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BIODEGRADABLE POLYMER MICRONEEDLES FOR CONTROLLED-RELEASE DRUG DELIVERY

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ABSTRACT

Biopharmaceuticals, which include proteins, DNA, vaccines and other biologically related molecules, make up one of the fastest growing segments of the overall pharmaceutical market. However, there are significant delivery limitations. Specifically, oral delivery is difficult due to Poor absorption and degradation that occurs in the GI tract and liver and more sensitive drugs including proteins must survive the harsh environment of gastro intestinal tract. Transdermal drug delivery is an attractive alternative that involves transport of drugs across skin from a patch. This present review focused to increase the skin permeability different methods like chemical enhancers, electric fields, ultra sound and thermal methods have been approached. However the application of these has been limited because of strong barrier function of the skin. The future of drug delivery is assured to be significantly influenced by micro fabrication technologies. These micro fabricated drug delivery devices can enable efficient drug delivery that was unattainable with conventional drug delivery techniques, resulting in the enhancement of the therapeutic activity of a drug.

Keywords: Transdermal drug delivery, Microneedles, Biodegradable Polymer.

INTRODUCTION

Pharmaceutical therapy is an increasingly important part of medicine; biopharmaceuticals are an increasingly important part of current drug formularies and drugs in the pipeline. Biopharmaceuticals, which include proteins, DNA, vaccines and other biologically related molecules, make up one of the fastest growing segments of the overall pharmaceutical market. However, there are significant delivery limitations. Specifically, oral delivery is difficult due to Poor absorption and degradation that occurs in the GI tract and liver and more sensitive drugs including proteins must survive the harsh environment of gastro intestinal tract. Transdermal drug delivery is an attractive alternative that involves transport of drugs across skin from a patch. Several transdermal patches have been developed for delivery of, for example, nicotine for smoking cessation and synthetic steroids for birth control that achieve systemic medication through a topical application to the intact skin surface. Despite a number of successful patches, very few drugs can be delivered across the skin as the rates of transdermal delivery are limited by the extraordinary barrier properties of the stratum corneum, the outer 10–15µm of skin. To increase the skin permeability different methods like chemical enhancers, electric fields, ultra sound and thermal methods have been approached. However the application of these has been limited because of strong barrier function of the skin. Currently, the most common delivery vehicle for these molecules is the hypodermic needle, which is effective, but also has limitations, including

- Painful delivery
- Inconvenient
- Bolus delivery reduces the effectiveness of drugs that would benefit from controlled release overtime
- Require patient training or involvement of medical personnel, especially for children and elderly.
- The disposal of biohazardous sharps wastes after injections, and problems in a mass immunization scenario.

Devices for controlled release of such compounds have been developed, which enable slow delivery over hours to years. Polymer microneedles offer a delivery option that can meet all of the above goals.

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INTRODUCTION TO MICRONEEDLES

Micro needles are one of the recent advances in drug delivery and have been proposed as a novel drug delivery system.

The polymeric micro particles redesigned to have the shape of microneedles and are suitable to overcome the individual limitations of both injections and patches**,** thereby give the functionality of both needles and drug matrices for controlled release.

Microneedles are microscopic needles that are large and strong enough to insert into the skin and deliver drugs into the skin, but short enough that they do not reach the deeper layers of the skin to stimulate nerves.

Dissolving polymer microneedles add an additional benefit of a lack of biohazardous sharps waste after delivery. The mode of delivery for these microneedles is by the degradation or dissolution of the polymer in the skin after insertion, resulting in delivery of the encapsulated molecule and no needles left afterwards. This could be extremely beneficial for places where biohazardous sharps are a problem, including home use and developing countries. One current limitation to the use of polymer microneedles is the fabrication process, which should be at room temperature, to allow for retention of activity of biomolecules during encapsulation.

Microneedles offer an efficient method of delivering the antigen to the skin in a self-administered manner. Dissolving polymer microneedles in particular would allow for vaccination against the influenza virus via a self-administered microneedle patch that results in no biohazardous sharps waste [1,2].

Microneedles offer an attractive delivery option for a number of classes of biomolecules, and are particularly appealing for the delivery of vaccines to the skin. Research has shown that the skin offers an appealing target for vaccine delivery due to the large number of immune cells present in the epidermis and dermis.

However, skin vaccination via an intradermal injection is a difficult process that requires highly trained personnel and can be time consuming. Specifically, the influenza vaccine has been shown to possibly allow for dose sparing in skin delivery versus the current intramuscular injection.

IDEAL PROPERTIES OF BIODEGRADABLE POLYMERS USED IN MICRONEEDLE FABRICATION

Microfabrication technology has been adapted to create microneedles suitable for transdermal delivery as constrained by efficacy, safety and manufacturing cost considerations.

Biodegradable polymers may provide the ideal material for microneedles, for their

- **Safety**: Microneedles are made of FDA-approved, biodegradable polymer, Even after breaking off in the skin by accident, or intentionally to provide controlled release of encapsulated drugs, biodegradable polymer needles can safely degrade in the skin.
- **Efficacy**: Designing microneedles with sharp tips and sufficient mechanical strength to penetrate skin without breaking.
- **Low-cost mass production**: Achieved by simple and versatile fabrication technique.

SIGNIFICANCE OF MICRONEEDLES:

- Ease of use
- Self administration(compared to surgical implantation)
- Bolus and sustained delivery of drugs into the skin
- Elimination of dangers associated with improper needle disposal and intentional re-use, especially in the developing world
- Less time and reduced expenses of trained clinical personnel

- **Lack of pain**:

A formidable barrier to transdermal drug delivery is the stratum corneum, the superficial layer of the skin. Micro needles were proposed as a mechanical tool to pierce through the stratum corneum , in order to create drug delivery channels without stimulating underlying pain nerves , and the other basic reason is stratum corneum do not have pain nerves. Conventional needles which pass this layer of skin effectively transmit the drug but may lead to infection and pain. On the other hand, microneedles can be fabricated such that they are long enough to penetrate the stratum corneum, but short enough not to puncture the nerve endings, thus reducing the chances of pain and deliver drug to epidermis and superficial dermis. Kaushik *et al* determined that, microneedles are perceived as painless by human subjects.

- **Effective response through skin:**

Skin is very sensitive organ of the body, and it represents the first immunological defense barrier to outside injury and has evolved into a major immune competent organ. Foreign agents and antigens that penetrate the outer most stratum corneum encounter a defense network of potent antigen-presenting cells, the epidermal langherhans cells, and the dermal dendritic cells. This will enable the drugs to produce a pharmacological response or effect on administration which is faster when compared to traditional methods of drug delivery These langherhan cells readily take up foreign antigens, and initiate antigen specific immune responses, The skin is therefore is an attractive

target site for vaccine delivery, allowing the most effective immunization with the least amount of antigen. A robust, practical cost effective convenient and efficient intracutaneous antigen delivery technology will have broad application in the field, especially if the delivery can be achieved by minimally invasive and pain less technique [1].

LIMITATIONS OF CONTROLLED RELEASE FROM MICRONEEDLES:

- Exposes encapsulated drug to elevated temperatures. Hence not suitable for heat sensitive substances
- Although polymer microneedles can be designed to be strong enough toreliably insert into skin, the addition of encapsulated drug can weaken them.
- The greatest shortcoming of controlled-release microneedles is the limited dose that can be administered.

DESIGN PARAMETERS

In general terms the design parameters to be considered are:

- Microneedles should be capable of inserting into skin without breaking
- Polymers should be selected to have sufficient mechanical strength
- Biocompatibility
- They should not produce any pain
- Micro needle geometry is also important, where sharpness of tip strongly effects the microneedles insertion into skin.

PROPERTIES OF MICRONEEDLES

1. Ruggedness: Microneedles must be capable of inserting into the skin without breaking .They are to be manufactured in optimal size parameters. If they are too long, upper portion of microneedles may not have enough flexural rigidity and could break off before penetration they must be able to withstand insertion force without buckling, delamination, or fracture.

