Evaluation of the *in vitro* Human Skin Percutaneous Absorption of Ketoprofen Using the Franz Finite Dose IVPT Model

SUMMARY: The skin percutaneous absorption of ketoprofen incorporated in Anhydrous Lipoderm® (PCCA formula 12940) was evaluated using the Franz Finite Dose IVPT model and it was concluded that ketoprofen penetrates through and into human cadaver skin *in vitro*.

Introduction:

The human skin percutaneous absorption of ketoprofen incorporated in Anhydrous Lipoderm® was evaluated using the Franz Finite Dose *in vitro* Permeation Test (IVPT) model by the PRACS Institute, Ltd (Study No.: R07-1222). Ketoprofen is an analgesic and anti-inflammatory drug commonly used in the management of chronic musculoskeletal pain. It is commercially available in the U.S. for oral administration but, although effective, it can lead to gastrointestinal (GI) complications when used for long periods of time. The transdermal delivery of ketoprofen is a potential alternative that bypasses the GI exposure and hepatic metabolism. Bassani *et al.* (2016) studied the percutaneous absorption of ketoprofen in Lipoderm versus PLO and concluded that Lipoderm has the ability to potentially deliver higher concentrations of ketoprofen to underlying soft tissues and at a more rapid rate[1]. Anhydrous Lipoderm® is a proprietary transdermal base that belongs to the Lipoderm® family by PCCA. It was designed specifically to incorporate active substances which are unstable in water. It is egg-free, soy-free, gluten-free and casein-free; it also presents good salt and shear resiliency[2].

The Franz Finite Dose IVPT model has proven to be a valuable tool for the study of percutaneous absorption and determination of the pharmacokinetics of topically applied drugs. It has also proven to accurately predict *in vivo* percutaneous absorption kinetics since this model uses *ex vivo* human torso skin mounted in specially designed diffusion chambers allowing the skin to be maintained at a temperature and humidity that match normal *in vivo* conditions[3]. Therefore, this model was selected to characterize the percutaneous absorption of ketoprofen into and through the skin by evaluating the total absorption, rate of absorption and the skin content of ketoprofen in Anhydrous Lipoderm® applied to the outer surface of the skin.

Methodology:

The percutaneous absorption of ketoprofen was measured using human cadaver trunk skin samples, without obvious signs of disease, from three male donors (Hispanic and Caucasian races). The skin samples were dermatomed, cryopreserved, sealed in a water-impermeable bag and stored at approximately -70°C prior to use. The skin samples were then rinsed in water and cut into small sections to fit on nominal 1 cm^2 Franz diffusion cells – chambers specially designed to maintain the skin at a temperature and humidity that match *in vivo* conditions[3]. The dermal (receptor) chamber was filled to capacity with a receptor solution. The integrity of each skin section was evaluated by testing its permeability to titrated water prior to the experiment[4].

Ketoprofen 10% (w/w) was incorporated in Anhydrous Lipoderm® (PCCA formula 12940; Table 1) and the resulting compounded formulation was applied to the skin samples: 5 µL/cm^2; 3 replicates per donor; and one blank control. A receptor solution was placed bathing the inner surface of the skin sections in order to measure the rate of appearance of ketoprofen. The percutaneous absorption of the drug was evaluated over a period of 48 hours. During the exposure period, samples of the receptor solutions were removed at pre-selected times, as follows: 4, 8, 12, 24, 32 and 48 hours. The quantification of ketoprofen was performed by the analytical method High Performance Liquid Chromatography with Ultraviolet Detection (HPLC/UV).

Ketoprofen USP, Special Micronized	5 g
Diethylene Glycol Mono Ethyl Ether, NF	1 g
Propylene Glycol	4 g
Base, PCCA Anhydrous Lipoderm®	40 g

Table 1. *PCCA formula 12940: Ketoprofen 10% Topical Anhydrous Lipoderm®.*

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After the last sample of the receptor solutions (collected at 48 hours), the skin samples were washed twice with equal parts of ethanol and water to collect unabsorbed formulation from the surface of the skin. The skin samples were then removed from the chamber, separated into the epidermis and dermis, and were extracted overnight (ethanol/water) to evaluate the skin content of the ketoprofen.

Results and Discussion:

The total absorption, rate of absorption and the skin content (distribution) of ketoprofen were determined for all skin samples and the mean results are presented.

The absorption results indicate the percutaneous absorption of ketoprofen through the skin whereas the distribution results indicate the percutaneous absorption into the skin. The total absorption of ketoprofen (i.e., the total recovered in the receptor solutions over 48 hours from a single application) was 31.574±1.621 µg/cm^2. The skin content of ketoprofen (i.e., the mass recovered after 48 hours) within the dermis and the epidermis was 1.453±0.485 µg/cm^2 and 9.342±2.514 µg/cm^2, respectively.

The rate of percutaneous absorption, on the other hand, is a time-averaged value and it was determined as the mean flux of ketoprofen collected at the receptor solution under the skin (µg/cm^2/h) over the 48-hour period. It is a value reported at midpoint of sample collection, as displayed in Figure 2.

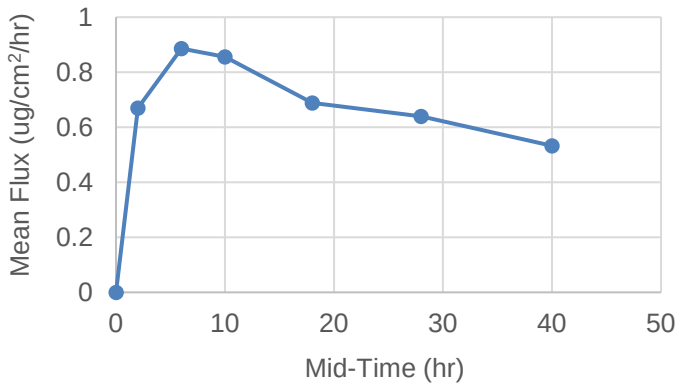

Figure 1. *Percutaneous absorption of ketoprofen in Anhydrous Lipoderm® over 48 hours.*

The rate of percutaneous absorption shows a rapid penetration to a peak flux of ketoprofen occurring approximately 7-8 hours after dose application, followed by a steady decline in flux thereafter. Although the rate of percutaneous absorption should not be directly extrapolated to the *in vivo* conditions, practitioners and pharmacists can utilize these results to demonstrate the percutaneous absorption of PCCA formula 12940.

Conclusions:

Chronic musculoskeletal pain affects the quality of life of most patients and the oral medications, although effective, are commonly associated with GI complications. Ketoprofen transdermal is a viable alternative for pain management provided that the drug penetrates into and through the skin. This *in vitro* study has demonstrated that the proprietary transdermal base Anhydrous Lipoderm® facilitates the percutaneous absorption of ketoprofen across human cadaver skin. PCCA formula 12940 may then be considered an alternative treatment option for patients with chronic musculoskeletal pain.

References:

1. Bassani, A.S., Banov, D. and Phan, H. (2016) 'Characterization of the Percutaneous Absorption of Ketoprofen Using the Franz Skin Finite Dose Model', *Postgraduate Medicine*, 128 (2), p. 262-267. DOI:10.1080/00325481.2016.1144448.
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