Presented at CRS conference, June 2007

Demonstration of Dose-controlled Delivery by Dissolvable Micro-needle Arrays

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ABSTRACT SUMMARY:

The TheraJect MAT™ transdermal patch consists of dissolvable microneedles comprised API in various inert GRAS matrixes. A dose-controlled delivery system was demonstrated by using the cellulose microneedles impregnated with nano-scale components in the needle tip area. The components were released from the cellulose microneedles in less than six minutes and rapidly dispersed in the human cadaver skin.

INTRODUCTION:

TheraJect's microneedle technology, Microneedle Array for Transdermal drug delivery system (MAT™) employs small needles prepared from a biocompatible, dissolvable material, like cellulose, in the form of a patch where the sub-millimeter or millimeter needles are impregnated with the biomolecules to be delivered (Figure 1a). Applied to the skin in the same manner as a typical Band-Aid, the cellulose micro-needles penetrate the skin and dissolve in the interstitial fluid rapidly while delivering the biomolecules, such as lidocaine [1], ascorbic acid [2], or the influenza HA vaccine [3].

The skin is viscoelastic with a thin plastic stratum corneum on the surface. When microneedles are pressed against the skin, the skin tends to bend, causing the dissolvable microneedles, fabricated by the mold-casting method, to be partially inserted into the skin (Figure 1b). The degree of penetration varies depending on the amount of the insertion force and the mechanical property of the skin. The variation in the penetration depth causes dose-inaccuracy of the drug-loaded micro-needle intradermal method.

In this study, a dose-controlled delivery was demonstrated with the cellulose microneedles. The delivered components were loaded in the needle tips that almost always penetrated into the skin when applied with an injector.

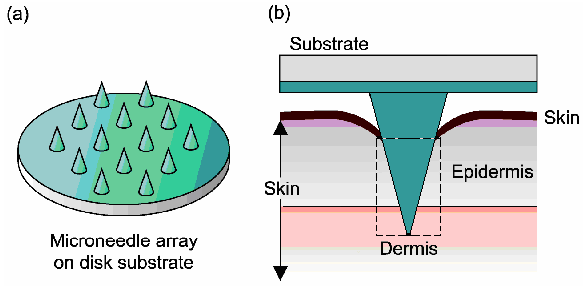

Figure 1 *Sketches of Microneedles and Skin penetration*

EXPERIMENTAL METHODS:

Polystyrene black dyed microspheres of 0.5µm diameter (Polysciences, Inc) and violet dye (Sigma) were used as delivery components. Sodium carboxymethyl cellulose (Sigma) was dissolved in deionized water at a predetermined ratio. The delivery components were blended in the cellulose gel and spun in a mold that has cone-shaped cavities at 3000 rpm for 5 minutes. The cavity depth was 1.5mm and the top diameter was 0.67mm. The excess polystyrene blended gel on the exterior of the cavities was removed and the pure cellulose gel was added to the mold surface. The gels were dried and separated from the mold.

It is known in the previous study [1] that the cellulose microneedles penetrated through the stratum corneum layer of the human cadaver skin when applied with a spring-driven injector (Figure 2). In this study, for visual examination of the deposition and dispersion of the delivery components in the dermal layer over 20 minutes, the microneedle array was directly inserted into the dermal layer that was separated from the stratum corneum layer. The dermal layer sat on top of filter paper soaked with water to maintain the hydration state. The microneedle array that had the delivery components concentrated in the needle tips was inserted by thumb-pressing into the dermal layer and stayed for six minutes before it was removed. The

surface of the dermal layer was covered with a vinyl film to prevent drying and examined under the optical microscope.

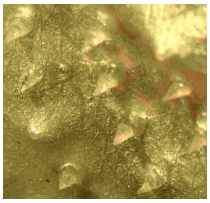

Figure 2: *Microneedles penetrating across stratum corneum shortly after insertion. Image was taken on the inner side of the stratum corneum separated from the dermal layer [1]*

RESULTS AND DISCUSSION:

While the gel dried and shrunk to the bottom of the cavities, the black polystyrene particles remained in the gel. Consequently the particles were confined in the needle tips (Figure 3(a)). In contrast, during the drying stage, some of the dye molecules diffused out of the cavities and mixed with the cellulose gel coated on the dye gel. Most of the dye still remained in the cavities (Figure 4(e)). The particle size and the gel viscosity determined the degree of particle concentration in the needle tips.

When the basal layer separated from the dermal layer in 6 minutes after insertion, the tip areas disappeared (Figure 3(b)), indicating that the cellulose microneedles were hydrated and disintegrated in the dermal layer. The polystyrene particles gradually diffused out from the deposition sites until they overlapped with the particles from the neighboring sites approximately in 20 minutes (Table 1). The dye microneedles showed similar trends (Figure 4). Interestingly, the dispersion rate of the dye was similar to the polystyrene particles.

CONCLUSIONS:

The spin-casting method allows the production of the cellulose microneedles with the active component concentrating in the needle tips. The dose is determined by the concentration of the active component in the gel, the volume of the cavities, and the number of inserted microneedles. The cellulose matrix allows the administration time to be less than six minutes to deposit and disperse the active components in the skin. The cellulose microneedles have a capacity for the controlled delivery of drugs.

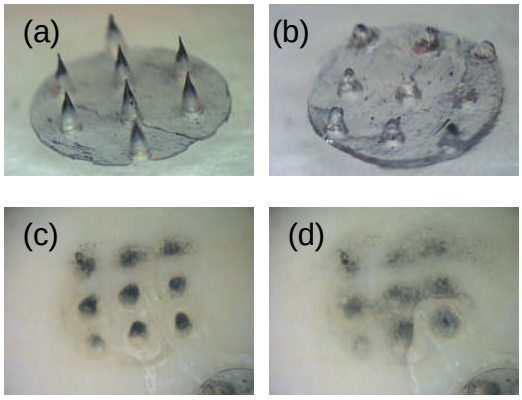

Figure 3 *(a) Black polystyrene particles are concentrated in the needle tips. Spacing of needles is 1.5mm. (b) The tips were lost to the skin in 6 minutes. Particle dispersion in 8 minutes (c) and 20 minutes (d).*

Table 1 *Particle dispersion rate*

t(min.)	0	8	11	16	20
dia.(mm)*	0.35	0.6	0.8	1.2	1.5

* diameter of tips remained in the dermis.

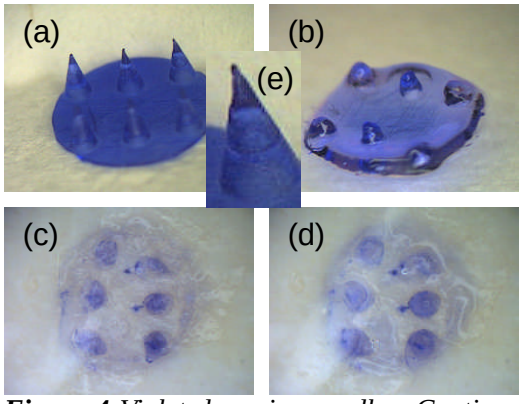

Figure 4 *Violet dye microneedles. Captions are the same as figure 3. The tip area is magnified in (e).*

REFERENCES:

1. S.-Y.Kwon, S.Oh, T.L.Burkoth Rapid Intradermal Drug Delivery by a Dissolvable Microneedle Patch, Controlled Release Society 32st Annual Meeting 2005, #306.
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3. S.Oh, et al., Intradermal influenza vaccine delivery using skin-penetrating dissolvable vaccine microneedles, AAPS meeting, San Antonio, TX, Oct. 2006