2. Controlled release: The microneedles should be capable to deliver controlled amount of drug at specific rate

3. Penetration: The microneedles should be able to deliver the drug to the required depth in the tissues of the body. Painless insertions of micro needles into the skin can be accomplished by gentle pushing, using approximately 10 N forces. Microneedle geometry is also important, where sharpness of tip strongly affects the force required for the insertion into skin. Other parameters including microneedle length, width and shape also influence the force required for microneedle fracture [2].

DIMENSIONS OF MICRONEEDLES

The dimensions of micro needles can be different depending on their types. Typical microneedle geometries vary from 150-1500 microns length, 50-250 microns in base width, 1-25 microns in tip diameter.

The tips of microneedles are in various shapes like triangles, rounded or arrow shaped[16].

FABRICATION OF BIODEGRADABLE POLYMER MICRONEEDLES

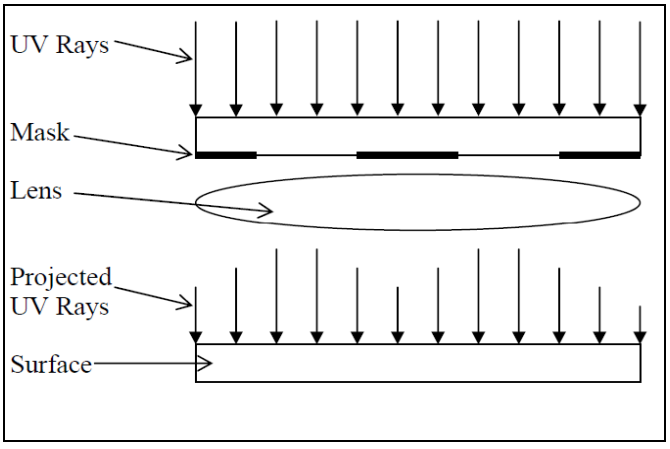
The process to fabricate biodegradable polymer microneedles is based on micromolding using high aspect ratio SU-8 epoxy photoresist or polyurethane master structures to form PDMS (polydimethyl siloxane) molds from which biodegradable polymer microneedle replicates are formed [3].

1. SU-8 epoxy mixed with a solvent, gamma-Butyrolactone (GBL, an organic solvent, determines the viscosity, which determines final thickness of the film to be coated) and a photoinitiator triarylium-sulfonium salts (Epoxy resins could be cationically polymerized by utilizing a photoinitiator).

2. The SU-8 epoxy mixtures was coated to a thickness of 300–350 µm onto a silicon wafer and lithographically patterned into 100 µm diameter cylinders, which defined the shape of the desired needles.

UV Lithography

UV lithography is perhaps the most commonly used photolithography technique. As the name implies, the crux of UV lithography centers around the properties and attributes of UV (ultraviolet) light. The overall concept of UV lithography is quite simple. UV light is shined through a mask onto a photoresist covered wafer. As the diagram shows, the mask stops some of the light from proceeding onto the resist covered surface.



Overall Process

The overall process of UV lithography contains about 8 steps:

a. Surface Preparation
b. Resist Coating
c. Pre-Bake
d. Mask Alignment
e. Exposure
f. Development
g. Post-Bake
h. Photoresist removal/Processing

a. Surface Preparation

Because of the extreme delicacy of the lithography process, great care must be taken when preparing a surface for lithography. All surface contaminants must be cleaned to perfection. Some common surface irritants include dust, lint, bacteria, water, and oil. To remove such pesky particles, the surface is soaked and rinsed in a number of different chemicals. The surface is then primed with more chemicals to aid in the resist adhesion.

b. Resist Coating

After the surface is cleaned and primed, the photoresist is applied by a method known as spin coating. Simply put, the surface is spun rapidly inside a vacuum, while being coated with the photoresist. The photoresist bonds uniformly to the surface, with the excess flying off during spinning. A coating solvent is then used to dissolve the build-up along the edge of the surface.

c. Pre-Bake

The pre-bake is a simple process of heating the surface in a convection oven or through a heated plate placed below the surface. The purpose of the pre-bake is to evaporate the excess coating solvent and to compact and harden the photoresist.

d. Mask Alignment

Photomask: A photomask is a desired pattern that can be transferred onto a surface by means of light waves. The mask creates a sort of shadow between the light and the surface. Less light passes through sections blocked by the mask. Masks can be created by several different ways, but one of the most common and an accurate method is using an electron beam to etch a desired mask.

The mask must be aligned correctly in reference to the surface. This procedure is accomplished by hand using certain marks on the mask and the surface, or by using an automatic pattern recognition device. There are several different ways the mask can be placed in reference to the surface, including:

. **Contact:** The mask is in contact with the surface during exposure.
. **Proximity**: The mask is close but not touching the surface during exposure.
. **Projection**: The mask is not close to the surface, and the light passing between them is subject to imaging optics.

e. Exposure

The photoresist, surface, and mask are subjected to UV light via a UV lamp.

f. Development

During the development stage, chemicals are applied to the surface causing either a positive photoresist reaction or a negative photoresist reaction.

Negative: The molecules in the resist that are subjected to the most UV rays are bonded strongly together in long chains (polymerization). After the subsequent development process, the non-polymerized sections of the resist decompose and only the polymerized resist remains.

Positive: Opposite of a negative photoresist. Sections of the resist are chemically altered to decompose when exposed to UV light; therefore after the development, only the sections not exposed to UV light remains.

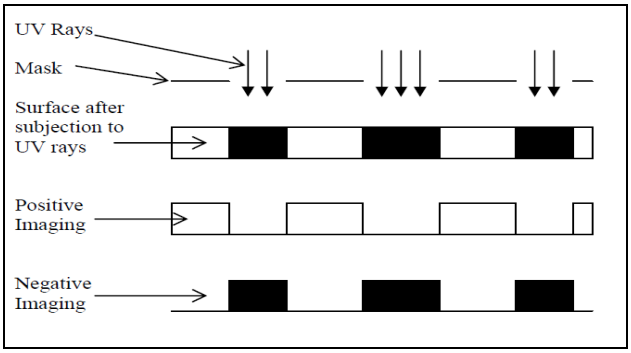


Fig 1.Photoresist Reaction

g. Post Bake

The post bake is used to stabilize and harden the photoresist. It also removes any trace of development chemicals.

h. Photoresist Removal/Processing

Remember that the photoresist is only a means to an end; the important thing is the surface either underneath or below the photoresist. To remove the excess photoresist, simple solvents are used. The following cases are the results when the photoresist is applied on top or on bottom of the desired surface.

- **Etch-back**: The photoresist is applied overtop the layer that is wanted to be patterned. The unwanted material is etched away.
- **Lift-off**: A layer is deposited over top of the photoresist. When the resist is removed, the unwanted layer is also removed.

Although these cylinders were usually circular in cross-section, sometimes a different mask was used to create cylinders with a notch of 30-µm radius cut out of one side. These cylinders were arranged in an array, where the center-to-center spacing between cylinders in each row was 1400 µm and between each column was 400 µm. The array contained 20 cylinders in each row arranged in 6 columns for a total of 120 cylinders in an area of 9×9 mm.

3. The space between cylinders was filled with a sacrificial polymer (PLGA 85/15), and the entire surface was coated with a 600-nm thick layer of copper by electron beam deposition. This copper layer was etched with acid (H_2SO_4:H_2O_2:H_2O at a volumetric ratio of 1:1:10) to leave a pattern of rectangles with 0.6 mm width and 10 mm length that asymmetrically covered the tops of the epoxy cylinders and some of the sacrificial polymer on one side of each cylinder.

4. Reactive ion etching partially removed the uncovered sacrificial layer and asymmetrically etched the tip of the adjacent epoxy cylinders.

Reactive ion etching (**RIE**) is an etching technology used in microfabrication. It uses chemically reactive plasma to remove material deposited on wafers. The plasma is generated under low pressure (vaccum) by an electromagnetic field. High-energy ions from the plasma attack the wafer surface and react with it.

5. All remaining sacrificial polymer was removed by ethyl acetate, leaving an array of epoxy cylinders with asymmetrically beveled tips.

