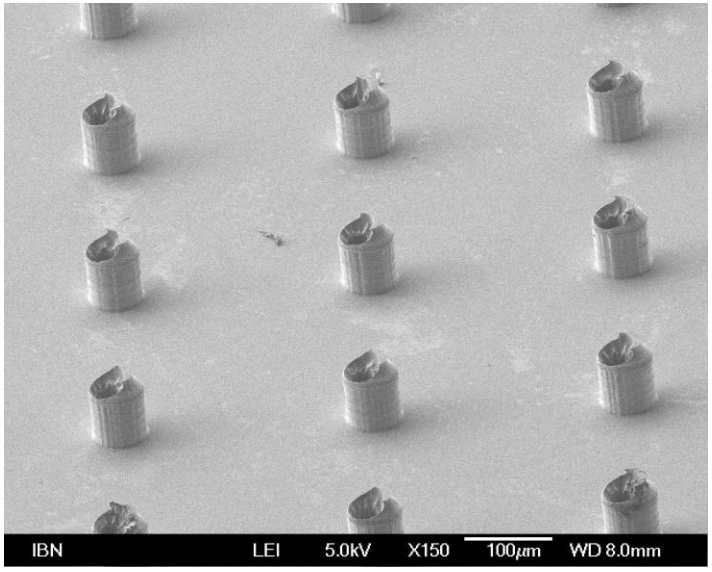
c) DRIE to get the reservoir; d) patterning the glass substrate;

e) etching of glass holes; f) bonding of the silicon with glass substrate,

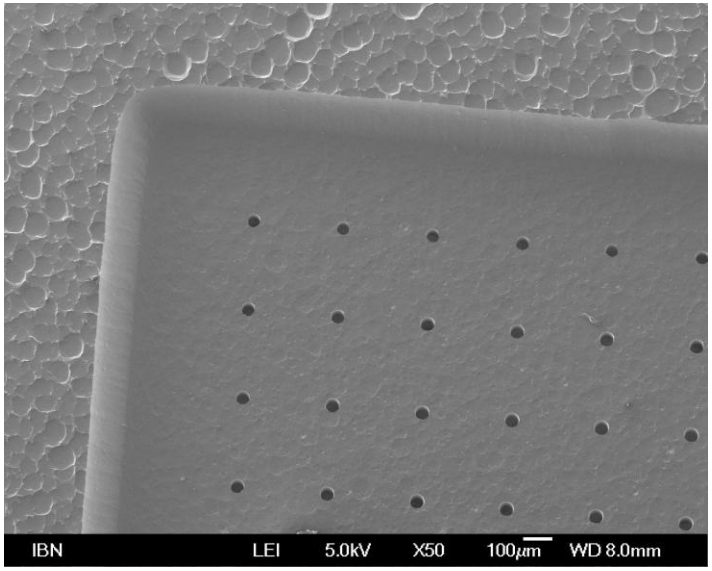
g) Isotropic etching of needle tips; (i) DRIE to get needle out-rings

Fabrication of microneedles array



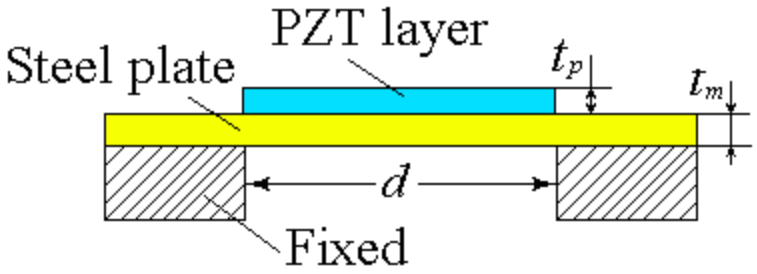


Typical dimensions of the microneedles:
Length of 100 µm,
out-diameter of 50~80 µm,
inner-diameter of 30~40 µm

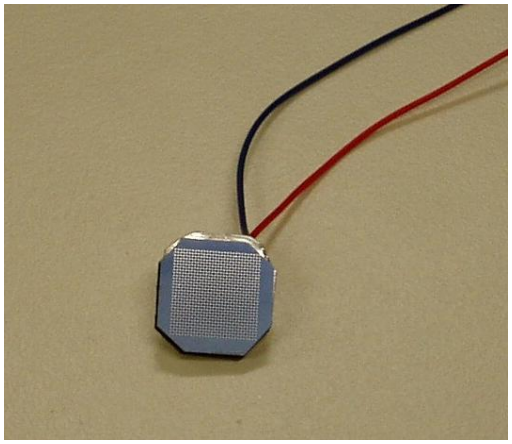


Low frequency sonophoresis

- PZT bar was used as ultrasound emitter to generate sonophoresis
- Key parameters of the PZT bar:



PZT thickness t_p = 200 μm,
steel substrate t_m = 200 μm.

