

Evaluation of the *in vitro* Human Skin Percutaneous Absorption of Ketoprofen in PCCA PermE8™ Anhydrous Gel vs. PCCA Lipoderm®

SUMMARY: The skin percutaneous absorption of ketoprofen in PCCA PermE8 Anhydrous and PCCA Lipoderm was evaluated *in vitro* and it was shown that PermE8 performs comparably to our industry-leading Lipoderm. Since PermE8 has water activity below 0.6, it may provide an excellent option for compounding pharmacists who rely on anhydrous transdermal formulations for extended default BUDs without compromising on transdermal performance.

Introduction:

Ketoprofen is a potent nonsteroidal anti-inflammatory drug (NSAID) that is widely used for pain relief and arthritis by oral administration. However, due to its non-selective cyclooxygenase (COX-1 & COX-2) inhibitory activities, it carries a boxed warning of serious gastrointestinal bleeding, ulceration and perforation [1]. Transdermal delivery of ketoprofen is a potential alternative that bypasses GI exposure to reduce risk of GI adverse effects. 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 concentration of ketoprofen to underlying soft tissues at a more rapid rate [2].

The PCCA PermE8 Anhydrous Gel is a new proprietary base for transdermal delivery with extended stability. It has water activity below 0.6 ($a_w < 0.6$), classifying it as an anhydrous base. This allows extended default BUDs for preparations that do not have stability studies. Additionally, PermE8 can hold multiple drugs at once, including those in salt form [3].

In this study, we used a full-thickness human skin model which is a better representative of patient skin than previous studies [2]. The purpose of this report is to compare the percutaneous absorption of ketoprofen incorporated into PCCA PermE8 Anhydrous Gel or PCCA Lipoderm (Table 1.) using the Franz skin finite dose model.

Ketoprofen 10% Topical Gel (PermE8™ Anhydrous)

100Gm

Ketoprofen USP, PCCA Special Micronized	10g
Propylene Glycol USP	10g
Base, PCCA PermE8™ Anhydrous Gel	80g

Ketoprofen 10% Topical Lipoderm®

100Gm

Ketoprofen USP, PCCA Special Micronized	10g
Propylene Glycol USP	8g
Diethylene Glycol Monoethyl Ether NF	2g
Base, PCCA Lipoderm®	q.s. 100g

Methodology:

Skin preparation

The percutaneous absorption of ketoprofen was measured using human cadaver abdomen skin tissue from three Caucasian, female donors. Full-thickness skin samples were purchased from Genoskin (Salem, MA) and were cryopreserved and stored at -20°C in tightly sealed plastic bags. Prior to use, the skin samples were defrosted and then soaked in diffusion medium for at least 30 min at 32°C. The samples were visually checked for any significant damages, such as cuts, or holes. Skin tissues from 3 donors and 3 replicates were used for each compounded formula.

Franz cell diffusion

The Franz diffusion system (surface area of 1.77 cm²) was used in this study. The diffusion cells were mounted in the diffusion apparatus and the physiological diffusion medium was added to the receptor compartment. A skin integrity test was performed using Precision LCR meter. Intact skin has transcutaneous electrical resistance at least 3 times greater than the diffusion medium. The finite dose, approximately 10 mg/cm² of the compounded formula was applied on each skin sample using a positive displacement pipette and a pellet pestle to spread the product across the skin surface. The receptor solution (HBSS #14175-079, 25 mM HEPES, #15630-080 and 50 µg/mL Gentamicin, #15750-060, Gibco) was stirred magnetically at 600 rpm with the water jacket temperature maintained at 32±0.5°C. During the exposure period, samples of the receptor solutions (1mL) were removed at predetermined time points: 8, 24, 30 and 48 hours after applying the compounded formula.

Skin wash and extraction

By the end of the diffusion process (after 48 hours), the skin samples were washed with 50% ethanol solution, and wash solution was centrifuged at 6000 rpm for 10 minutes. The supernatant was transferred into a UPLC vial for analysis. Then the skin samples were split into epidermis and dermis, cut into small pieces and transferred to a separate test tube for overnight extraction with 50% ethanol.

Ketoprofen quantification

The quantification of ketoprofen was performed by UPLC (Ultra Performance Liquid Chromatography), using a reverse phase, gradient chromatography with mobile phases A of purified water, and mobile phase B of 0.1% formic acid in acetonitrile. The 1.7µm ACQUITY UPLC BEH C18 columns were used.

Table 1. Compounded formulas (PCCA formula 13195 and 6558) were used in the percutaneous absorption study.

Evaluation of the *in vitro* Human Skin Percutaneous Absorption of Ketoprofen in PCCA PermE8™ Anhydrous Gel vs. PCCA Lipoderm®

Results and Discussion:

Ketoprofen that was absorbed, distributed in the skin, and the rate of absorption were determined in 3 skin samples from each donor for each compounded formula and the mean results are presented.