6. This array of needles was coated with poly (dimethylsiloxane), which was subsequently peeled off to make an inverse mold.

B. Chisel-tip Microneedle Master Structures

1. Chisel-tip microneedles were fabricated using a combination of wet silicon etching and reactive ion etching of polymers.

2. Silicon nitride was deposited onto a silicon wafer to a thickness of 4000 A^o chemical vapor deposition to make a hard mask to protect silicon against KOH etching.

3. Next, the silicon nitride layer was lithographically patterned to expose a 15×15 array of square dots each measuring 100 µm in width with 600 µm center-to-center spacing.

4. The exposed silicon nitride layer was removed using reactive ion etching and the photoresist was then removed using acetone. KOH (30 wt.%, Aldrich) heated to 80 ^oC was then applied to the wafer to etch inverted pyramid-shaped holes. Etching occurred along the crystal plane to form 55 ^{o}-tapered walls terminating in a sharp point, which provide the chisel shape of the needle tips.

5. To form the shape of the needle shaft, SU-8 epoxy photoresist with photoinitiator was spin-coated onto the etched wafer to form a 500-µm thick film.

6. A second mask was aligned with the wafer to expose the SU-8 coating to UV light in the same 15×15 array of square dots in vertical alignment with the silicon nitride pattern.

7. After post-baking to crosslink the UV exposed SU-8 on a hotplate for 30 min at 100 ^oC and then cooling, the non cross linked epoxy was developed with PGMEA to leave behind obelisk-shaped SU-8 structures with their tips still embedded in the silicon wafer.

8. To finally make master needle structures, the space between the obelisk structures was filled with PDMS.

9. The cross linked SU-8 was removed by reactive ion etching with an oxygen plasma to leave a PDMS-silicon mold. Subsequently, polyurethane (Poly 15),was poured into the mold and crosslinked to form polymeric microneedles with chisel tips.

10. Removal of these needles from the mold yielded the final master structure.

2. Fabrication of Microneedle Master Molds

Polydimethylsiloxane(PDMS) molds that were made from the tapered SU-8 master structures. PDMS was poured over the SU-8 master structure and cured by placing in a 40^oC incubator for12h.

The cured PDMS mold was then peeled of from the master.

The SU-8 master structure could then be reused to make additional PDMS molds, although sometimes(10%of the time),removal of the PDMS mold damaged the master structure.

Polydimethylsiloxane (PDMS) is commonly used to prepare micromold microdevices, because it

- low surface energy (21.6 dyne/cm),
- chemically inert,
- non-hygroscopic,
- good thermal stability,
- optically transparent down to wavelengths of ~300 nm,
- mechanically durable and,
- low cost
- elastomer with 0.5 MPa Young's modulus.
- ability to conformally coat microstructures and fill micromolds
- poor adhesion to facilitate separation of microstructures from micromolds

3. Fabrication of Biodegradable polymer Microneedles

Three formulations were used to achieve different timescales of controlled release.

1) **For rapid release**, the model drug was directly encapsulated within the microneedles.

2) **For slower release**, drug was first encapsulated either within carboxymethylcellulose (CMC) or poly-L-lactide (PLA), which was then encapsulated within microneedles.

Consider encapsulation of a model drug,

''Model drug'' indicate that these compounds have physicochemical and transport properties representative of certain classes of drugs, but not to suggest that these compounds have pharmacological activity representative of drugs [4].

1) For rapid release

Calcein or Texas-Red-labeled bovine serum albumin (BSA) powder was suspended in acetonitrile at a solids content of 10% (w/v) and then homogenized for 5min at 10,000 rpm (PowerGen 700 homogenizer) to make drug microparticles.

The homogenized particles, with a broad size distribution over the approximate range of 1–100 μm, were filtered first through a 30-μm filter, and then the filtrate was passed through a 1-μm filter (nylon net filter, Millipore).

The final solids cake containing particles 1–30 μm in size was redispersed in acetonitrile at a solids content >20% (w/v). The resulting suspension was poured onto a PDMS microneedle mold and placed in a vacuum chamber at -20 kPa for 5 min.

This filled the mold with drug particles by first allowing the vacuum to force the drug suspension into the mold cavities and then evaporate off the organic solvent.

Residual particles remaining on the surface of the mold were removed using adhesive tape.

The mold was then filled with melted PLGA (PLGA 50/50, 1.2 dL/g), in a vacuum oven at 135°C and -70 kPa for 10–20 min. After cooling, the resulting microneedles with encapsulated drug were manually removed from the mold.

2) For slower release

a) Preparation of microneedle matrix

Polymers used are,

1. Carboxymethylcellulose(CMC)
2. Amylopectin
3. Bovine serum albumin(BSA)

These polymers are preferred as they are,

- Mechanically strong due to relatively high Young's modulus
- Highly water soluble for rapid dissolution in the skin

To serve as microneedle matrix materials, ultralow viscosity carboxymethylcellu-lose, amylopectin and bovine serum albumin were dissolved in deionized water. Water was then evaporated off until the concentration of solute (e.g.,CMC) was approximately 27wt%, which resulted in a viscous hydrogel.

CMC was concentrated by heating at 60-70°C at ambient pressure or vacuuming at -50kPa at room temperature. Amylopectin and BSA were concentrated only by the heating method at 60-70°C or 37°C,respectively. Solute concentration was determined by measuring solution mass before and after evaporation. Viscosity of concentrated hydrogels was measured using a Couette viscometer. In somecases, a model drug was added by hand mixing to solubilize or suspend the compound in the concentrated hydrogel [5].

b) Casting

To mold microneedles from concentrated hydrogels, 100-300mg of hydrogel was placed on a PDMS mold in a conical centrifuge tube and centrifuged in a 45° angled rotor at 3000×g and 37°C for up to 2 h to fill the microneedle mold cavities and dry the hydrogel.

To prepare microneedles with model drug encapsulated only within the microneedles and not in the backing layer, 8-10mg of hydrogel mixed with model drug was filled just into the microneedle cavities in the

mold and then dried under centrifugation for upto30min.Residual hydrogel on the surface of the mold was removed with dry tissue paper and 100-200mg pure hydrogel without drug was then applied and dried onto the mold to form the backing layer.

To prepare microneedles with model drug encapsulated only in the backing layer and not within the microneedles, the same 2-step process was followed, except pure hydrogel was filled into the microneedle mold cavities and a hydrogel mixed with model drug was used to form the backing layer.

EVALUATION

In-Vivo Testing of Microneedles

For the in-vivo preclinical evaluation, generally used like mice, rabbits, guinea pigs, mouse and monkey are used. The main purpose of the In vivo tests is the assessment of safety as well toxicity of the test compound or device. There are at least two species of animals used *in vivo* preclinical study for determination of different kind of toxicity concerning with microneedles.

The key objectives of the In vivo testing of the microneedles are as follows.

Key Objectives

1. To perform skin toxicity test.
2. To determine penetration force in different skin.
3. To determine mechanical stability of microneedle.
4. To determine bending breakage force.
5. To perform various non-clinical safety study and pharmacological study.
6. To determine various parameters like immunogenicity, genotoxicity, skin sensitization and allerginisation.

study, developmental toxicity, acute and chronic dermal toxicity, carcinogenicity.

Method 1

In this *In vivo* method employs testing microneedles, by pricking microneedles into tail vein of the mice in laboratory hairless mice. This method is used for the determination of the penetration force of the microneedle into the skin.

Method 2

In this method for the *In vivo* testing of the microneedles, the Rhodamine B is given into laboratory mouse-tail and anaesthetized rabbit ear for the determination of penetration, penetration force and bending breakage force.

Method 3

This method has been performed for a vaccine delivery by using microneedles. In this method ovalbumin as a model protein antigen was administered into hairless guinea pig by using solid metal microneedles at the rate of 20µg ovalbumin in 5s up to 80 µg.

Method 4

This method was used for a vaccine delivery through microneedles. In this method rabbits have been were used. The anthrax vaccine that contains recombinant protective antigen (rPA) of Bacillus anthracis has been administered (lethal aerosol dose of anthrax spores) in the rabbits by using solid and hollow microneedles [6].

