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**AN EXPERIMENTAL STUDY OF IN VITRO TRANSDERMAL DRUG DELIVERY  
ASSISTED BY CRYOPNEUMATIC TECHNOLOGY**

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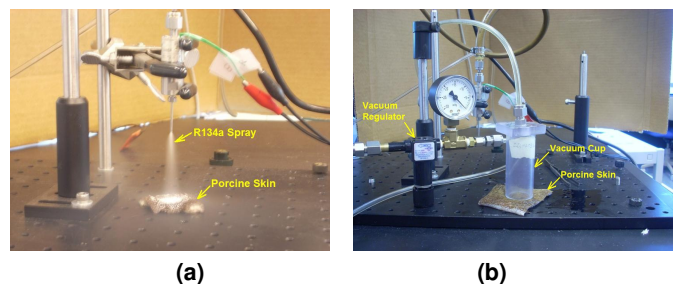
**INTRODUCTION**

Transdermal drug delivery (TDD) is a promising alternative to conventional drug delivery approaches, such as oral or injectable routes. In comparison, the primary benefits of TDD include [1]: 1) avoidance of first pass metabolism and other variables associated with the GI tract such as pH changes and gastric emptying time. 2) sustained and controlled delivery over a prolonged period of time. 3) reduction in side effects associated with systemic toxicity. 4) improved patient acceptance and compliance. 5) direct access to targeted or diseased site, e.g. treatment of skin disorders. 6) ease of dose termination in the event of any adverse reactions either systemic or local; 7) convenient and painless administration; 8) ease of use and reduction of overall health care treatment costs; 9) viable alternative in circumstances where oral dosing is not possible (in unconscious or nauseated patients).

However, human skin is a protective barrier against the loss of excessive endogenous material such as water, and it also prevents the access of foreign materials (chemicals and microbes). As a result, very few drugs can be administered transdermally due to the low permeability of human skin. Cryopneumatic (CPx) is a new technology under development which combines the quick freezing of stratum corneum (SC) and upper epidermis followed by or simultaneous with mechanical stretching. The central hypothesis behind CPx technology is that the SC becomes increasingly brittle at subzero temperatures. Thus, rapid cooling combined with mechanical stretching can produce micro-cracks in the SC and upper epidermis, which may be used as “express” channels for TDD. This paper presents an *in vitro* experimental study to validate the hypothesis.

**EXPERIMENTAL MATERIALS AND METHODS**

FITC-Dextran (4k Da) was ordered from Sigma-Aldrich Co. (St. Luis, MO). Porcine skin samples with intact SC were obtained from a local meat processor and stored at -80°C. Frozen skin samples were thawed in phosphate buffer solution (PBS) one hour before experiments. The SC side of skin sample was rapidly cooled by short spurts of R-134a (boiling point -26.3 °C at 1 atm) for 10 s., as shown in Figure 1(a). Immediately following the spurt, the cooled site was stretched with vacuum pressure applied via a customized vacuum cup as shown in Figure 1(b). Thereafter, aqueous solution of FITC-Dextran (250 μM) was topically applied on both stretched and control skin samples for 60 min.



**Figure 1. Experimental setup to freeze and stretch porcine skin: (a) R134a spurt; (b) skin stretch by vacuum cup.**

After topical application, a “tape stripping” method, described in detail by Weigmann et al. [2], was used to measure the lateral and perpendicular distribution of FITC-Dextran that penetrated into the skin samples. This method consists of applying a piece of adhesive

film (3M, St. Paul, MN) onto the skin surface and pressing the film with a roller. The tape strip is then removed with a quick movement and mounted by a water-based mounting media (Triangle Biomedical Science, Durham, NC). Ten consecutive tape strips were obtained for both control and CPx treated skin samples. It is estimated that each tape stripping removes approximately 0.5  $\mu\text{m}$  layer from the SC. The fluorescence on the tape strip was observed and photographed by a fluorescence microscope (Leica MZ FLIII). Thereafter, the fluorescence images were quantitatively analyzed by a self-developed Matlab code. The code sums up the fluorescence intensity of all pixels in the image. The summation value ( $Sum_{flu}$ ) is then used as the quantitative parameter to assess the enhancing effect of CPx. On the other hand, a scanning electron microscope (Hitachi TM-1000) was used to scan the surface of skin samples to visualize the micro-crack produced by CPx.