The distribution of ketoprofen refers to the absorption into different layers of skin, including epidermis and dermis. Ketoprofen in receptor solution represents the component across skin into systemic circulation. The percutaneous absorption of ketoprofen illustrated by the total amount of ketoprofen recovered from receptor solution and dermis of skin. As the abundance of blood vessels in dermis, ketoprofen once penetrates across stratum corneum and reaches dermis, it will eventually be absorbed into systemic blood flow. Higher percutaneous absorption of a transdermal product correlates with better *in vivo* bioavailability. The 48-hour percutaneous absorption of ketoprofen facilitated by PermE8 was $11.0 \pm 1.9\%$ of total applied dose, compared with $11.1 \pm 3.3\%$ by Lipoderm. There was no significant difference in percutaneous absorption or distribution between the two compounded formulas ($p > 0.05$) (Figure 1.)

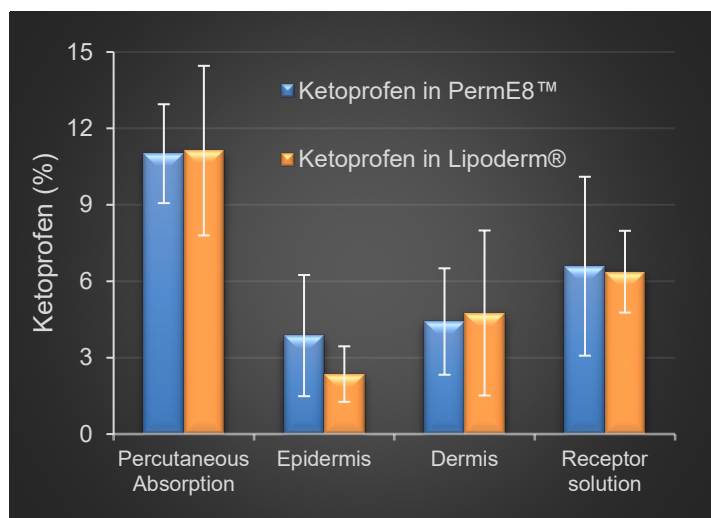


Figure 1. Across donor summary: mean percutaneous absorption and distribution of ketoprofen (as percent applied dose) in two compounded formulas after 48 hours diffusion. Percutaneous absorption was represented by the total percentage of ketoprofen recovered from receptor solution and dermis of skin.

The rate of percutaneous absorption, or flux rate, is a time-averaged value and it was determined as the mean flux of ketoprofen collected at the receptor solution under the skin ($\mu\text{g}/\text{cm}^2/\text{h}$) over 48-hour period. It is a value reported at midpoint of sample collection, as shown in Figure 2. The rate of percutaneous absorption shows a rapid penetration upon application and the maximum flux was achieved at approximately 27 hours post-application in both

PermE8 and Lipoderm based formulas, followed by a slow decline. The mean flux profiles of ketoprofen were similar in both compounded formulas and there was no statistical difference of flux rate at each time point between the two formulas ($p > 0.05$) (Figure 2).

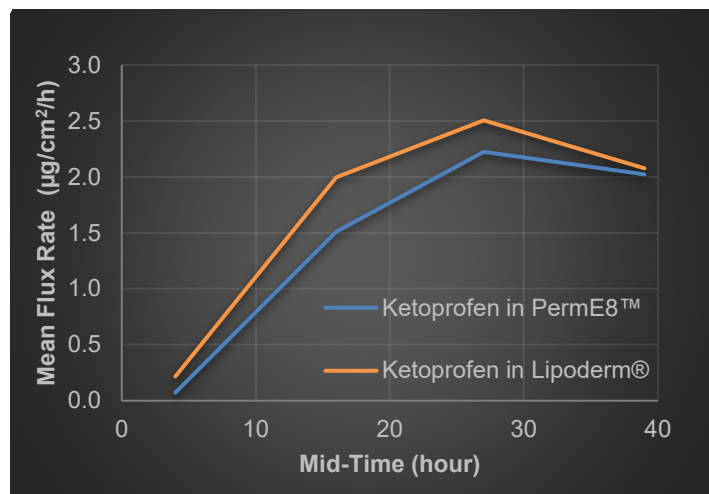


Figure 2. Across donor summary: mean flux rate of ketoprofen in ($\mu\text{g}/\text{cm}^2/\text{h}$) in two compounded formulas (error bars not shown).

Conclusions:

Chronic musculoskeletal pain and arthritis affect 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 performed in the full-thickness human skin model has demonstrated that the proprietary transdermal base PermE8 Anhydrous Gel facilitates the percutaneous absorption of ketoprofen across human cadaver skin. The extent and rate of absorption is comparable to our industry-leading Lipoderm. Since PermE8 has water activity below 0.6, compounding pharmacists may now rely on extended default BUDs for anhydrous transdermal formulations, with the assurance of an excellent transdermal performance.

References:

- Ong CK, Lirk P, Tan CH, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clin Med Res. 2007;5(1):19-34.
- 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.
- PCCA (2018) *PCCA PermE8™ Anhydrous Gel*. Document number 99608. Last accessed: February 24, 2018.