I. MICRONEEDLE MECHANICS

1. Microneedle failure force measurement

Mechanical failure tests were performed with a displacement-force test station, A 3×3array containing 9 microneedles was attached to the mount of a moving sensor and an axial force was applied to move the mount at a speed of 1.1mm/s. The mount pressed the microneedles against a flat, rigid surface of stainless steel oriented perpendicularly to the axis of mount movement. The test station recorded the force required to move the mount as a function of distance [7].

a. Mechanical analysis of Axial failure force of polymer microneedles

Critical buckling load, P_{cr},, For the fixed-free case, where the microneedle base was fixed in position and the microneedle tip could move freely, the square-based pyramidal and circle-based conical geometries were modeled using the equations for P_{cr5} and P_{cr7}, respectively:

$$P_{cr5} = E\left[120\left\{H_2\left(H_2^2(H_2-2H_1)+2H_1^3\right)-H_1^4\right\}+\pi^2\left\{20\left(H_2\left(H_2^2(-H_2+H_1)-H_1^3\right)+H_1^4\right)+\pi^2\left(H_2\left(H_2\left(H_2(H_2+H_1)+H_1^2\right)+H_1^3\right)+H_1^4\right)\right\}\right]/ \times\left(240\pi^2L^2\right)\ \left(\text{pyramidal geometry}\right) \quad (1)$$

$$P_{cr7} = E\left[120\left\{R_2\left(R_2^2(R_2-2R_1)+2R_1^3\right)-R_1^4\right\}+\pi^2\left\{20\left(R_2\left(R_2^2(-R_2+R_1)-R_1^3\right)+R_1^4\right)+\pi^2\left(R_2\left(R_2\left(R_2(R_2+R_1)+R_1^2\right)+R_1^3\right)+R_1^4\right)\right\}\right]/ \times\left(80\pi L^2\right)\ \left(\text{conical geometry}\right) \quad (2)$$

Here, E is Young's modulus; L is microneedle length;
H1and H2 are microneedle widths at the base and tip of pyramidal microneedles, respectively; and
R1 and R2 are radii at the base and tip of conical microneedles, respectively.

Microneedle design as a function of base width/diameter also shows that increasing base dimensions (i.e., decreasing aspect ratio) increases needle strength. Thus, using pyramidal microneedles with a small aspect ratio can provide added mechanical strength for mechanically weak biomaterials like CMC. However, microneedles with an aspect ratio that is too small will also have poor insertion due to fabrication difficulties to make a sharp tip and insertion difficulties to force the rapidly widening needle shaft into the small hole made in the skin by the needle tip.

b. Mechanical Analysis of Transverse Failure Force of Polymer Microneedles

Although microneedles might ideally insert with a completely axial force, during actual insertion microneedles could experience a bending moment generated by a transverse tip force due to misalignment and deformation of the skin.

The maximum bending stress, σ , can then be expressed as

$$\sigma = \frac{M(z) \cdot c}{I(z)} \quad (3)$$

where *c* is the distance from the centroidal axis to the outermost
edge of themicroneedle,
M(z) is the bendingmoment, and
I(z) is the moment of inertia of the cross section.

By replacing the bending moment with the tip force, F_t , multiplied by the needle length, L, the maximum transverse tip force that the needle can support is

$$F_t = \frac{S_z \cdot I(z)}{c \cdot L} \quad (4)$$

where S_z is the yield strength of material.was interpreted as the force of needle failure. As shown in Fig.(B), needles were examined by microscopy (IX-70, Olympus, Melville, NY) before and after failure testing to determine the mode of failure, e.g., buckling failure due to inelastic or elastic instability. In most cases, failure was observed for all needles in an array. Data were discarded if only some of the needles were broken. Data are reported as the force per needle required for failure. Using arrays ranging from 20 to 60 needles at a needle density of 300 needles/cm^2, this per-needle normalization accounted for the data, as shown in results section. To measure the failure force under a transverse load, a row of 5–10 microneedles was mounted vertically on a metal plate using epoxy adhesive (Pacer Technology, Rancho Cucamonga, CA). To apply the transverse load, a glass slide was prepared by bonding a PDMS film (1×1×0.5 cm) with cyanoacrylate adhesive (Instant Krazy glue, Elmer's Products, Columbus, OH) to the glass slide to make a stepped structure. The PDMS film extended 500 µm beyond the edge of the glass slide to provide a surface of defined dimensions. Using the force displacement–force test station, the PDMS extension from the glass slide was pressed perpendicular to the microneedle axis against a 500 µm length of the microneedle shaft starting at the needle tip. As shown in Fig.(C), needle force and displacement were continuously measured until the needles were broken, as verified by microscopy.

APPLICATIONS OF MICRONEEDLES

1. Immunization and vaccination:

Immunization programs in developing countries or mass vaccination or administration of antidotes in bioterrorism incidents, could be applied with minimal medical training. Immunization to the model antigen ovalbumin was investigated using a novel intra cutaneous delivery system consisting of antigen coated microneedle arrays. Vaccination delivery of influenza vaccine via microneedle patches elicited immune responses comparable to or better than intramuscular injection in mouse model [30]. Immunization to the model antigen ovalbumin was investigated using a novel intra cutaneous delivery system consisting of antigen coated microneedle array patch system[31

2. Molecular and cell biology:

Micro needles have been applied for the delivery of membrane impermeable molecules into cells for application in molecular cell biology, methods for the delivery of peptides, proteins, olio nucleotides, DNA and other probes that alter or assay cell function is desired. Arrays of micro needles were fabricated and utilized to deliver DN into plant and mammalian cells, as a method for transforming cells.

3. **Acne Treatment:**

Dissolvable microneedle patches have been successfully demonstrated in the treatment of acne and has shown promising results in the first 24 hrs of use. There is rapid intradermal drug delivery by the micro needle patch. (The versatile theraject MAT, dissolvable micro needle path contains API in an inert GRAS matrix. The system can deliver hundreds of µg of API rapidly through the stratum corneum into epidermal tissue. Thus microneedle patch technology can be applied effectively for various cosmetic applications.

4. Transdermal Drug Delivery

The conventional transdermal drug delivery limits the applicability to small drug molecules because the stratum corneum does not have any nerves. Since microneedles that are long enough and robust enough to penetrate across this layer, but short enough to not stimulate the nerves in the deeper tissue, have the potential to make transdermal delivery a painless and much more viable option. With the use of hollow microneedles it allows the delivery of medicines, insulin, proteins, or nanoparticles that would encapsulate a drug or demonstrate the ability to deliver a virus for vaccinations. An array of needles ranging from 300-400 needles can be designed to puncture the skin and deliver the drug.

5. Target drug delivery

Additionally, microneedles have been utilized to target drug delivery to a specific region or tissue in the body, thus avoiding detrimental effects that can result from administering certain drugs systemically. This targeting can reduce side effects, minimize the dose of an expensive drug, and/or provide a means of delivery to a location that is difficult to treat. For instance, a multichannel silicon microneedle has been microfabricated to deliver bioactive compounds into neural tissue while simultaneously monitoring and stimulating the neurons in vivo. In addition, microneedles have been used to penetrate vessel walls of normal and atherosclerotic rabbit arteries in vitro demonstrating potential use for targeted delivery of antirestenosis drugs.

6. Insulin delivery "poke with patch" technique has been tried for transdermal drug delivery which has reduced glucose levels to about 80% within 4 hours.

7. Desmopressin is a synthetic peptide hormone chiefly used for treatment of eneuresis in young children. It is available in the form of injectable, intra nasal and oral formulation. Administration by injection is not advisable for a routine use in children. Intra nasal and Oral administration results in low and variable bio availability of desmopressin. If administered transdermally by using micro needle patch 0f 2cm× 2cm array the bioavailability was found to be 85% and peak levels in serum reached after 60 min.Only 10 % of the drug was found on the skin surface after application [8].