## RESULTS AND DISCUSSIONS

Figure 2 presents  $Sum_{flu}$  for all tape stripes. It can be seen that  $Sum_{flu}$  dramatically drops as tape strip index increases from 1 to 4, implying significant gradient of Dextran concentration exists in SC. One can also see that except for the 1<sup>st</sup>, 7<sup>th</sup> and 10<sup>th</sup> tapes,  $Sum_{flu}$  of frozen/stretched sample are higher than that of the control sample.

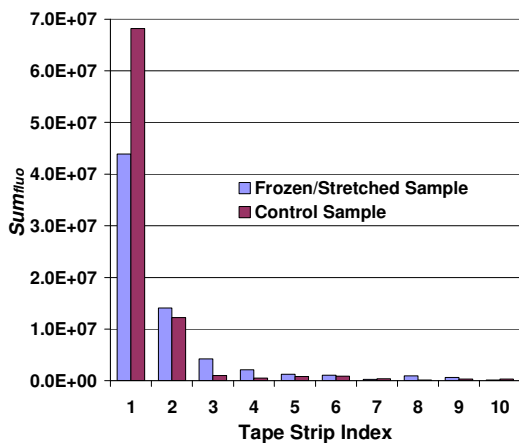


Figure 2. Comparison of  $Sum_{flu}$  for frozen/stretched and control samples.

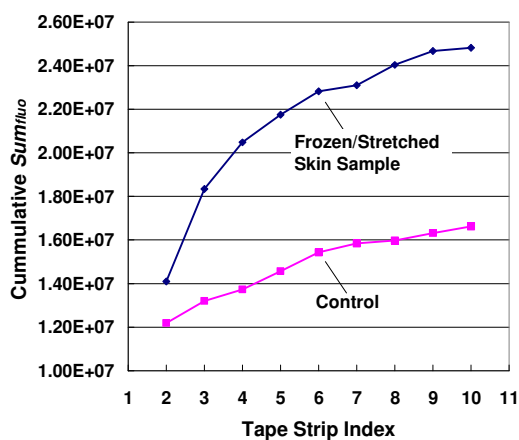


Figure 3. Cumulative  $Sum_{flu}$  from the 2<sup>nd</sup> to 10<sup>th</sup> tape strip.

Considering the 1<sup>st</sup> tape strip is easy to be affected by skin surface conditions, e.g. surface moisture and residues, one can safely neglect the 1<sup>st</sup> tape strip and calculate the cumulative  $Sum_{flu}$  from the 2<sup>nd</sup> tape strip to the 10<sup>th</sup>, as shown in Figure 3. Results in Figure 3 evidently indicate that the penetration of FITC-Dextran (4K Da) is enhanced by CPx anywhere between 15 to 38%.

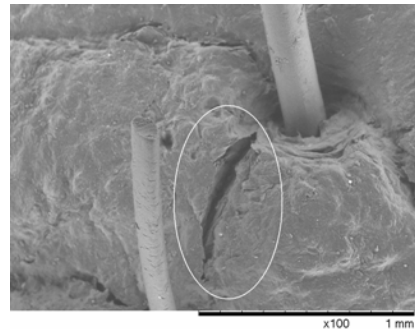


Figure 4. SEM image of CPx treated skin sample.

Figure 4 is a SEM image of CPx treated skin sample, which clearly shows a micro-crack at skin surface between two hairs, as highlighted by the ellipse in the figure.

## CONCLUSION

CPx technology can produce micro-cracks at skin surface and therefore enhance the TDD of hydrophilic substances.

## ON-GOING WORK

Systematic experiments are currently conducted to explore the enhancing effect of CPx on the TDD of various hydrophilic and lipophilic drug surrogates, including FITC, FITC-Dextran (10k – 70k Da), curcumin and DyLight Fluor. Results will help to screen drug candidates, for which TDD can be significantly enhanced by CPx.

## REFERENCE

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