Current Status of Skin Ablation/Perforation Techniques

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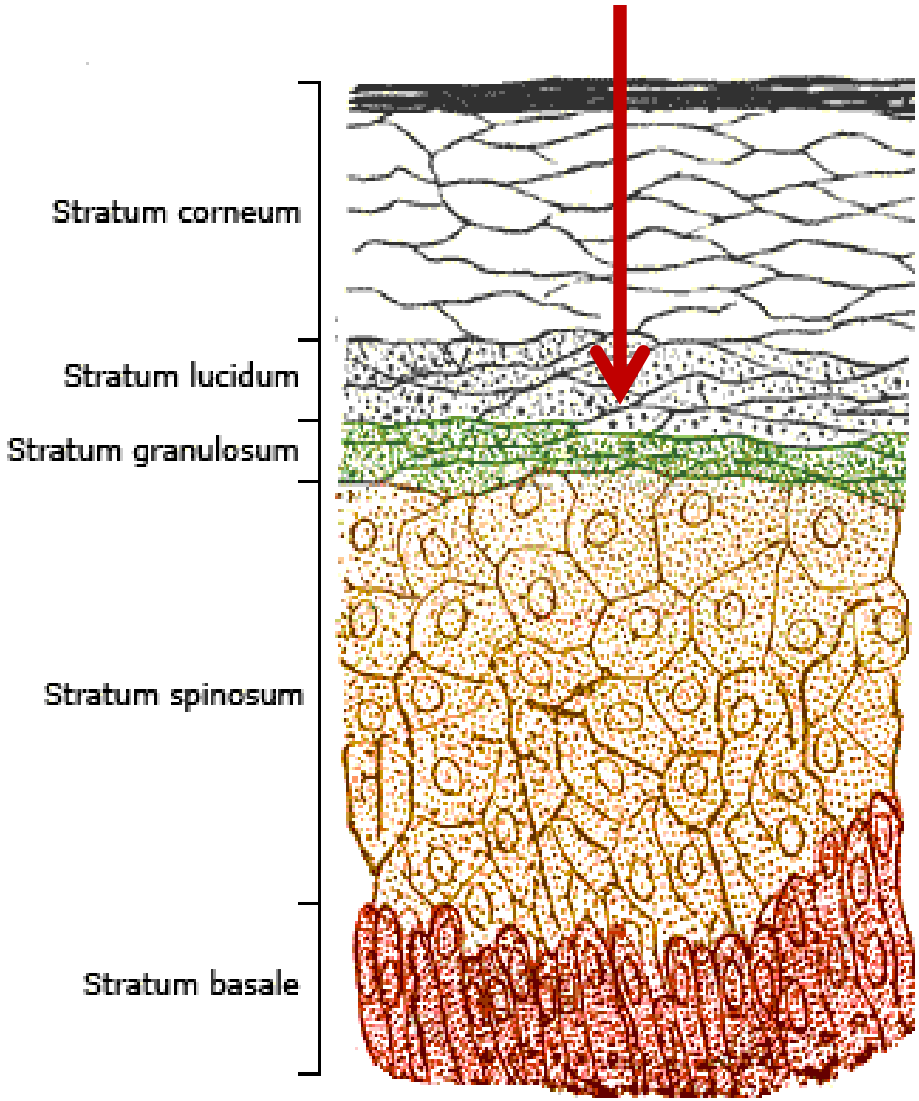
The stratum corneum is rate-limiting



The outer 10 to 20 μm is the stratum corneum.

This is the primary barrier to drug delivery

Effective delivery must overcome this barrier.

Phases of TD delivery products

- Phase I – passive delivery
  - Original TD products ~1980s
  - Deliver low dose of small, lipophilic drugs

DRUG	MW	Log Ko/w	Dose (ng/mL)
Scopalamine	**303**	**1.2**	**<0.1**
Nitroglycerin	**227**	**2.1**	**<10**
Nicotine	**162**	**1.2**	**<30**
Clonidine	**230**	**0.8**	**<2**
Testosterone	**288**	**3.3**	**<100**

Phases of TD delivery products

- Phase II – Deliver higher dose of larger &/or more hydrophilic drugs, including *small* peptides
  - Increased skin permeability by disrupting the stratum corneum
    - Chemical Enhancers
  - Increased driving force
    - Iontophoresis
  - Issue – Skin irritation
    - The effects aren't limited to the stratum corneum

Phases of TD delivery products

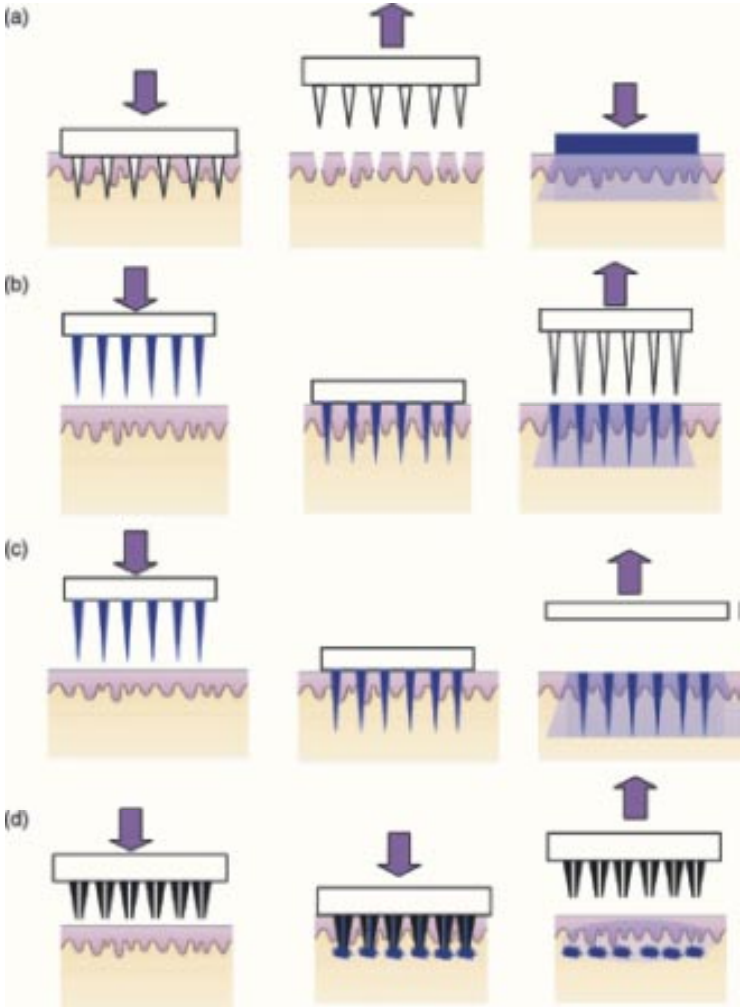
Phase III Deliver macromolecules

- More selective disruption of the SC
  - Electroporation
  - Ultrasound
  - Perforation
  - Ablation

Skin perforation using microneedles

Microneedles – Various types

Four types of micro-needles



SOLID

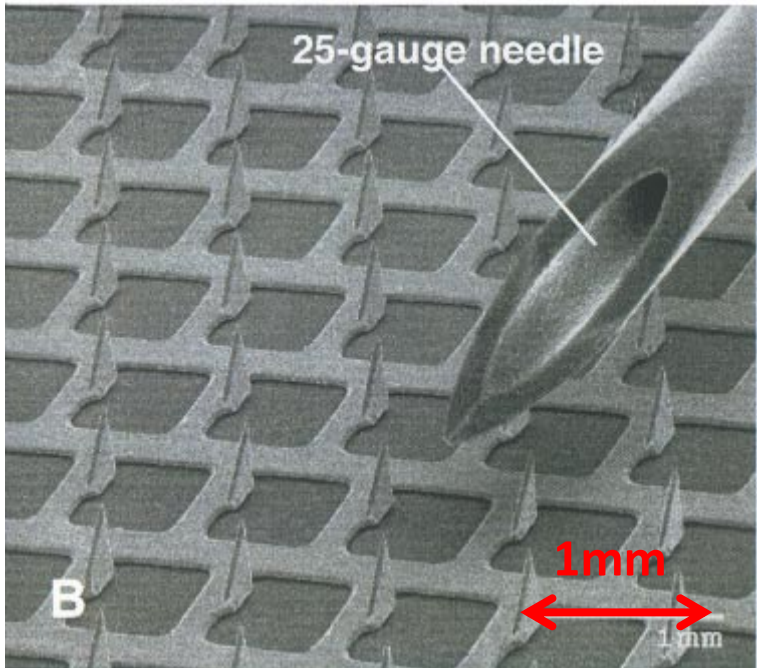
Drug-coated

Polymeric with encapsulated drug

Hollow

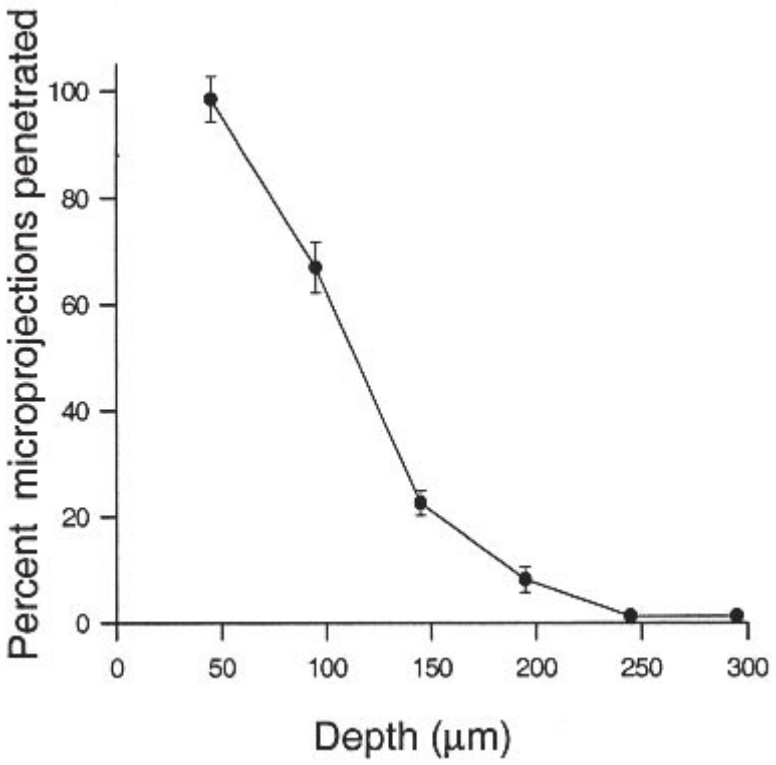
From Jagannathan et al. *Advanced Biotech* May 2009