Fig. 2. Polymeric controlled release is often achieved by encapsulating drug within microparticles, which are then injected into the body using a hypodermic needle (shown on left). Polymer microneedles can similarly be designed to encapsulate drug for controlled release, but can be directly inserted into the skin without the need for hypodermic injection (shown on right).

CONTROLLED-RELEASE DRUG DELIVERY USING POLYMER MICRONEEDLES

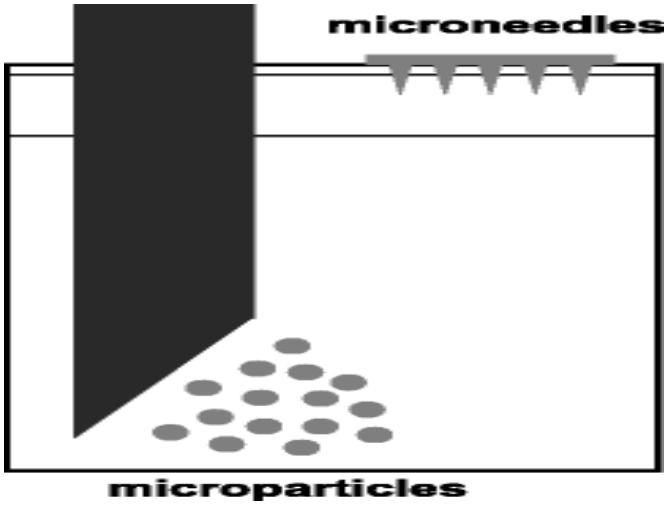
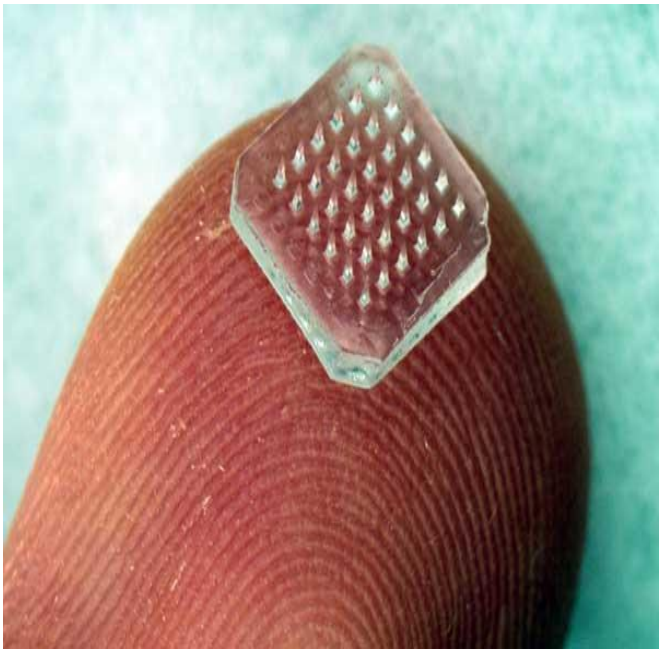
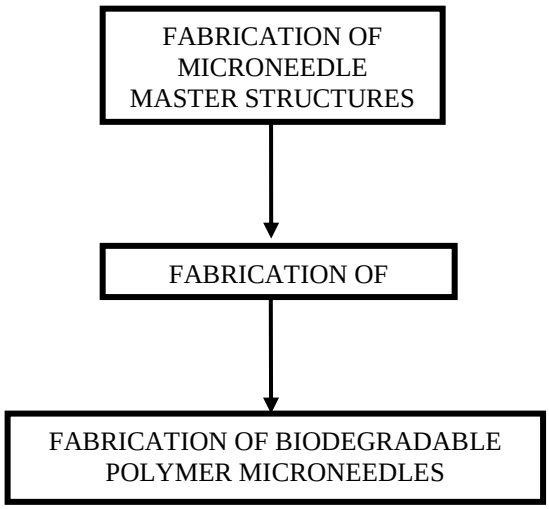


Fig. 3. Vaccine-Delivery Patch With Dissolving Microneedles Eliminates 'Sharps,' Boosts Protection Polymer microneedle flu vaccine that users could self administer in their own homes[5]



The steps involved in fabrication of Biodegradable polymer microneedles are,



Fabrication of Microneedle Master Structures

Three types of Microneedle Master Structures have been prepared. They are,

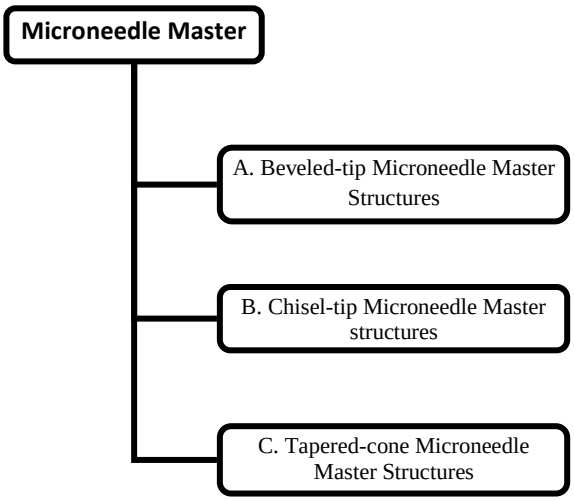


Fig. 4. Single molecule contains 8 epoxy groups, hence the "8" in SU-8.

STRUCTURE OF SU-8 MOLECULE WITH EPOXY GROUPS

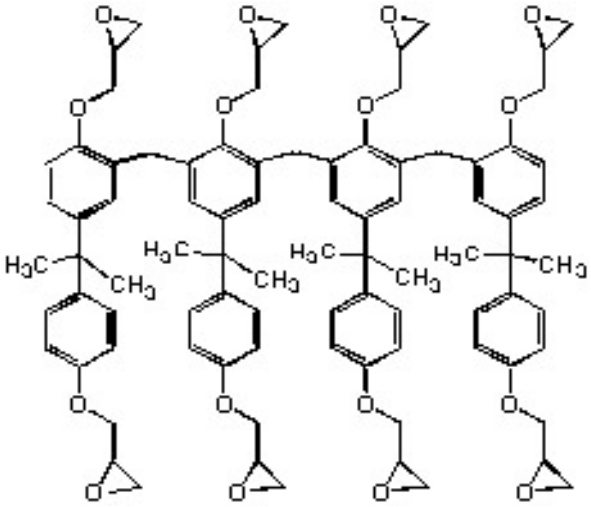


Fig. 5. Bevel-tip microneedles used as master structures (imaged by SEM). Making a mold and using it to prepare polymer microneedles as described in above figure yielded

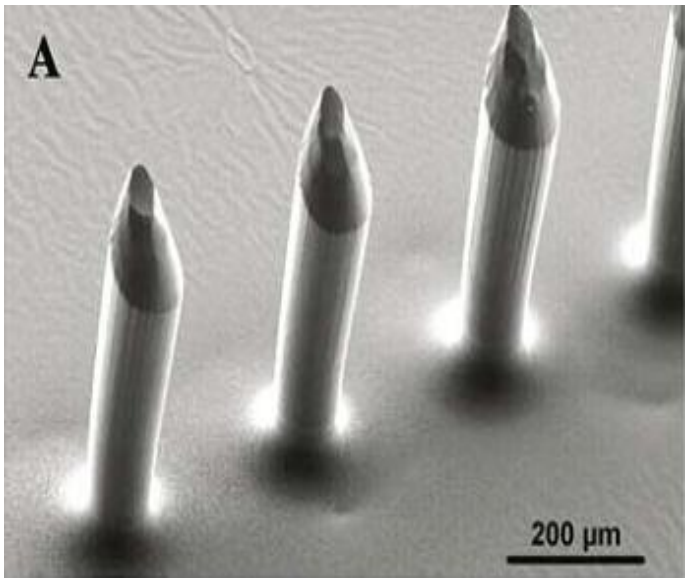


Fig. 6. Schematic of process to fabricate beveled-tip microneedles. SU-8 photoresist is lithographically defined and developed to yield an array of cylinders. After filling the spaces between cylinders with a sacrificial polymer and lithographically placing a metal mask asymmetrically on top of each row of cylinders, the cylinders are ion etched to produce an array of microneedles with beveled tips to be used as a master structure for subsequent molding.