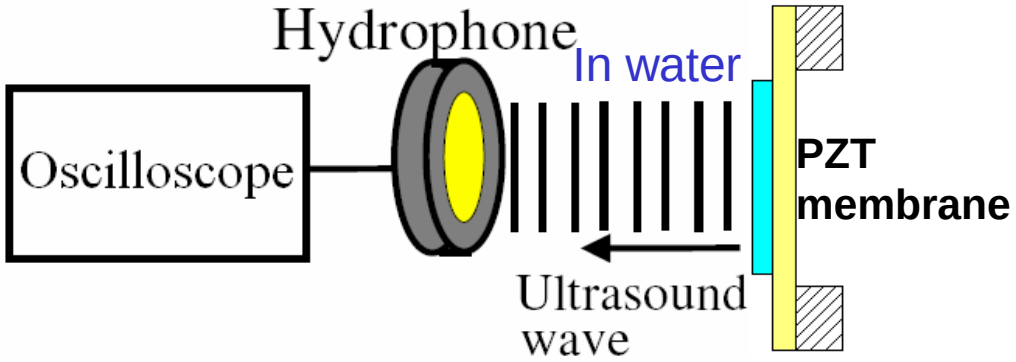


Measured resonant frequency is 21 kHz

Working frequency

- Why not therapeutic ultrasound (1~3 MHz)? The cavitational effect is reversely proportional to the ultrasound frequency.
- Low frequency (20 kHz ~ 50 kHz) sonophoresis proved to have better enhancement on TDD of macromolecules.

Low frequency sonophoresis



$$I = \frac{P^2}{\rho C}$$

P – sound pressure
ρ - density of media
C – sound speed in media

The threshold intensity of 20 kHz ultrasound is 0.11 W/cm^2.

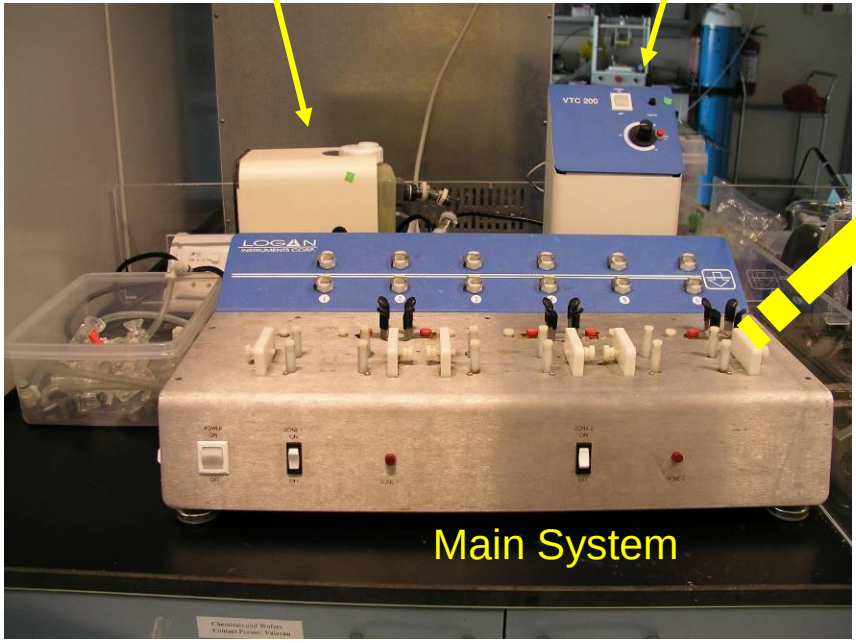
Safety concerns:

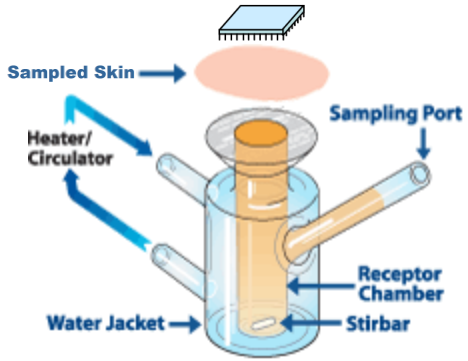
- The minimal thermal effect doesn't induce skin lesion or necrosis at ~μm level.
- Literature suggested that the integrity of insulin and peptides are not degraded
- Obvious skin lesions might be induced at intensities > 2.5 W/cm^2