Microporation - Alza Macroflux®



Matriano et al. Pharmaceutical Research, Vol. 19, No. 1, January 2002

Ti metal chemically etched
Micro-projections formed at 90°
Penetration to ~200 µm

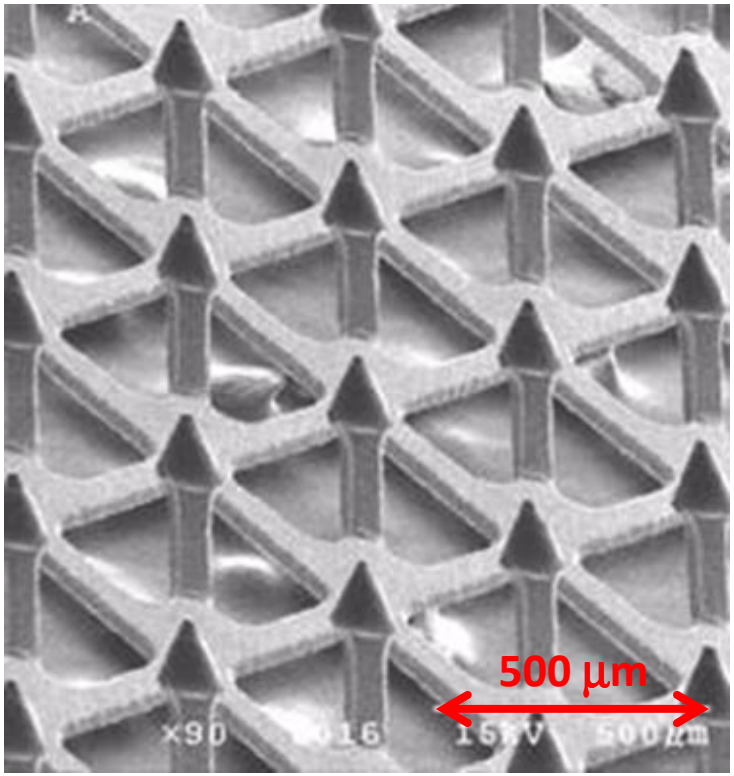


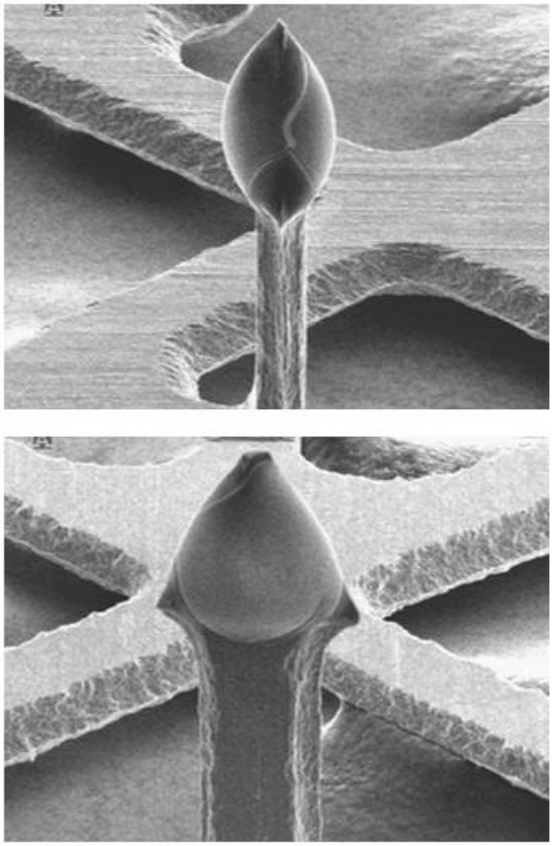
Drug coated on microneedle

Zosano delivery system

www.zosanopharma.com

Vaccines, PTH and EPO among the drugs investigated

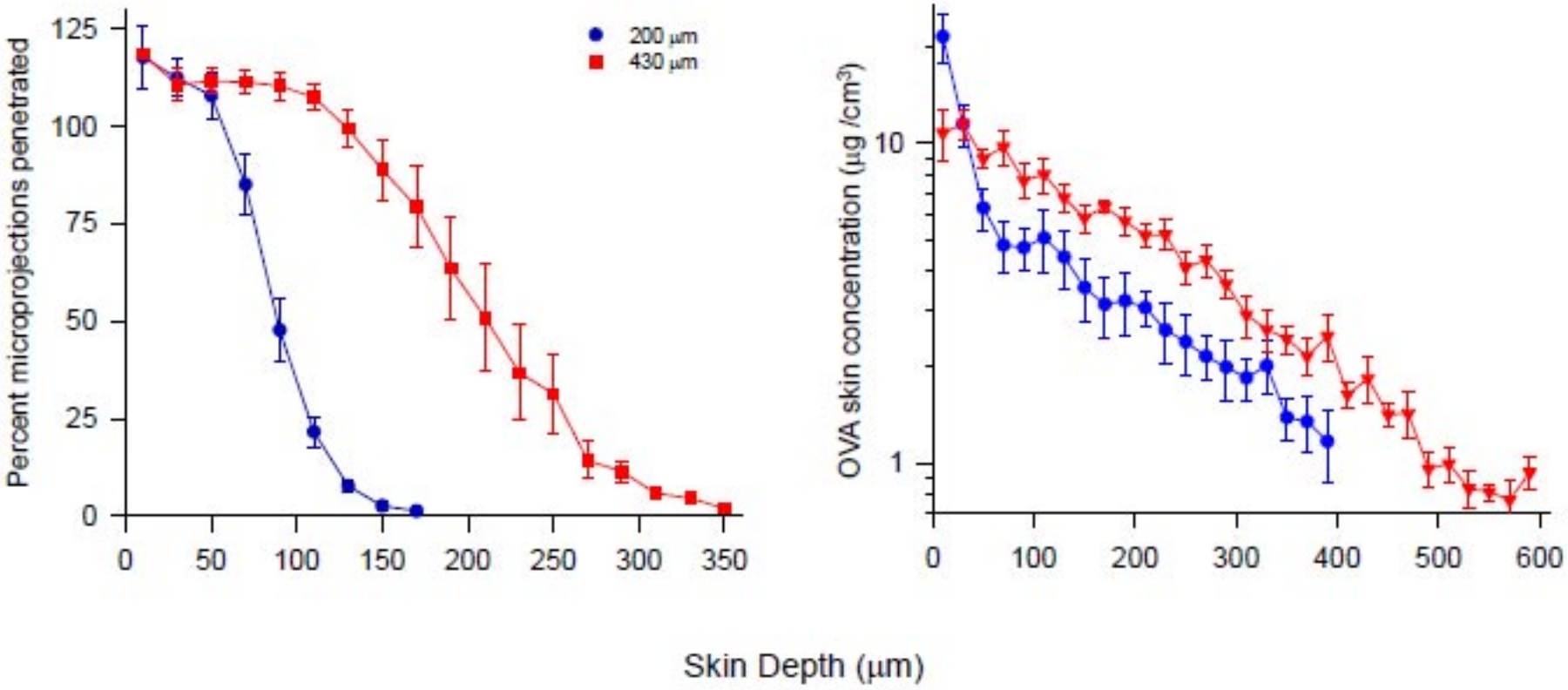




SEM of EPO coated microprojections (3,000 IU/30 mcg dose)

Drug coated on microneedle

Depth of skin penetration and amount of drug delivered increased with longer microneedles.