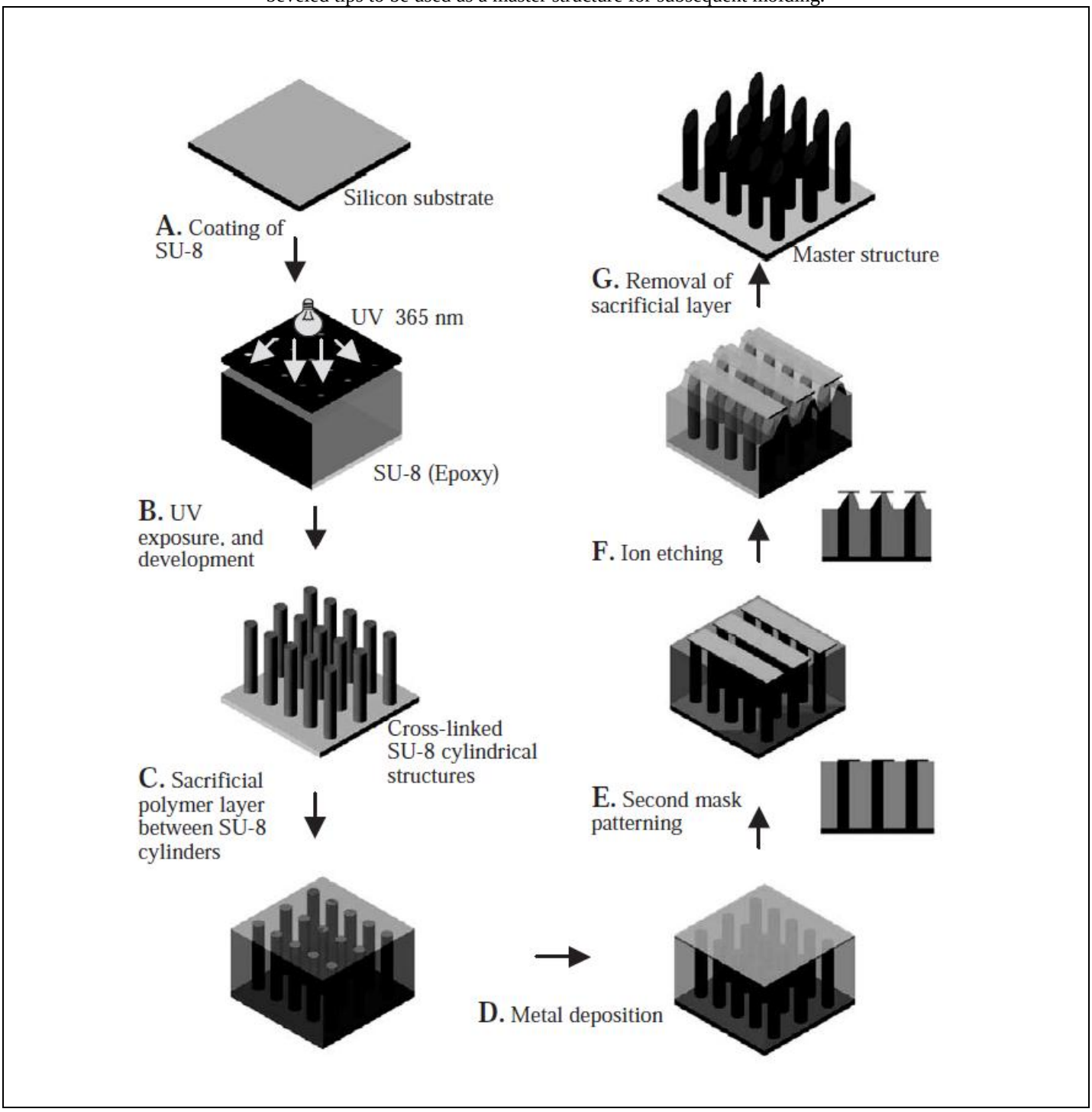


Fig. 7. Schematic of process to fabricate chisel-tip microneedles. Using a lithographically defined Si3N4 mask, inverted pyramids are wet-etched into a b1,0,0N silicon substrate. SU-8 photoresist is lithographically patterned into each pyramid hole and as square columns on top. After surrounding the array of SU-8 structures with PDMS and removing SU-8 by reactive ion etching, the resulting mold is used to form an array of chisel-tip microneedles out of polyurethane to be used as a master structure for subsequent molding.

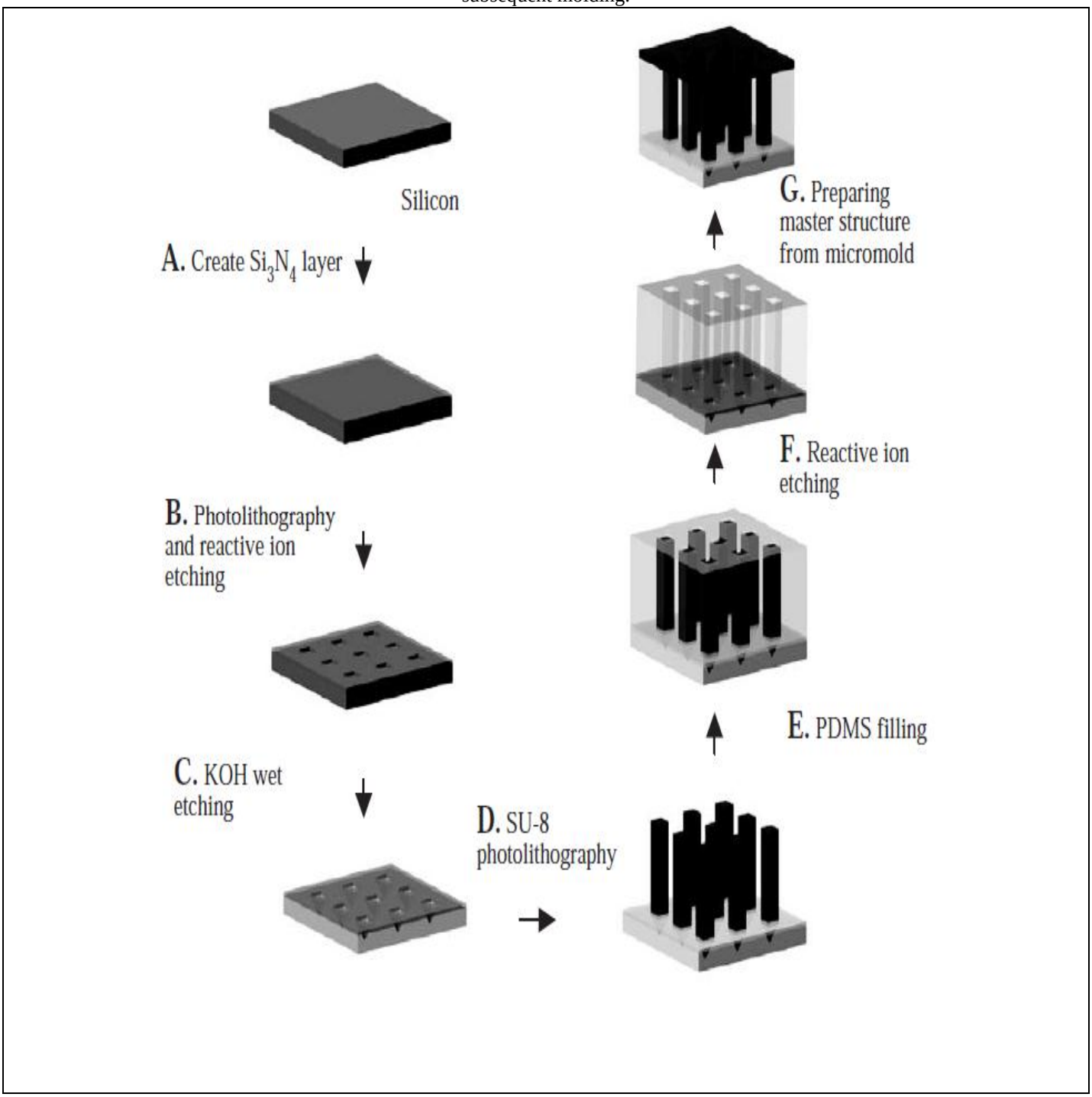


Fig. 8. Schematic of integrated lens process to fabricate tapered-cone microneedles. Using a lithographically defined metal mask, a glass substrate is wet-etched to produce an array of hemispherical invaginations that form microlenses. After filling and covering these invaginations with a thick layer of SU-8 photoresist, UV light is shined through the glass substrate, forming latent images in the SU-8 layer that define the shape of an array of tapered-cone microneedles produced after development that are used as a master structure for subsequent molding.