Testing setup for TDD

Water Bath Tank

Heater Circulator

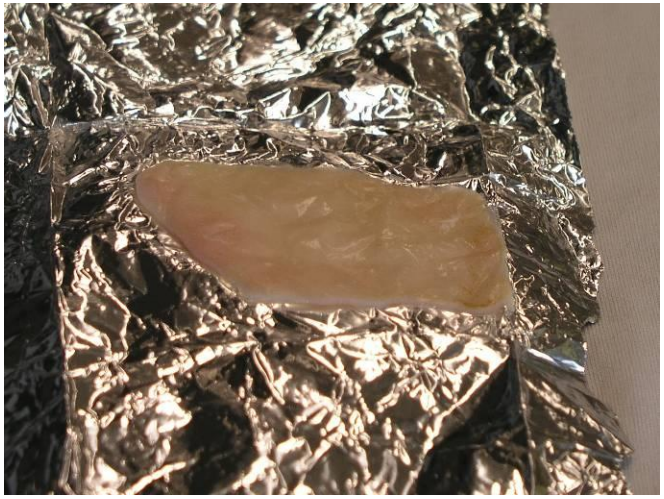




Skin preparation

Skin Preparation Protocol:

1. Excise the skin from abdominal area of rats/pigs;
2. Remove the hair from the sampled skins;
3. Remove the adhering fat and other visceral debris by tweezers;
4. Scrape off the underlying subcutaneous fat to leave the skin to be 1.5 mm-thick;
5. Wash the skin with physiological saline;
6. Wrap the skin in aluminum foil;
7. Store at -80^{o}C