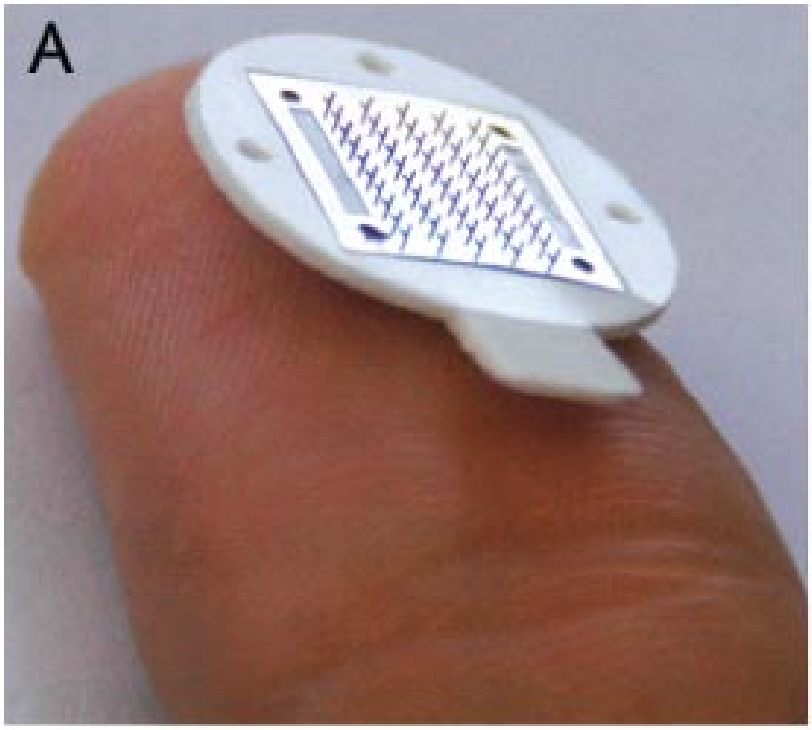
www.zosanopharma.com

Microneedle

Microneedles permit transdermal delivery of a skin-impermeant medication to humans

Daniel P. Wermeling*†, Stan L. Banks‡, David A. Hudson§, Harvinder S. Gill¶, Jyoti Gupta‖, Mark R. Prausnitz¶‖, and Audra L. Stinchcomb‡

2058–2063 | PNAS | February 12, 2008 | vol. 105 | no. 6



Metal microneedles cut with IR laser and bent at right angles

5x10 array – each needle

Length 620 μm

Width (base) 160 μm

Tip radius < 1μm

Pain on insertion far less than 5mm insertion of hypodermic needle

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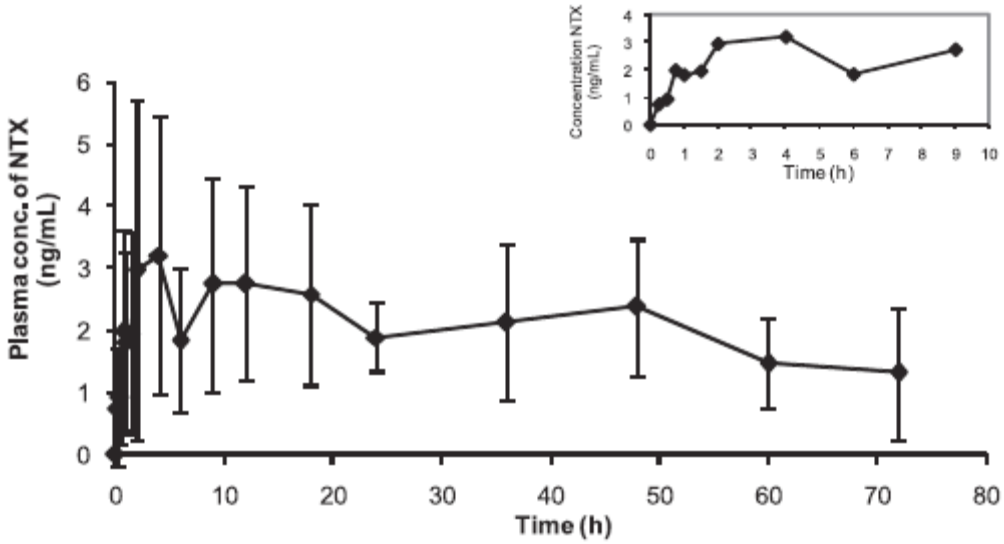

Fig. 1. Mean (SD) NTX plasma concentrations for 72 h of patch application. (*Inset*) Early sampling points.

The delivery of naltroxone (NTX) in human subjects

Microneedle insertion and removal, followed by TD patch application

Maintained drug delivery over 72 hours

Control subjects (no microneedle before TD patch) had plasma level below detection (< 1ng/ml)

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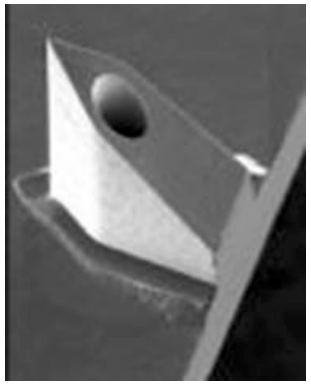
- **Naltroxone delivery maintained over 72 hours following use of MN**
  - **No NTX delivered by passive TD**
- **Some irritation seen at the site of application**
  - **Contact dermatitis persisted for several days**
- **Electrical impedance measured at the site**
  - **Resistance dropped from 400 to 10 KΩ after insertion**
  - **Resistance returned to “normal” after 30 hours**

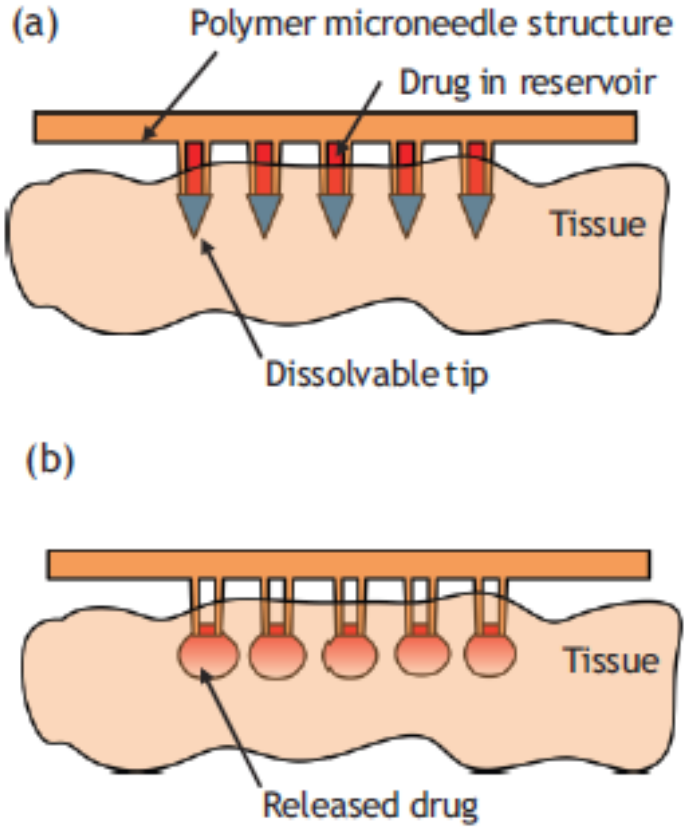
Hollow center microneedles

Nanopass www.nanopass.com



Debiotech – Nanoject www.debiotech.com

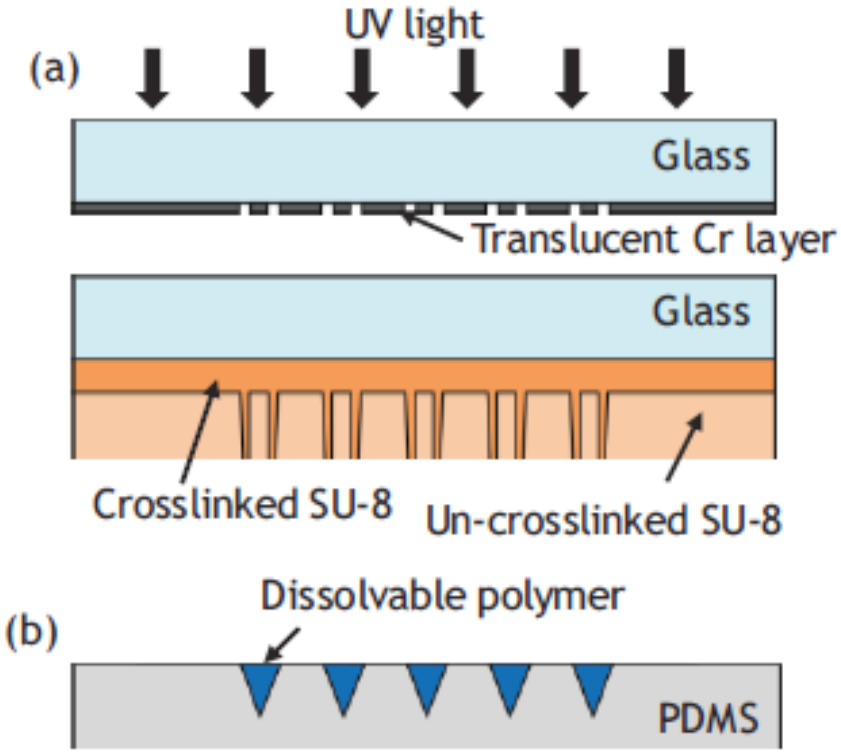
Dissolving Microneedles



DISSOLVABLE-TIPPED, DRUG-RESERVOIR INTEGRATED MICRONEEDLE ARRAY FOR TRANSDERMAL DRUG DELIVERY

Seung-Joon Paik, Seong-Hyok Kim, Po-Chun Wang, Brock A. Wester, and Mark G. Allen
Georgia Institute of Technology, Georgia, USA