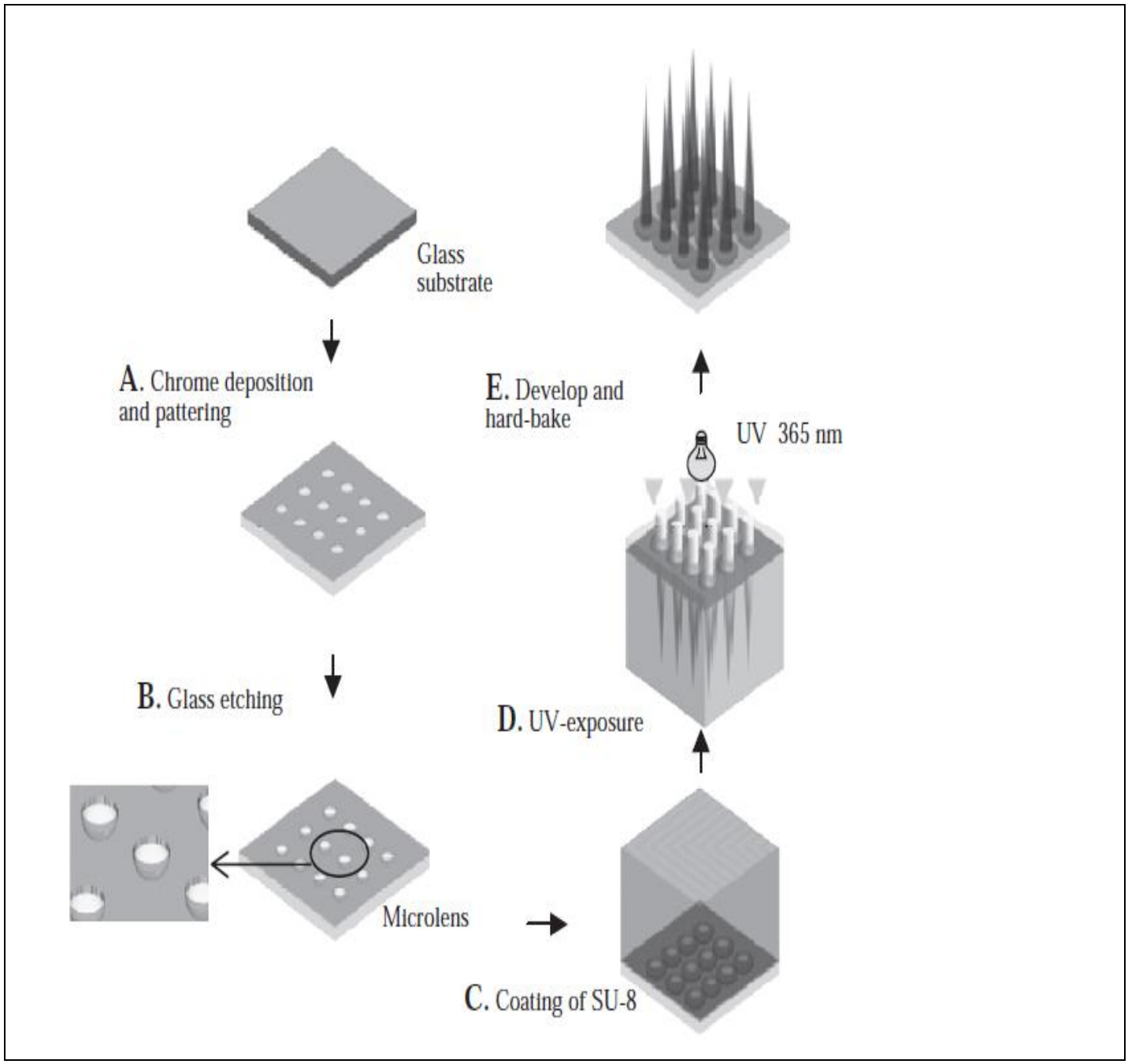


Fig. 9. Tapered-cone microneedles used as master structures (imaged by SEM). Making a mold and using it to prepare polymer microneedles as described as above yielded

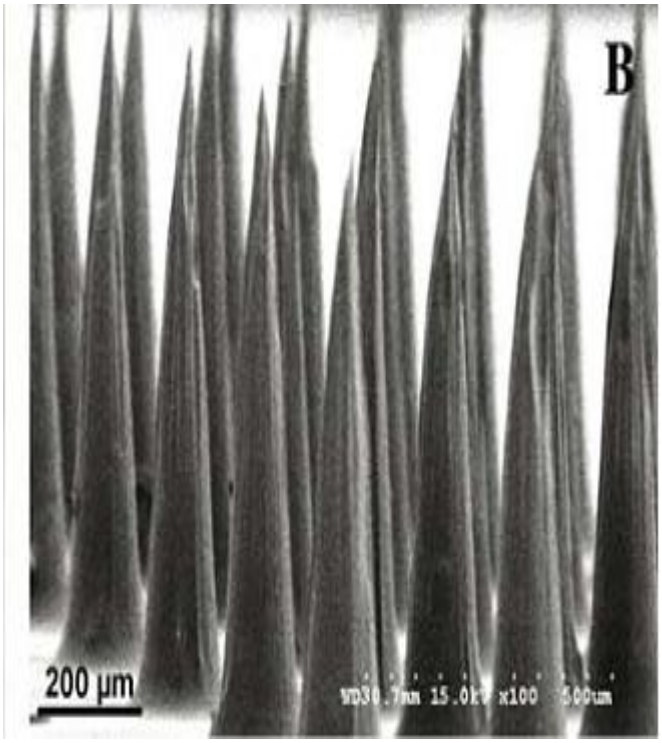


Fig. 10. Method to fabricate polymer microneedles that encapsulate drug for controlled release. First, a suspension of drug particles is filled into a microneedle mold. Evaporation of the solvent leaves solid drug particles partially filling the mold. Pellets of biodegradable polymer are then melted into the mold under vacuum. Cooling and solidification of the polymer yields biodegradable polymer microneedles with encapsulated drug particles.

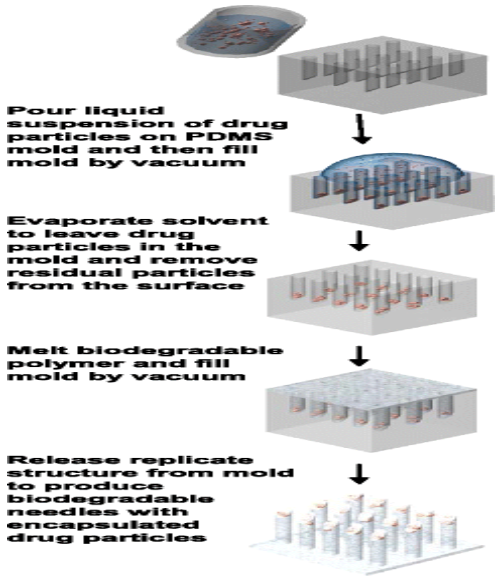


Fig. 11. Microneedle transverse failure force. Schematic diagrams showing how skin deformation around a microneedle during insertion can generate a transverse force on the microneedle.

