

# ***In Vitro* Modeling of Transdermal PTH Delivery by Dissolving Micro-needle Patch**

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## **ABSTRACT:**

The versatile TheraJectMAT™, dissolvable micro-needle patch, contains API in an inert GRAS matrix. The system can deliver hundreds of micrograms of API rapidly through the stratum corneum into the epidermal tissue or systemic circulation. In this study, we demonstrated the feasibility of rapid PTH delivery of a target amount. This micro-needle patch technology can be applied effectively for protein drug delivery applications other than parathyroid hormone.

## **INTRODUCTION:**

Parathyroid hormonal drugs are forecasted to grow rapidly among severe osteoporotic patients due to their effectiveness in building bone. However, current inconvenient syringe injection and high annual cost of therapy restrict patient base to those suffering from severe osteoporosis. Additionally, to minimize hypercalcemia side effect of PTH treatment, PTH peak should be within 4 hours [1, 2]. This provides a further opening for new technologies, which overcomes a principal problem associated with PTH osteoporosis therapy.

TheraJect Inc. has patented a novel technology that enables the systemic delivery of API to a patient without the use of a standard needle and syringe [3, 4]. These micro-needle arrays penetrate the skin and deliver the peptide to the interstitial fluid, but they neither look like a traditional needle nor cause pain or bleeding. In this study, we demonstrated the feasibility of PTH delivery with desirable delivery profile with the micro-needle delivery system.

## **EXPERIMENTAL METHODS:**

Human parathyroid hormone PTH (1-84) was donated from Green Cross Corporation in Korea and sodium carboxymethyl cellulose (SCMC) was purchased from Sigma. In order to make

PTH micro-needle, PTH and SCMC were dissolved in D.I. water to form gel and was cast into a mold by centrifugation and dried under ambient conditions. When the gel is fully dried, the micro-needle matrix was separated from the mold and cut into 1cm<sup>2</sup> discs each having 30 micro-needles. The PTH amounts in the micro-needle array and the basal layers were determined by HPLC.

For modeling in vitro flux test, a modified Franz cell was used with D.I. water as receiver medium and laminate film (3M Scotchpak 9723 polyester film laminate) as skin. The laminate is positioned on a ¼” thick shock-absorbing sponge base to which the PTH micro-needle patch was applied by applicator. The laminate and PTH patch were placed on the Franz cell and covered with occlusive backing film and the receiver compartment was filled with 1.87 ml receiver medium, which was maintained at 32°C and magnetic stirrer is rotated at 400rpm. At predetermined intervals (4, 8 and 24 hours) entire receiver volume were collected from the receiver of the diffusion cells and fresh receiver media were refilled. The samples were assayed for PTH content by HPLC.

## **RESULTS AND DISCUSSION:**

The Figure 1 is schematic diagram and image of the PTH micro-needle from the fabrication. The green regions are the PTH concentrated part. Table 1 is the summary of drug amount in the components of micro-needle. Total drug loading is 729 ±19 (µg) and 33% of drug loaded in the micro-needles and 67% of drug is located in the surface of the basal layer.

Fig1: Schematic diagram of micro-needle array.

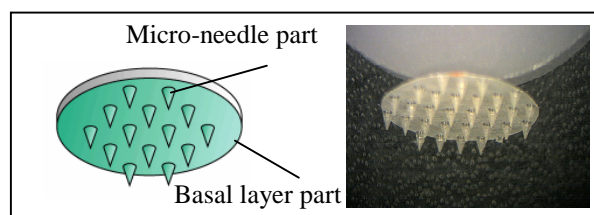


Table 1: The PTH amount in the micro-needle components

Patch (1cm <sup>2</sup> )	Amount (µg)	%
In micro-needles	243 ± 95	33
In substrate	486 ± 95	67
Total loading	729	100

Table 2 is the summary of drug delivery through the laminates over time after micro-needle insertion. Within 4 hours 64% of drugs which is from all of drug in the micro-needles and about half of drug in substrate were delivered through the laminates. Over 24 hours most of drug delivered with occlusive condition. Undelivered drug after 24 hours was extracted from the patches and assayed. The undelivered drug amount is 11 ± 9 (µg), which is 2% of total loaded drug.

Table 2: The PTH delivered amount through the laminate film simulated skin.

Delivery Time (hours)	Delivery Amount (µg)	%
0-4	464 ± 107	64
4-8	184 ± 101	25
8-24	70 ± 46	10
Undelivered	11 ± 9	2
Total Drug	729	100

Fig 2: PTH delivery profile over time

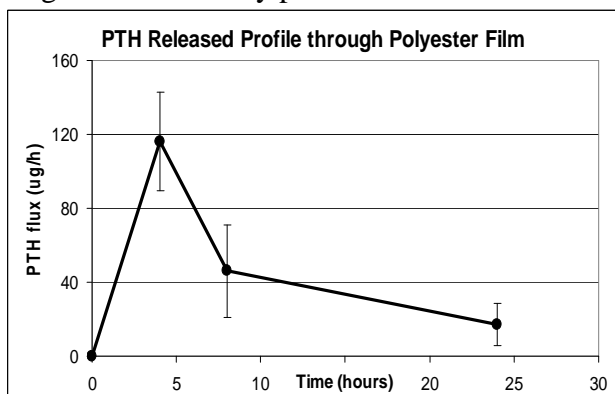


Fig. 2 displays the PTH release profile over 24 hours. Since most of PTH is concentrated in the micro-needle and bottom of basal layer, approximately 90% of drug loaded were delivered within 4 hours. That is quite promising release profile to minimize the hypercalcemia

side effect of PTH syringe treatment. The delivery efficiency within 4 hours is close to 90% which is ideal for expensive protein drug.

**CONCLUSION:**

From this study we can clearly demonstrate feasibility of PTH delivery with fast-dissolving micro-needle. The release profile looks quite promising for PTH treatment especially for minimizing hypercalcemia and delivery efficiency is quite high implying high bioavailability. In order to prove current PTH delivery with micro-needle patch technology in clinical, the pre-clinical PK study will be done in next stage.

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