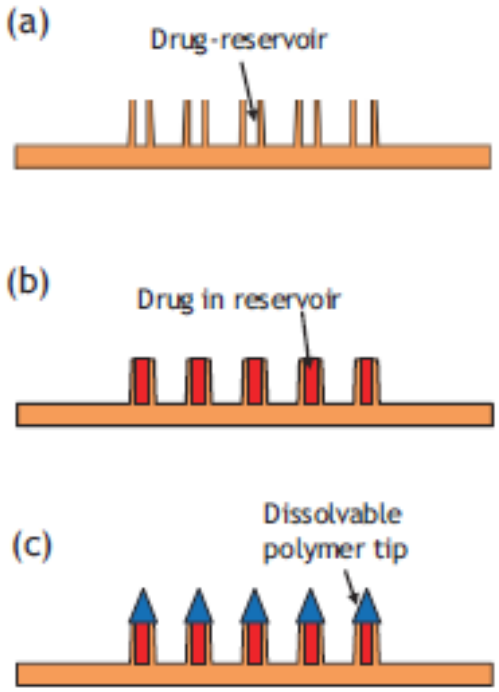
Dissolving Microneedles



The substrate is fabricated by photo-lithographic treatment of SU-8

The dissolvable polymer is placed in a PDMS mold

Dissolving Microneedles



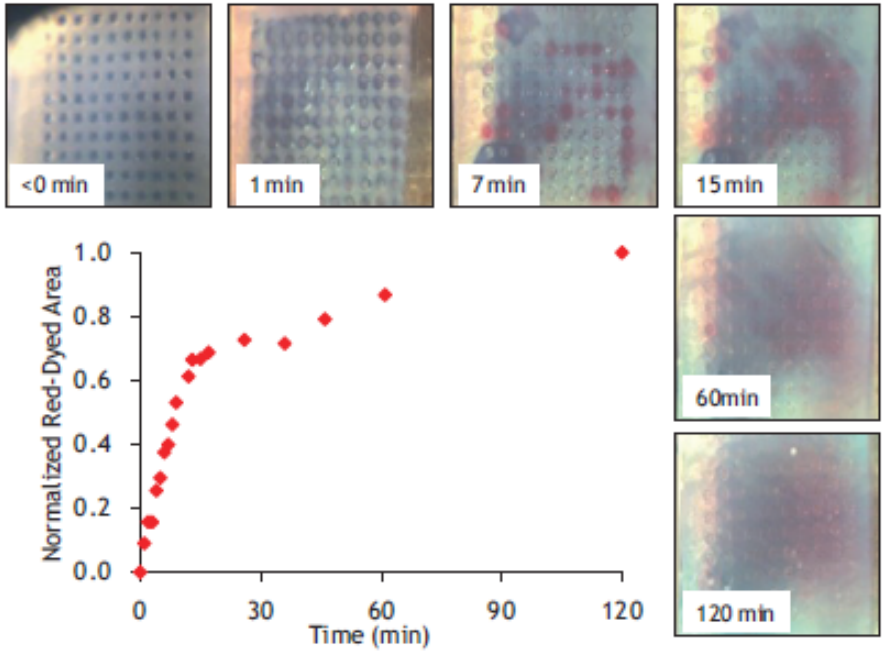


Figure 6. Diffusion kinetics of drug release into the agarose gel by the dissolvable-tipped microneedle array using diffusion of red-dyed surrogate.

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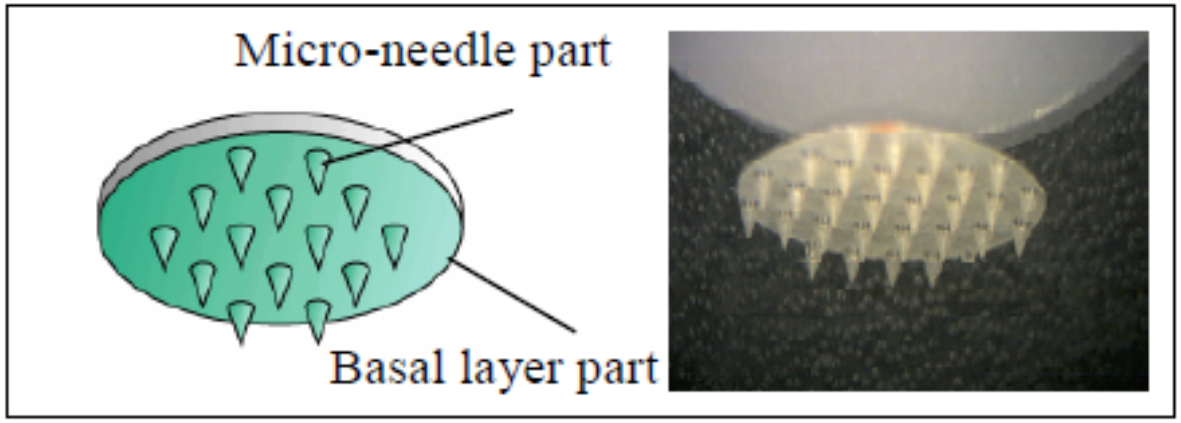
Dissolving Microneedles

- TheraJect
  - PTH dissolved in carboxymethyl cellulose (CMC)
  - Cast into a mold under centrifugation and dried
  - Cut into 1cm^2 discs, each having 30 microneedles with 730 µg of PTH
    - 1/3 in needles
    - 2/3 in substrate
  - 98% of PTH delivered in 24 hrs



www.theraject.com/files/In_Vitro_Modeling_of_Transdermal_PTH_Delivery_by_Dissolving_M.pdf)

Dissolving Microneedles

Dissolving polymer microneedle patches for influenza vaccination

Sean P Sullivan[1,4], Dimitrios G Koutsonanos[2,4], Maria del Pilar Martin[2], Jeong Woo Lee[3], Vladimir Zarnitsyn[3], Seong-O Choi[3], Niren Murthy[1], Richard W Compans[2], Ioanna Skountzou[2] & Mark R Prausnitz[1,3]

NATURE MEDICINE VOLUME 16 | NUMBER 8 | AUGUST 2010

Influenza virus encapsulated in PVP (3µg/patch)

Polymerized at 23°C using light – Virus remain immunogenic

The microneedles penetrate 200 µm into the epidermis

Dissolving Microneedles

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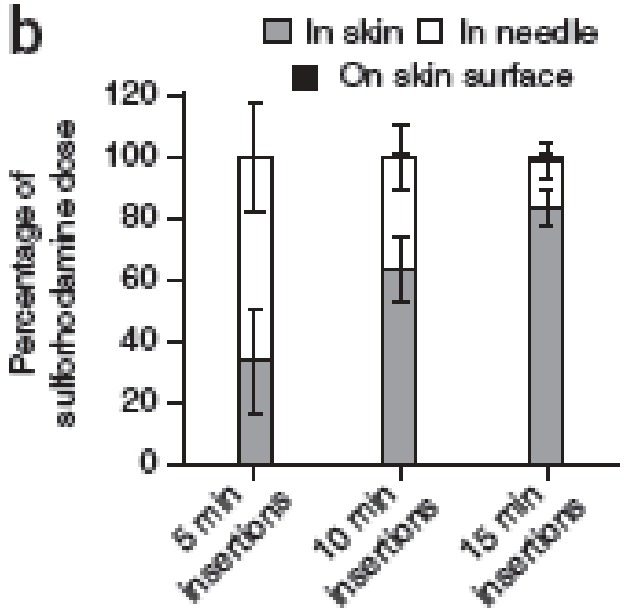
NATURE MEDICINE VOLUME 16 | NUMBER 8 | AUGUST 2010



In vivo dissolution in mice showed 83% of the vaccine was released in 15 minutes

Dissolving Microneedles

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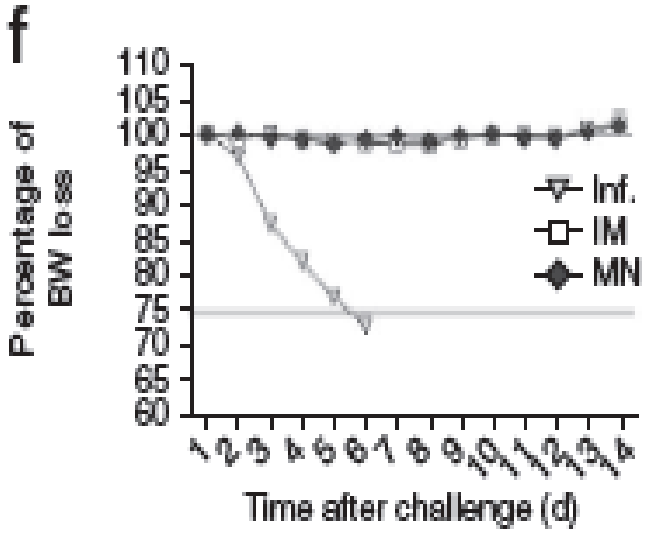
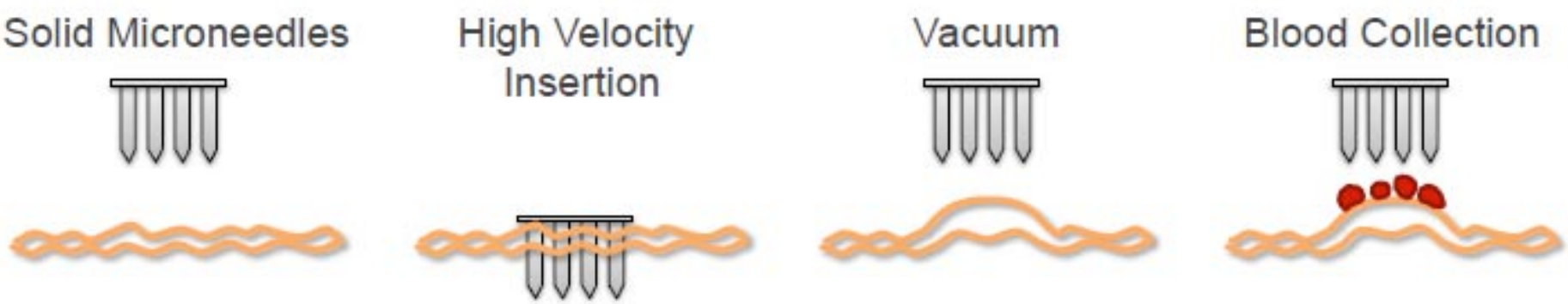
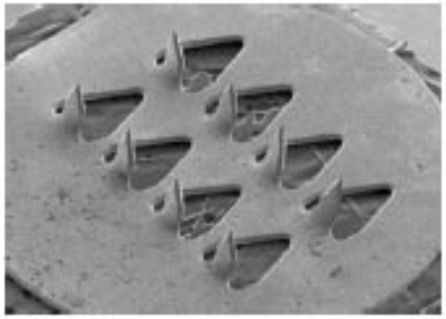