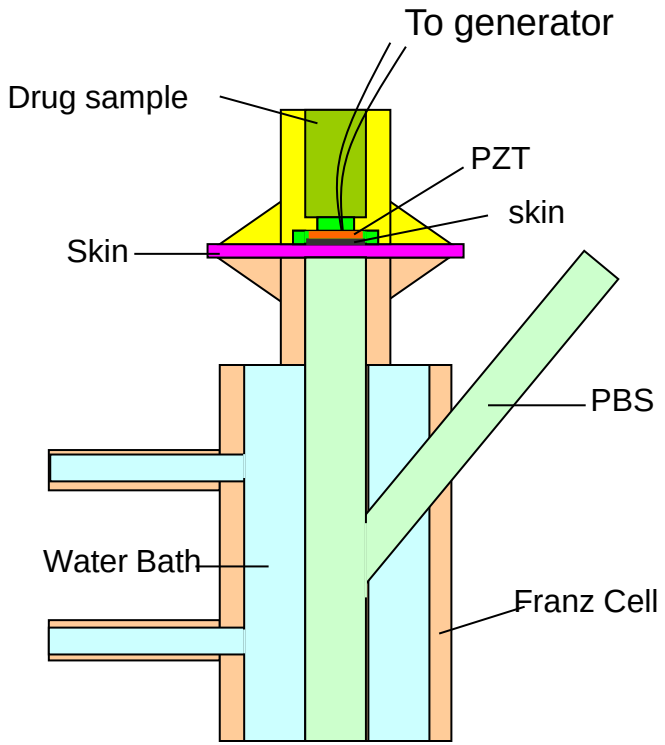


Rat Skin

Pig Skin

In vitro drug release with animal skin

Experiment set-up



Diffusion tool: Franz diffusion cell

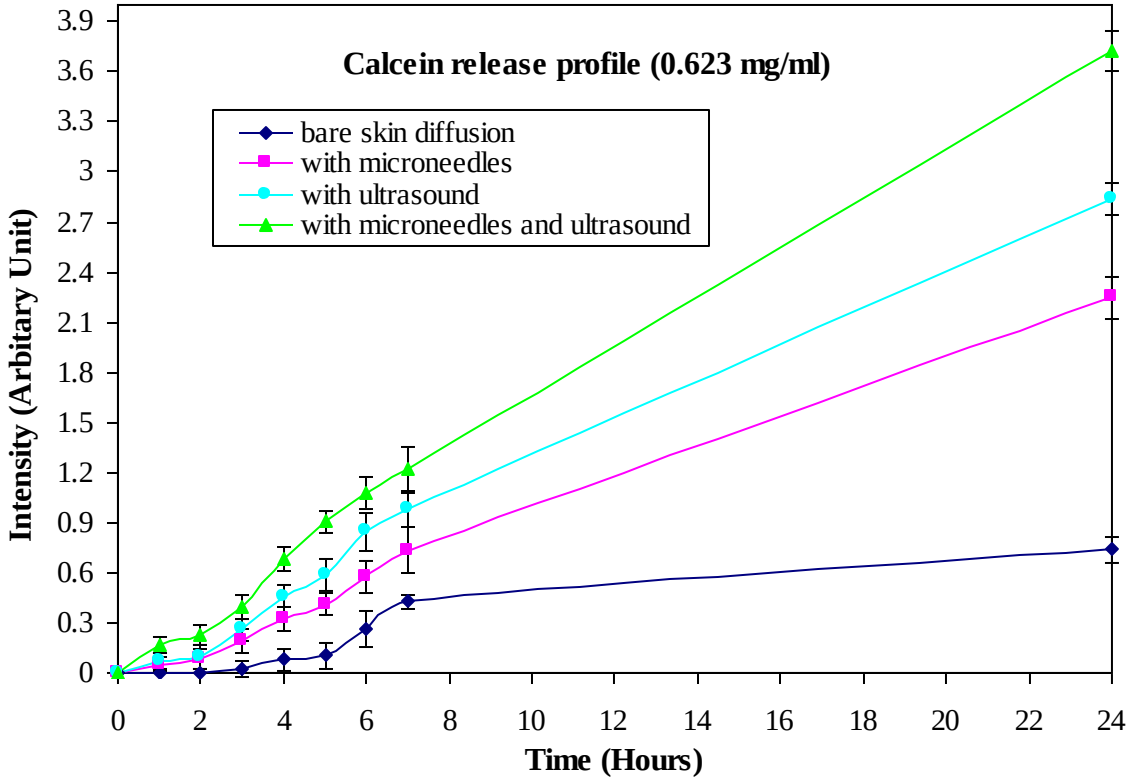
Skin model: rat skin, pig skin

Drug model: Calcein, BSA, Insulin (detected by UV spectra)

Microneedles: 30 by 30 array, length 100 μm, diameter 60 μm

Ultrasound energy: 20 kHz, 20% duty, intensity of 0.1~1 W/cm^2

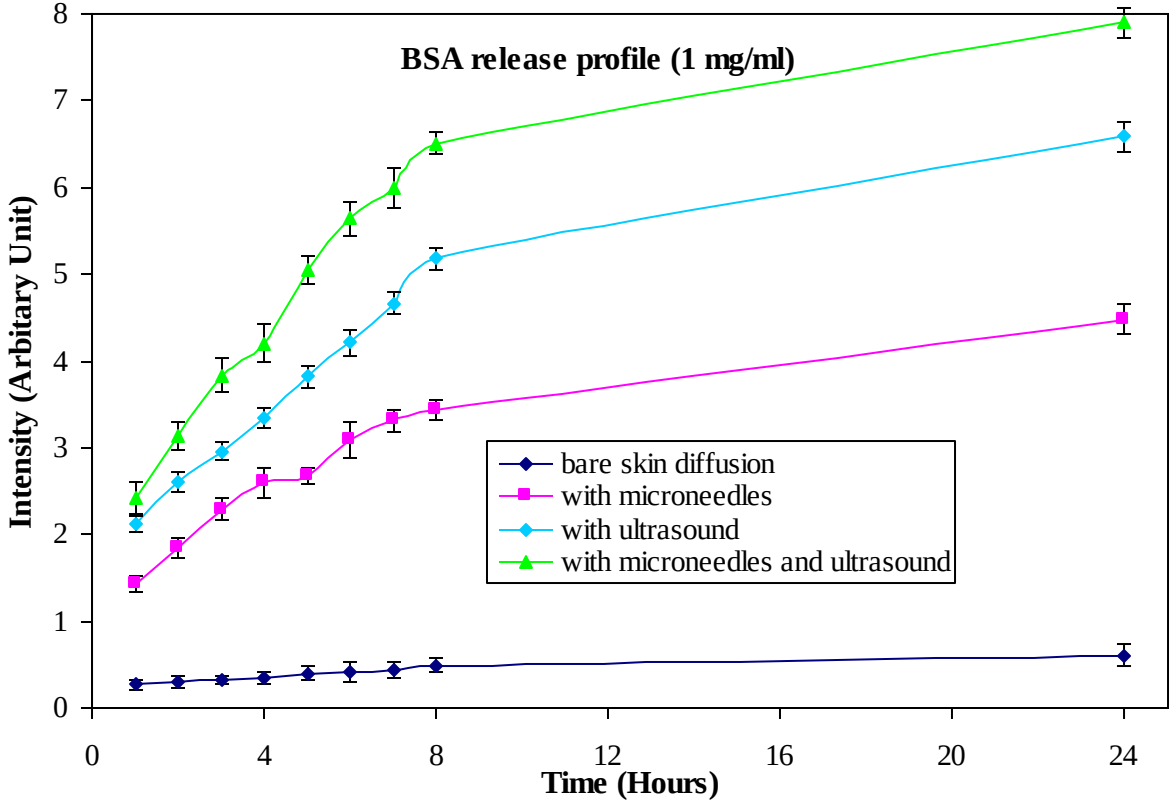
In vitro calcein drug release in animal skin



