

## MICRONEEDLES FOR TRANSDERMAL DELIVERY OF MACROMOLECULES

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**ABSTRACT** Transdermal drug delivery is limited by the extraordinary barrier properties of the stratum corneum, the outer 10 - 15  $\mu\text{m}$  of skin. Arrays of solid silicon microneedles inserted across the stratum corneum have been shown to painlessly disrupt this barrier and increase the permeability of skin to calcein up to four orders of magnitude [1]. In this study microneedles delivered bovine serum albumin (BSA) and insulin across human epidermis *in vitro* at similarly increased levels. To develop better microneedles, arrays of hollow silicon and metal needles have also been fabricated using microfabrication techniques including deep reactive ion etching, micromolding, and electroplating. The hollow needles have been successfully inserted through human epidermis and have been shown to permit water to flow through their bores.

**INTRODUCTION** Proteins, oligonucleotides, and other biotechnology drugs show great promise in the treatment of a broad range of diseases, but usually cannot be delivered orally due to poor absorption and enzymatic degradation. Transdermal drug delivery is an attractive alternative, but the skin barrier blocks the transport of most compounds. Microfabricated needles may provide a route across the skin barrier to make transdermal delivery of macromolecules possible.

**METHODS** Arrays of solid silicon microneedles (Figure 1a) were fabricated using a reactive ion etching process as previously described [1]. Hollow silicon needles are fabricated with an extra step, which consists of deep reactive ion etching a bore down the center of each needle simultaneously. Hollow metal needles are fabricated by first encasing an array of solid silicon needles in ultra-thick UV-light photosensitive epoxy (SU-8). Removal of the needles from the epoxy left behind an epoxy mold, which is partially filled by electroplating metal onto the mold. The mold is then etched away, leaving behind an array of hollow conical shells (i.e., hollow needles) similar in shape to the original solid silicon microneedles (Figure 1b).

Transdermal transport experiments were performed using human epidermis mounted in Franz diffusion chambers. The chambers contained well-stirred saline in the receiver compartment and 100  $\mu\text{M}$  fluorescein-labeled BSA or 100 U/ml insulin in saline in the donor reservoir. Microneedle arrays were inserted into epidermis and transdermal transport of BSA and insulin were determined by spectrofluorimetry and radioimmunoassay, respectively.

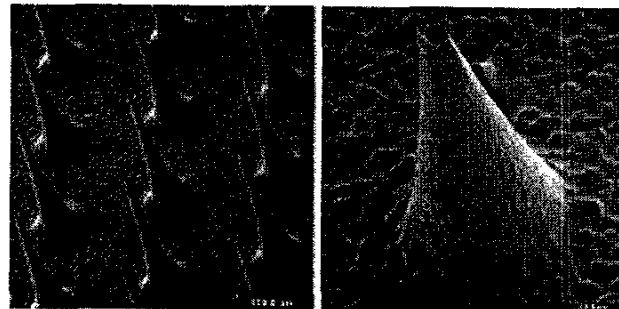


Figure 1 - Scanning electron micrographs of (a) a section of an array of solid silicon needles and (b) a section of an array of hollow metal needles.

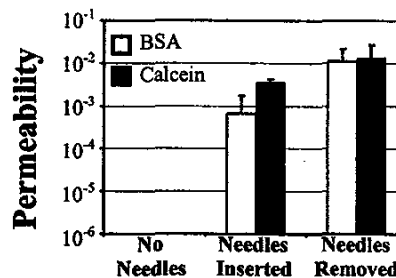


Figure 2 - Microneedle enhanced skin permeability to calcein and BSA.

**RESULTS AND DISCUSSION** Figure 2 shows skin permeability to calcein and BSA for three experimental protocols involving transport across: (1) normal skin, (2) skin with solid microneedles embedded, and (3) skin with solid microneedles inserted for 1 hour and then removed. Passive skin permeability to calcein and BSA is below the detection limit of the spectrofluorimeter ( $10^{-5}$  cm/h for BSA and  $10^{-6}$  cm/h for calcein) and most likely BSA does not cross the skin at all. Insertion of microneedles increases skin permeability by 3 to 4 orders of magnitude above the detection limit. Similar increases have also been seen for skin permeability to insulin (data not shown). The large permeabilities to BSA and insulin observed here are significant because macromolecules are extremely difficult to deliver across skin. Hollow metal needles were inserted through epidermis with little pushing and permit the flow of water through their bores.

**CONCLUSIONS** Solid and hollow microneedles show promise as a minimally-invasive and user-friendly method to deliver drugs across skin at therapeutic rates.

### REFERENCES

- [1] S.Henry et al., *J. Pharm. Sci.* 87:922-925 (1998).