Mice were provided a challenge with 5x the LD_{50} of the influenza pathogen

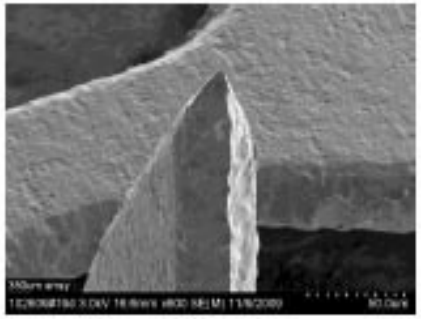
Intramuscular (IM) and microneedle (MN) immunization led to complete protection

Blood Access Using Microneedle Arrays





SEM of 8 needle array



SEM of needle tip showing double-bevel edge

Microneedles Summary

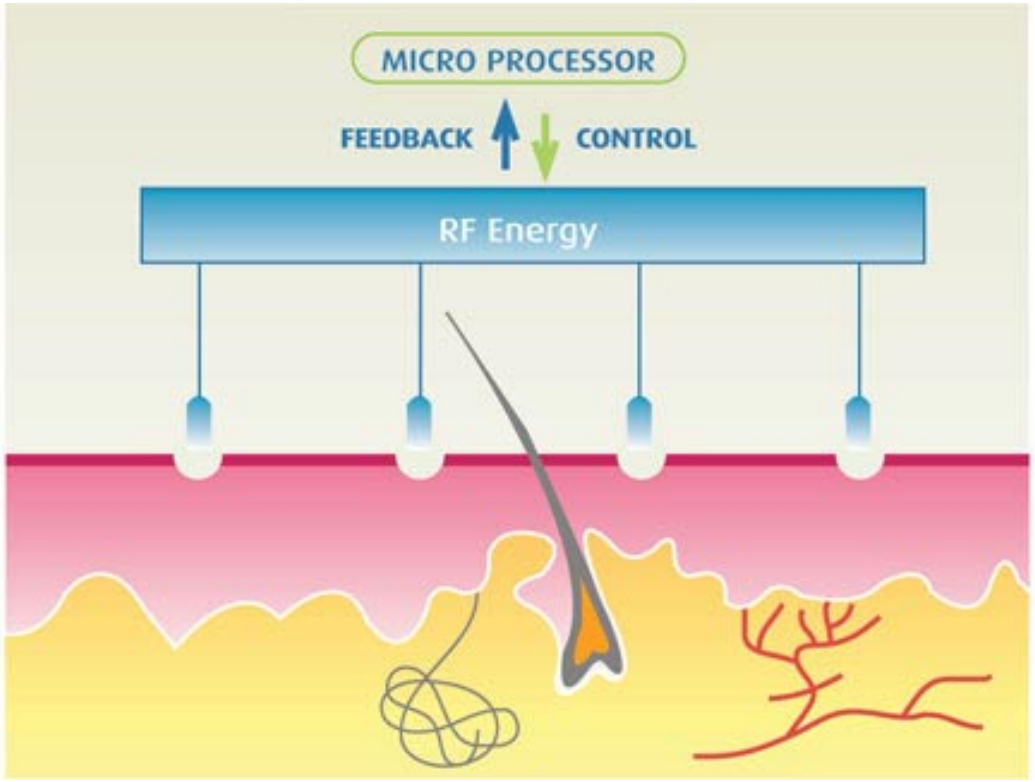
- Perforation followed by drug delivery or sample collection
  - Requires a two-step operation
- Hollow needles allow drug delivery or sample collection
  - Requires more complex needle structure
  - Requires “pumping” of some sort
- Drug coated needles
  - Drug loading is low – suitable for vaccines

Microneedles Summary

- General
  - Creates aqueous pathways
    - Best for hydrophilic compounds
  - Fabrication can be expensive
    - Use of polymers can lower cost
  - Leaves the skin permeable to other (potentially toxic) substances

Skin Ablation

RF Ablation



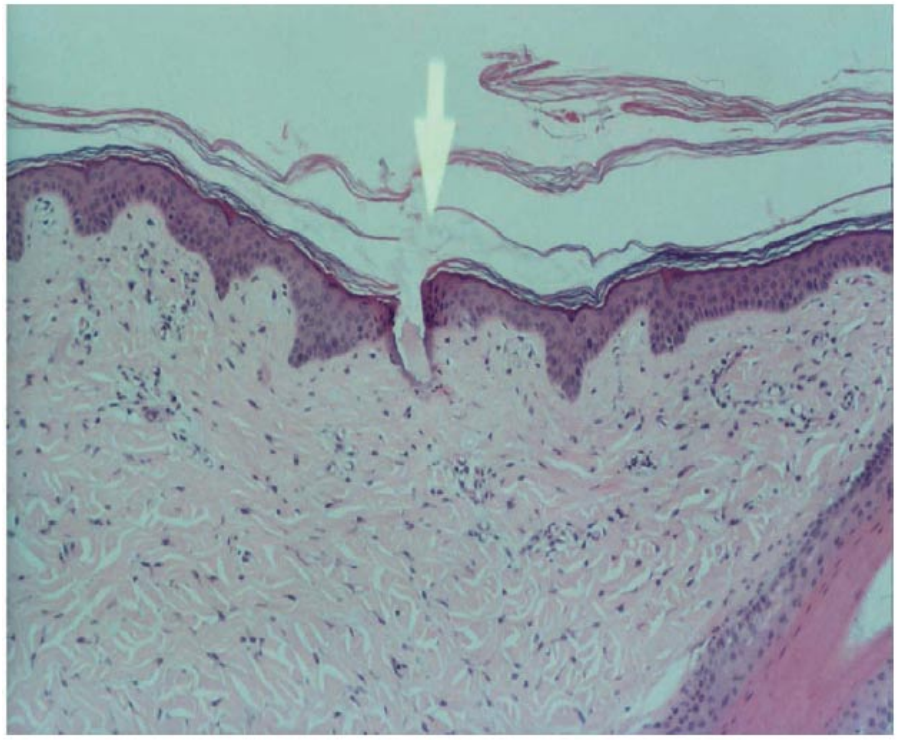
Radiofrequency (RF) pulses applied to skin using an array

- 100 electrodes/cm^2
- ~250V
- 100 Khz
- 1 msec duration pulse
- Pulse repeated ~ 15msec

www.**transpharma**-medical.com

A.C. Sintov et al. / Journal of Controlled Release 89 (2003) 311–320

RF Ablation



Ion movement in response to RF burst leads to localized heating

Water is vaporized and expels tissue

"Aqueous" channels

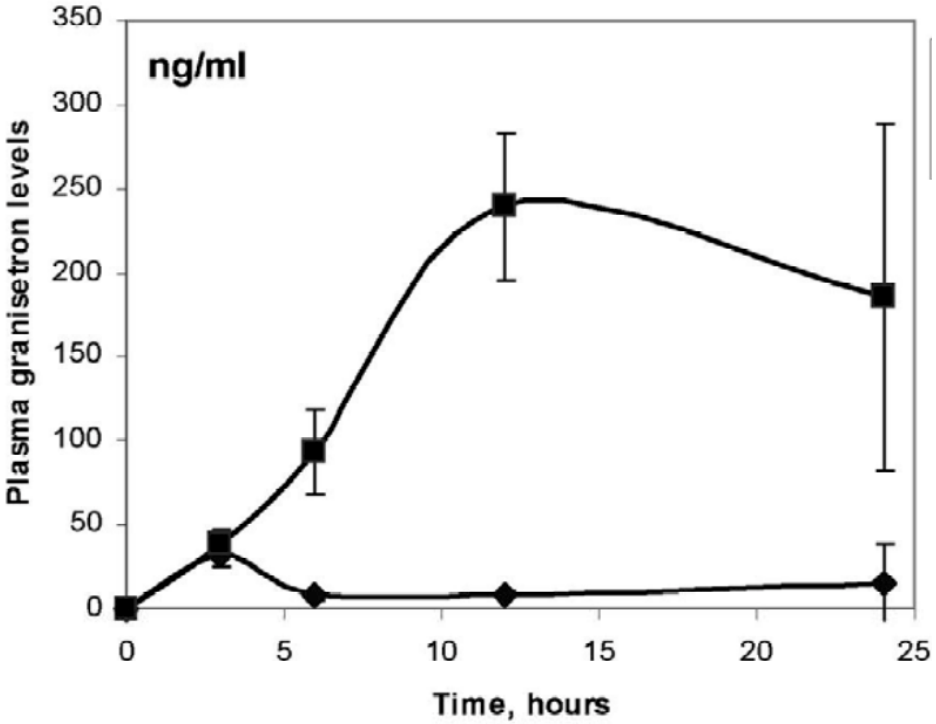
~40μm wide

~70μm deep

TEWL increased by three- to five-fold immediately after treatment

A.C. Sintov et al. / Journal of Controlled Release 89 (2003) 311–320

RF Ablation



Measured delivery of granisetron HCl over 24 hours in vivo (rats)