The *in-vitro* release profile was dependent on the skin and drugs

• For calcein release, the skin permeability was greatly enhanced (about 5 times) by the microneedles in comparison with the passive diffusion, 7 times for sonophoresis and further enhanced (~9×) using SEMA.

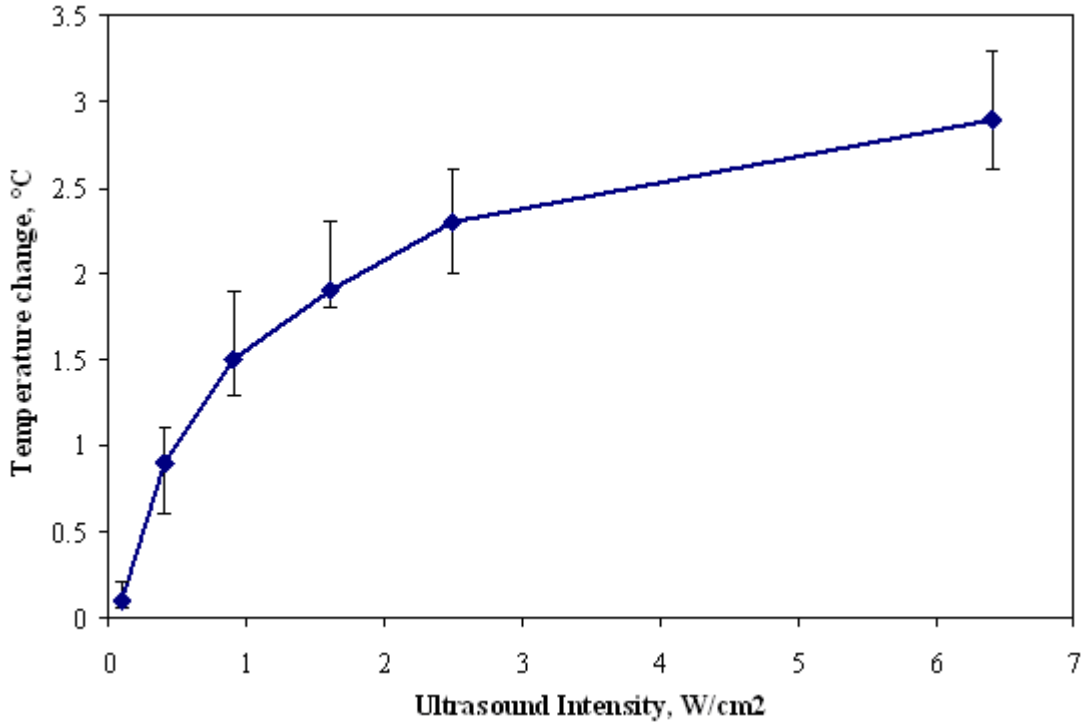
In vitro BSA drug release in animal skin



Preliminary results and challenges:

- The *in-vitro* release profile was dependent on the skin and drugs
- For BSA release, skin permeability enhancements of ~7 times (microneedles), ~8.5 times (sonophoresis) and ~12 times for SEMA

Thermal effect



- The temperature can induce vasodilatation !
- LFS can generates large gradients of temperature !

Summary

- Ultrasound integrated microneedle array device for TDD was designed to have better enhancements of TDD with macromolecules.
- The microneedles array were successfully fabricated with silicon materials. The device was packaged with PZT transducers.
- Characterization study showed that low-frequency and low-intensity ultrasound have better TDD enhancement.
- Preliminary *in vitro* TDD results proved the enhancement effect of ultrasound integrated microneedle device.


Thank you
for your attention!