

## In Vitro Evaluation of Transdermal Drug Delivery by a Micro-needle Patch

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### ABSTRACT SUMMARY:

Using micro-needles composed of drug and a soluble GRAS material to form a *dissolving* matrix, a TheraJect MAT™ transdermal drug delivery patch delivered lidocaine with up to 12X more flux than passive delivery *in vitro*. Drug delivery occurs when the needles dissolve and also through epidermal micro-channels created by micro-needles.

### INTRODUCTION:

There has been rapid progress in molecular biology, to identify and prepare specific peptide, protein and oligonucleotide drugs and vaccines to treat or prevent disease with minimal side effects. However, concomitant progress in delivery systems for these drugs has not been as dramatic. One reason is that current drug delivery systems cannot easily breach the barrier of dermal or mucosal membranes without becoming complicated or expensive.

A new drug delivery technology is being developed using solid micro-needle forms of therapeutic compounds. These needles penetrate transdermal or transmucosal tissues and thus overcome their barrier function<sup>1-4</sup>. TheraJect's proprietary micro-needle patch techniques provide simple, syringe-free and painless injection of traditional drugs, proteins, as well as vaccines and other therapeutic compounds. Our *in vitro* study aims to evaluate systemic delivery of a model low molecular weight drug, lidocaine, through human skin.

### EXPERIMENTAL METHODS:

Lidocaine hydrochloride, the model drug and the PBS receiver medium are purchased from Sigma. Sodium carboxymethyl cellulose (SCMC) was supplied by Hercules. The lidocaine and SCMC were dissolved in D.I. water at a predetermined ratio. The solution was cast into a mold, compressed, then dried under ambient conditions. When dried, the micro-

needle patch was separated from the mold and cut to an appropriate size. The needle size can be adjusted; the needle length was about 550-650  $\mu\text{m}$ . (Fig.1)

A modified Franz cell designed for investigation of transdermal flux was used with a D.I. water receiver medium. This reservoir was maintained at 37°C during the experiments and dermatomed human cadaver skin was ~300  $\mu\text{m}$  thick. The skin was placed on Parafilm® and the lidocaine micro-needle patches applied manually before the treated skin was punched to test size with a 1" diameter die. The skin was placed on the modified Franz cell filled with 6.9 ml receiver medium. At predetermined intervals, samples were collected from the receiver of the diffusion cells and were assayed for lidocaine content by HPLC.

Four different systems including three different patch designs were tested: 10% lidocaine solution as control, 20% lidocaine in micro-needles without a reservoir, micro-needles without lidocaine but with a reservoir of 0.1g/ml lidocaine solution and micro-needles with 20% lidocaine in the micro-needles and a lidocaine solution reservoir.

### RESULTS AND DISCUSSION:

Table 1 shows the summary table of average flux over 24 hours of tested systems. Fig.2 shows the flux profile over 24 hours of three patch systems and control. The system containing lidocaine in micro-needles or in the reservoir displayed similar average flux, 22 ( $\mu\text{g}/\text{cm}^2/\text{h}$ ) but the flux profile was different. The lidocaine from the micro-needles is released more rapidly than lidocaine in the reservoir (Fig.2) because the micro-needles need to dissolve and create channels to permit diffusion from the reservoir. The patch system containing lidocaine in the micro-needles and the reservoir displayed the highest average flux value, 98.6

( $\mu\text{g}/\text{cm}^2/\text{h}$ ), because it had the highest drug payload. It was observed visually that the full length of the micro-needles cannot be inserted into skin tissue because of the visco-elasticity of the tissue and the micro-needle materials. This observation indicates that the micro-needle length and distance between needles needs to be optimized in critical clinical studies. Enhancement doesn't look great because model drug has relatively high permeation.

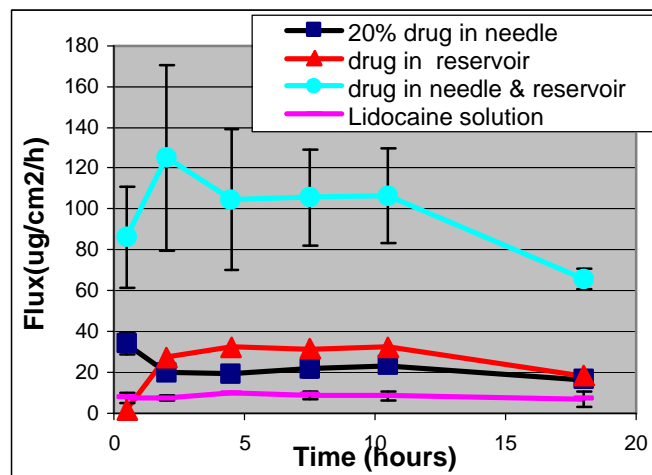
**Fig.1: Photomicrograph: Dissolvable Micro-Needle Array**



**Table 1: Summary, Average Flux of Tested Systems**

Systems Tested	Average $\pm$ S.D. ( $\mu\text{g}/\text{cm}^2/\text{h}$ )
Lidocaine solution (0.1g/ml)	$7.7 \pm 1.0$
Needles with 20% lidocaine, no drug reservoir	$22.4 \pm 1.4$
Needles without lidocaine, 0.1g/ml lidocaine reservoir	$22.6 \pm 0.9$
20% lidocaine in needles and reservoir	$98.6 \pm 18.5$

**Fig.2: Flux Profile Over 24 Hours**



**CONCLUSION:** Micro-needle patches composed of drug in a fast-dissolving matrix can enhance transdermal delivery by 2.5 - 12 fold by creating micro channels into skin. A desired delivery profile can be engineered by formulation of the solid micro-needles and by incorporation of a drug reservoir.

**REFERENCES:**

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