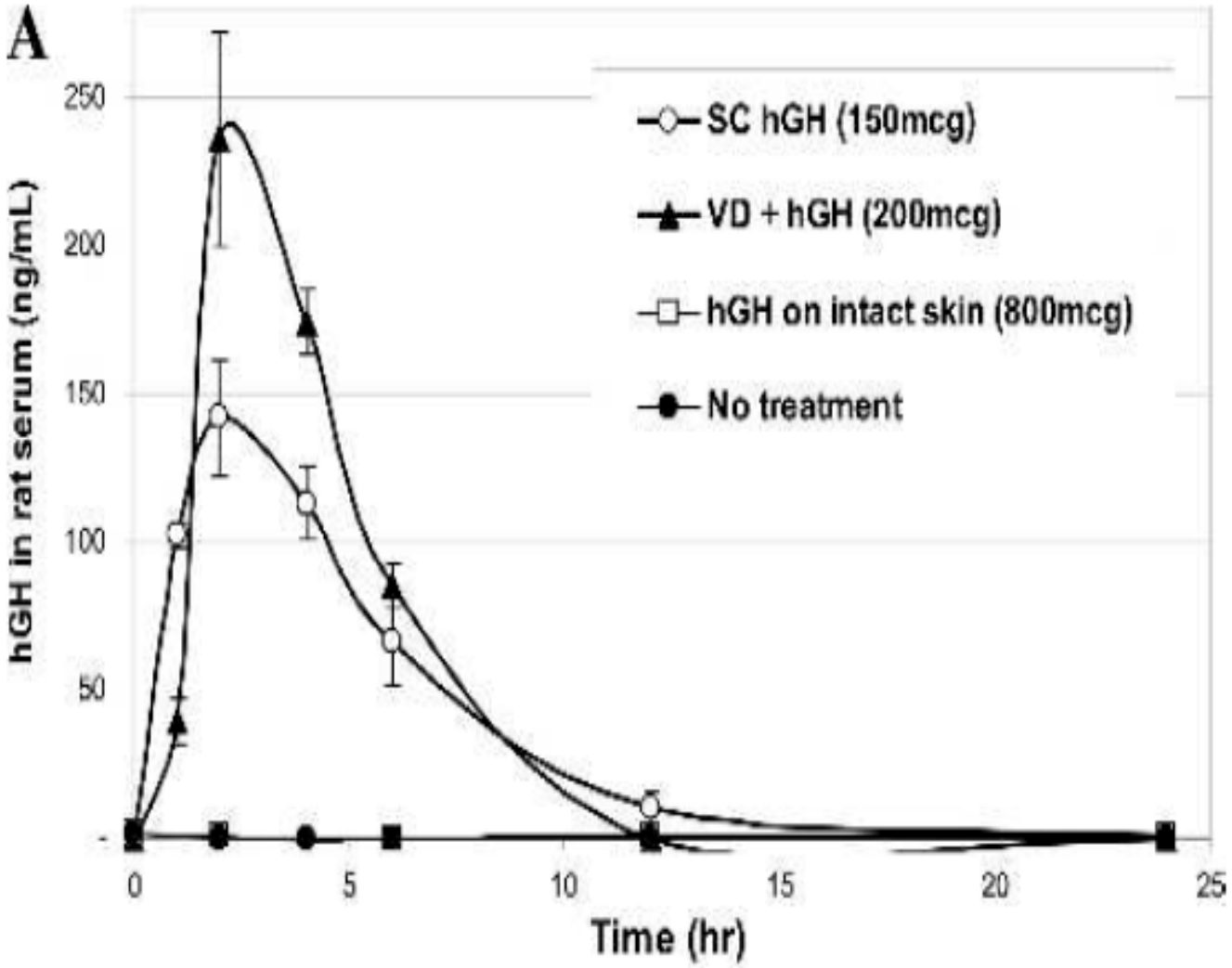
Drug applied after RF ablation

Significant increase which lasted over 24 hours

No evidence of skin irritation

A.C. Sintov et al. / Journal of Controlled Release 89 (2003) 311–320

RF Ablation



Serum levels of HGH (22kDa) in rats following RF treatment – ViaDerm (VD)

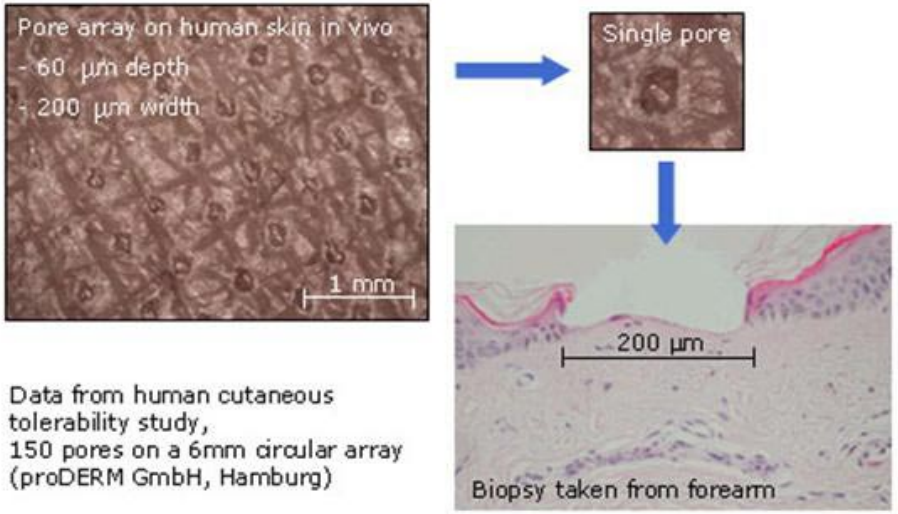
Achieved levels comparable to subcutaneous (SC) injection

10-fold increase in TEWL immediately after ViaDerm treatment

Levin et al. "Transdermal Delivery of Human Growth Hormone Through RF-Microchannels", ***Pharmaceutical Research* 22**:550 (2005)

Laser Ablation

- Pantec-Biosolutions
  - P.L.E.A.S.E.® - Painless Laser Epidermal System
  - Clinical trials in humans to deliver FSH
  - Depth of ablation depends on laser energy*
    - <14J/cm^2 – penetrate ~20µm
    - >23J/cm^2 – penetrate >150µm

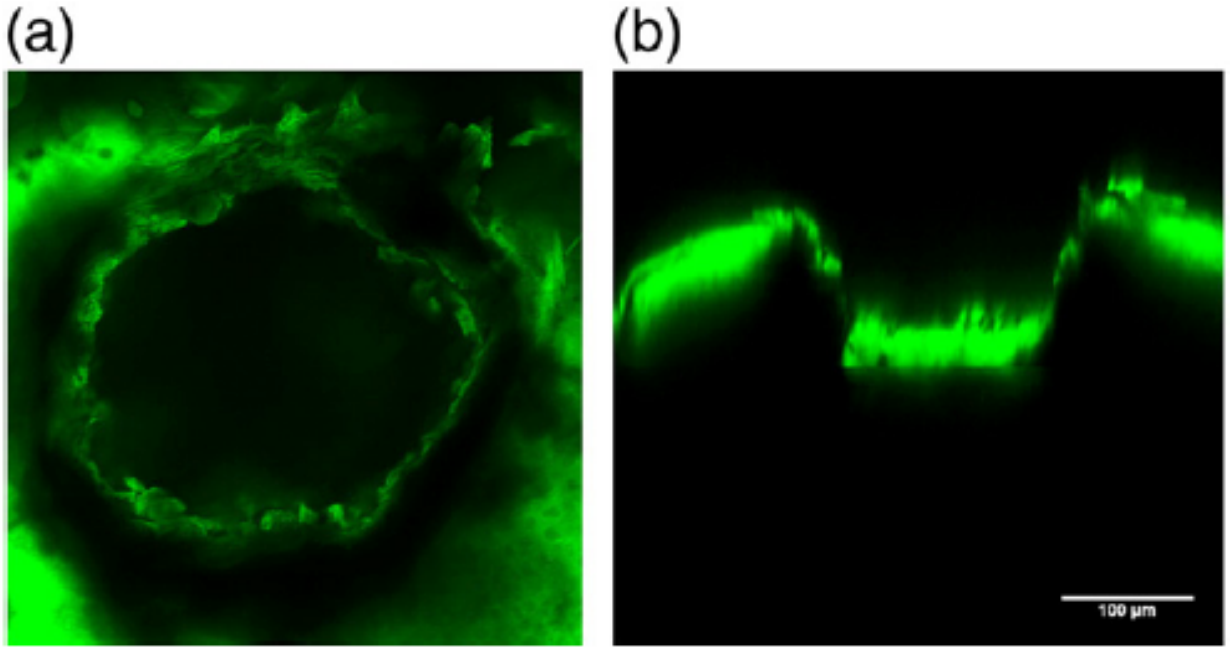


Data from human cutaneous tolerability study,
150 pores on a 6mm circular array
(proDERM GmbH, Hamburg)

*** Bachhav et al., J. Cont. Rel. 146:31-36 (2010)**

www.pantec-biosolutions.com

Laser Ablation



Er:YAG laser emits at 2.94µm

H_2O absorbance

H_20 is vaporized lead to pore formation

Fig. 1. Confocal images showing the distribution of FITC fluorescence in the (a) XY- and (b) XZ-planes following P.L.E.A.S.E.® poration of full thickness porcine skin.