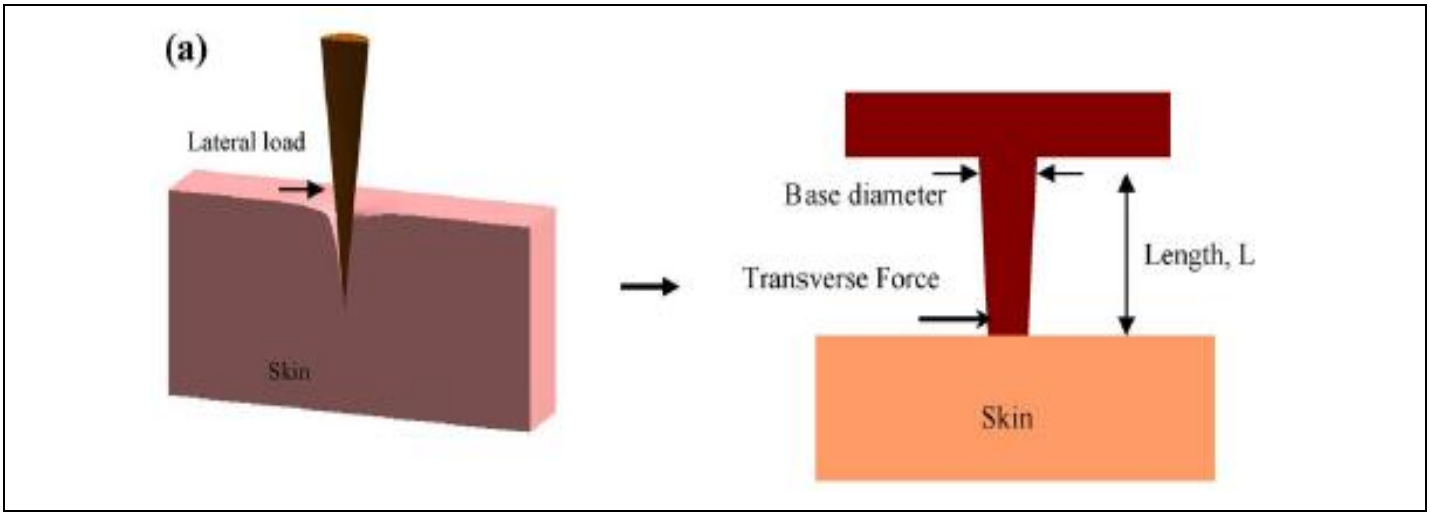
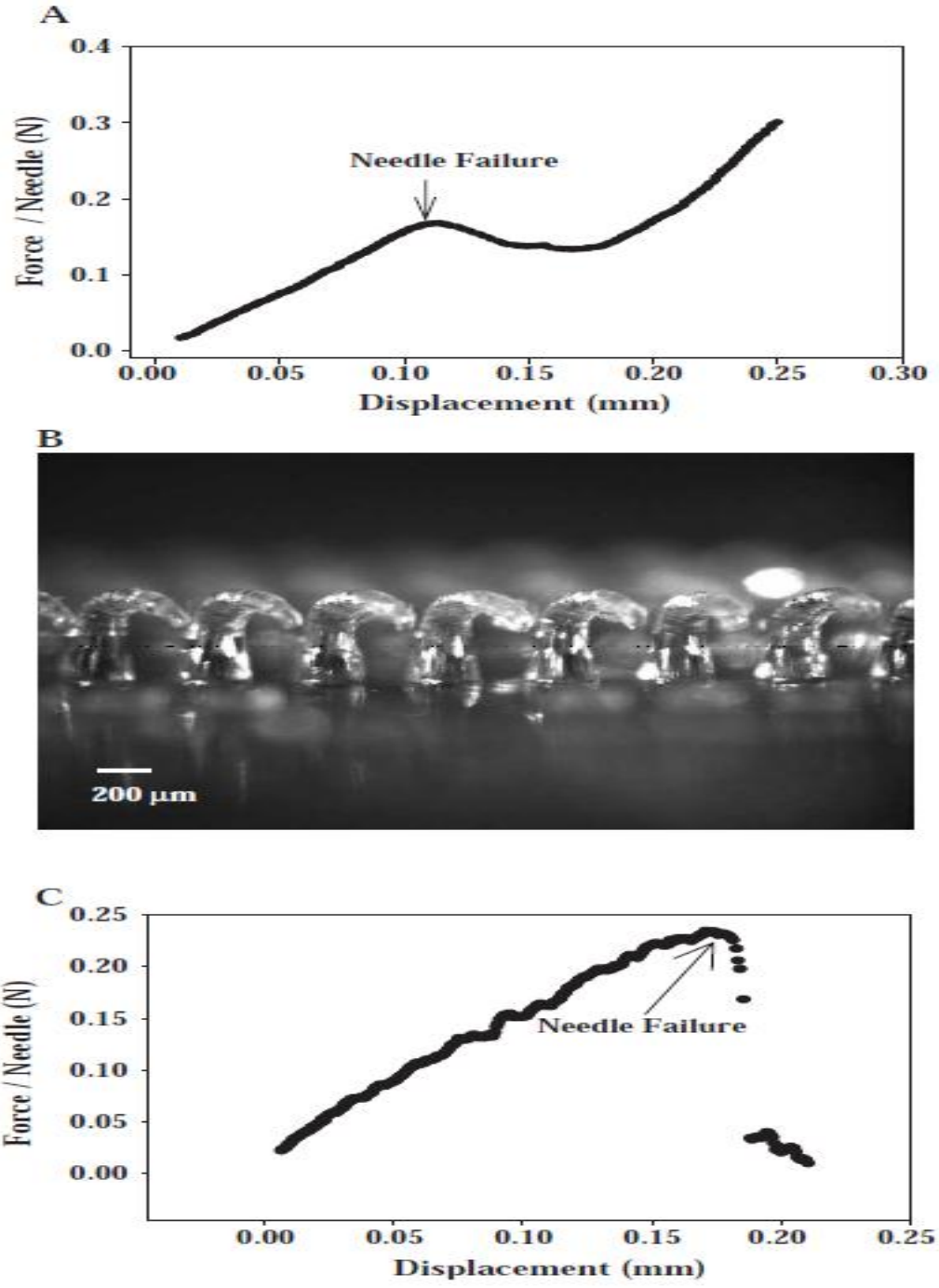


Fig. 12. Mechanical analysis of microneedles. (A) Typical failure behavior of microneedles under axial load. Needle failure is identified by a sudden drop in force. (B) Light micrograph of microneedles after an axial failure test. All microneedles were pressed and deformed with the same magnitude across the whole array. (C) Typical failure behavior of microneedles under transverse load. Needle failure is identified by a sudden drop in force.



CONCLUSION

Dissolving microneedle fabrication under mild conditions is suitable for protein delivery and amenable to mass production. It was developed by selecting FDA-approved polysaccharides and modifying a casting method with centrifugation. By using a low aspect ratio and pyramidal geometry, dissolving microneedles were formulated to have sufficient mechanical strength to insert into skin. By selectively loading microneedle shafts, microneedle patches provided bolus release of a model drug upon the dissolution of the microneedle matrix inside skin. By loading the backing layer, microneedle patches provided sustained release probably due to drug diffusion and swelling of the backing layer over time. In vivo delivery using such microneedles has been shown for peptides, such as insulin and desmopressin; genetic material, including plasmid DNA and oligonucleotides; and vaccines directed against hepatitis-B and anthrax. Human studies have demonstrated that microneedles can be inserted into the skin without causing pain or irritation. Overall, dissolving microneedles may be useful as a method for patients to self administer drugs without the pain, particularly children, are 'needlephobes'. In addition, many other disease conditions require the delivery of therapeutic agents to the skin, while the outbreak of a pandemic would necessitate mass vaccinations. A solution to the problems posed by needle based injections is the development of micro needles. This technology will help realize the development of new and improved devices, which will be smaller, cheaper, pain-free and more convenient with a wide range of biomedical and other applications. The future of drug delivery is assured to be significantly influenced by micro fabrication technologies. These micro fabricated drug delivery devices can enable efficient drug delivery that was unattainable with conventional drug delivery techniques, resulting in the enhancement of the therapeutic activity of a drug.

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