Y.G. Bachhav et al. / Journal of Controlled Release 146 (2010) 31–36

Laser Ablation

The depth is controlled by the energy density

Energy (J/cm^2)	Depth (μm)
4-14	20-30
23	60-100
>23	>150

The flux of lidocaine (applied after ablation) increased with the number of pores

Pores	Lidocaine delivered @ 24hr ($\mu g/cm^2$)
0	107
150	774
300	1400
900	1811

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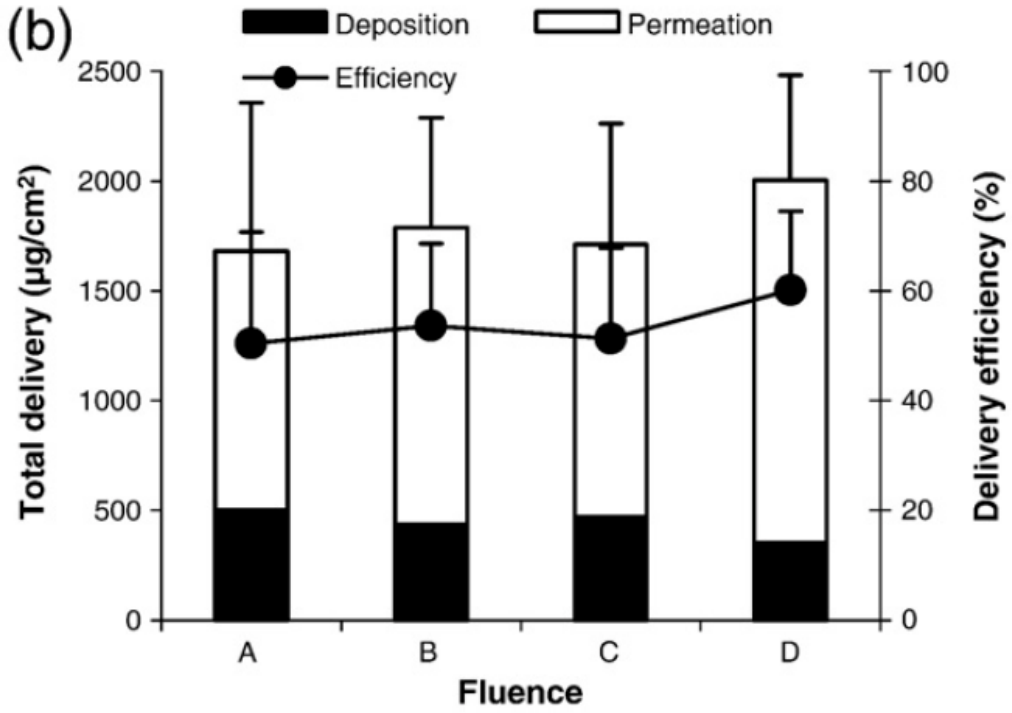
Laser Ablation



A = 22.65 J/cm^2
B = 45.3J/cm^2
C = 90.6 J/cm^2
D = 135.7 J/cm^2

The amount of lidocaine delivered was independent of depth once the stratum corneum was removed

Y.G. Bachhav et al. / Journal of Controlled Release 146 (2010) 31–36

Laser Ablation

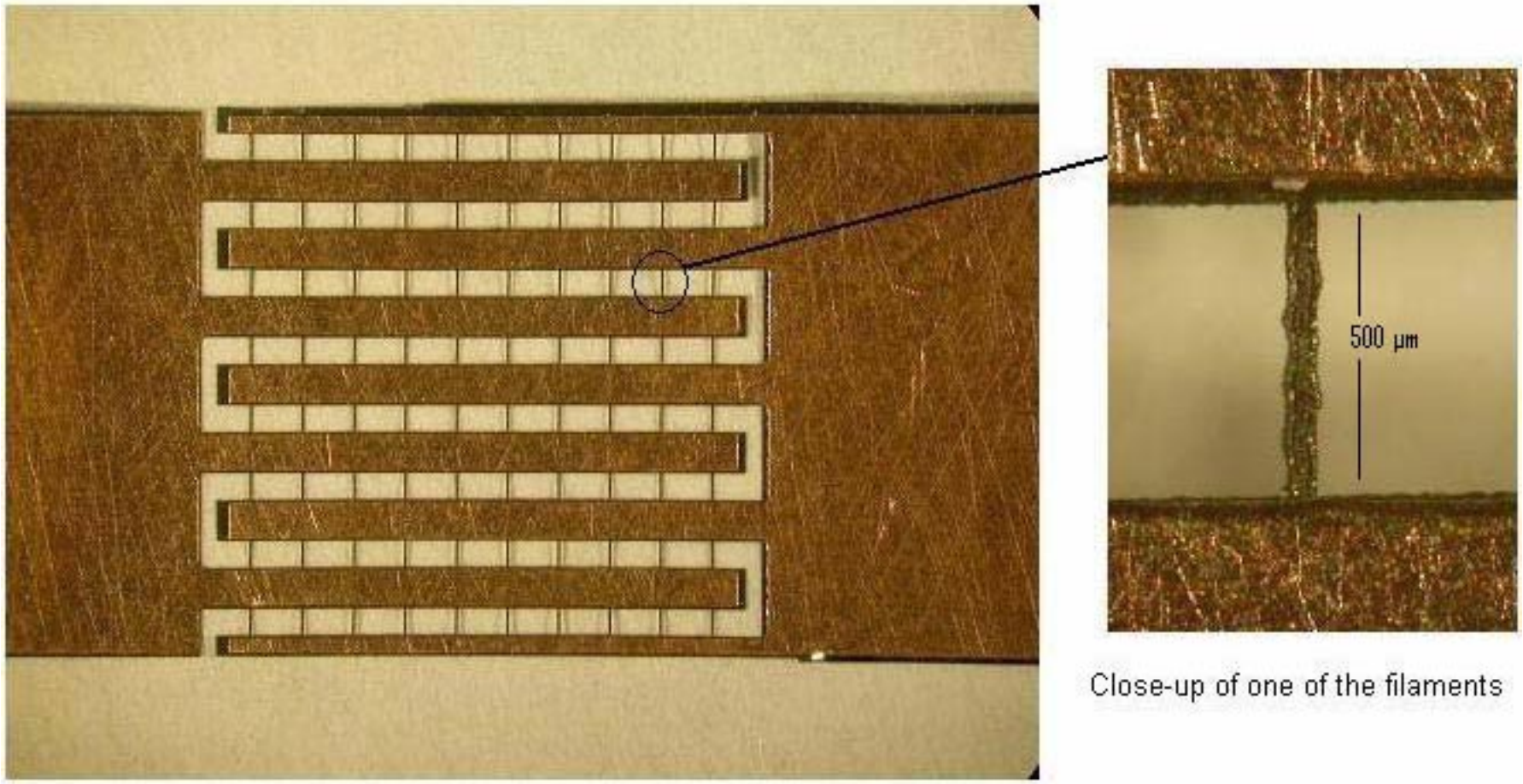
- Er:YAG pulsed laser (Norwood Abbey)
- 250 mJ/pulse; 300 msec pulse; 3mm diameter
- Followed by application of topical lidocaine for 5 minutes
- Assessed pain to a needle stick
- Laser pre-treatment led to >60% reduction in pain relative to lidocaine application alone

Laser-Assisted Penetration of Topical Anesthetic in Adults

Arch Dermatol. 2003;139:1288-1290

Elma D. Baron, MD; Lisbeth Harris, MSPH; William S. Redpath; Howard Shapiro, PhD; Fred Hetzel, PhD, JD; Grant Morley, MSc, MMedSc; David Bar-Or, MD; Seth R. Stevens, MD

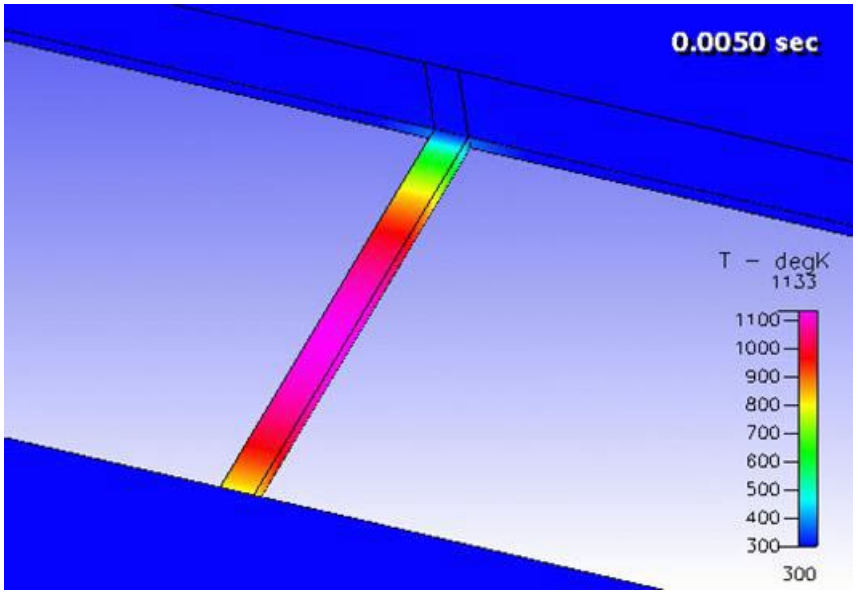
Thermal Ablation – Altea PassPort®



Close-up of one of the filaments

http://www.math.udel.edu/~rossi/Math512/2003/altea5.pdf

Thermal Ablation – Altea PassPort®



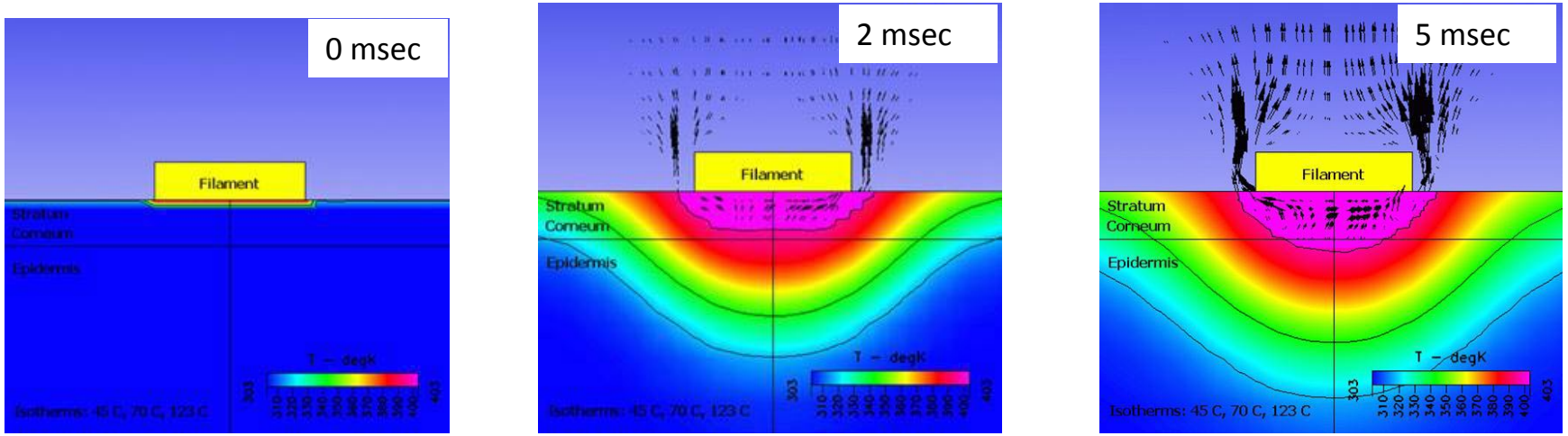
Use finite element analysis (FEA) to model heat in each thermal filament

Potential is applied across each thermal filament.

After 5 msec temperature > 1000°K obtained

Data provided by Altea Therapeutics

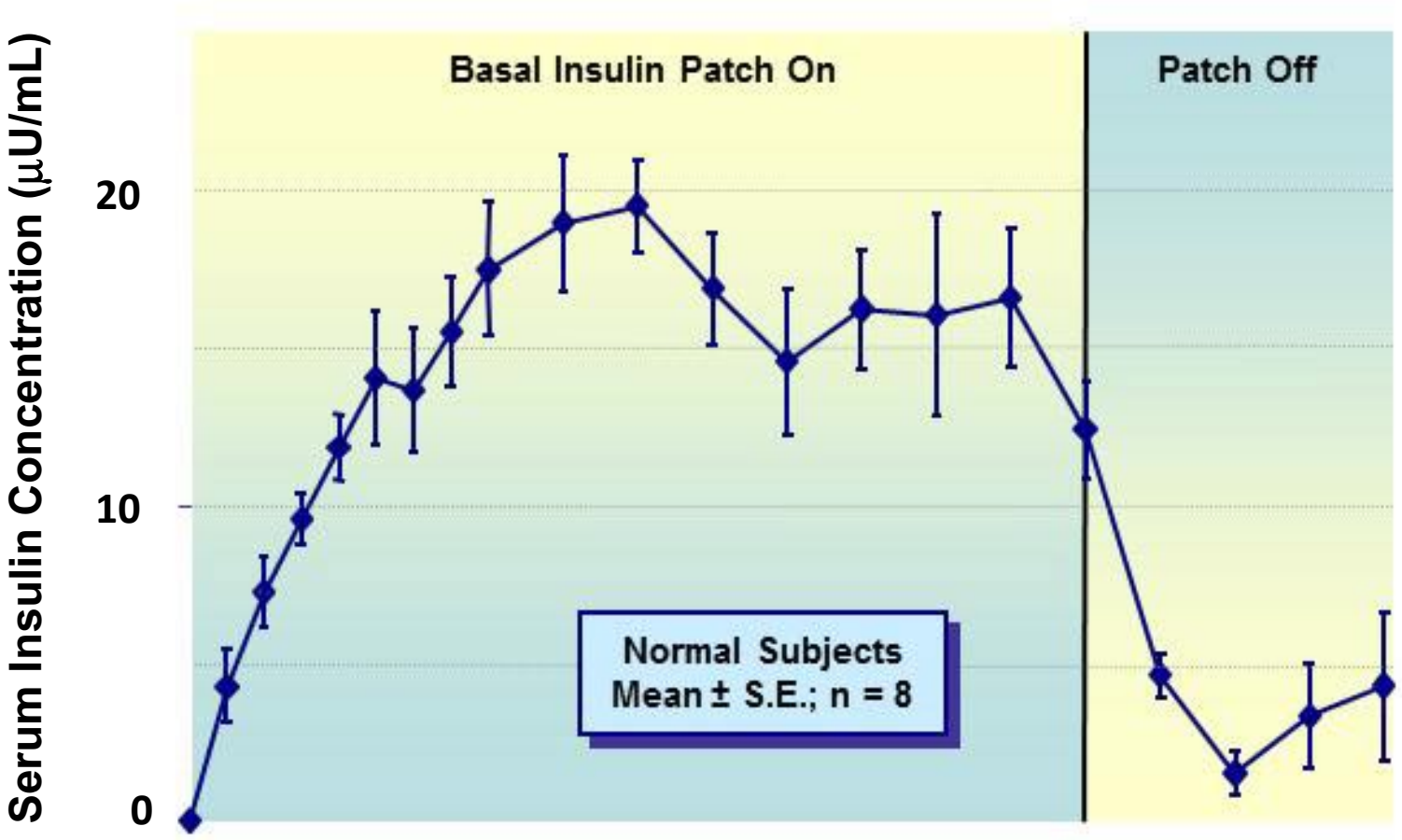
Thermal Ablation – Altea PassPort®



FEA modeling results show

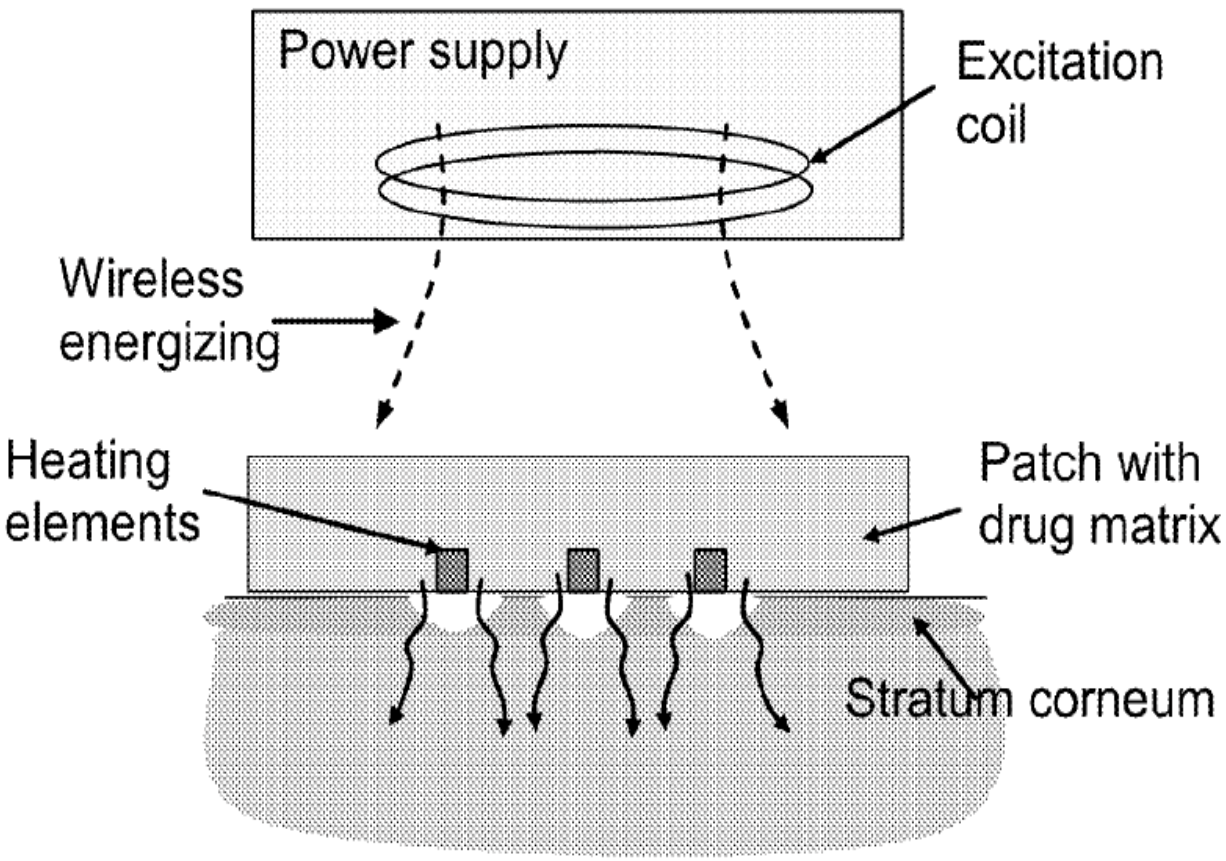
- Joule Heating
  - Skin temperature up to 400°K (~130°C)
  - 45°C isotherm penetrates to the less than 150 µm depth during 20 msec pulse
- Heat Transfer
- Phase change in skin
- Convection of vapors
- Pore formation & growth

Thermal Ablation – Altea PassPort®



Insulin delivery in Normal subjects

Thermal Ablation



Wireless ablation scheme

US patent appl. 2009/0318846

Prausnitz et al.

Fluid heated and ejected to skin surface

Rapid onset (<100μS)allows better control of ablation

Ablation Summary

- Requires a costly device
  - Drug in a disposable
- Requires a two-step operation
  - Ablation followed by drug application
- Creates aqueous pathways
  - Of primary benefit for hydrophilic compounds
- **Size and depth of pore can be controlled**
  - Leaves the skin permeable to other (potentially toxic) substances

Current Status of Skin Ablation/Perforation Techniques

Russell Potts, PhD

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