

Transdermal Drug Delivery of Ketoprofen Esters Through Human Cadaver Skin

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ABSTRACT:

Purpose. To evaluate esters of Ketoprofen in skin permeability through human cadaver skin contained in drug-in-adhesive (DIA) matrix transdermal delivery systems (TDSs). This experiment evaluated the effect of the molecular weight and polarity of the ester group on human cadaver skin permeation. **Methods.** Ketoprofen USP was esterified to produce three different ester forms of Ketoprofen, methyl, ethyl and isopropyl esters, respectively. These esters were incorporated into DIA matrices. Ketoprofen esters were held at equivalent concentrations based on dry weight. Identical blends of silicone pressure sensitive adhesive (PSA) and acrylic PSA were utilized in the three formulations. The blends were manually coated onto a release liner, dried in a convection air oven, and laminated to an occlusive backing. Patches of the laminate were mounted on separated stratum corneum from human cadaver skin and placed on modified Franz diffusion cells. Samples of the receiver solution were taken at specified time points and quantified by HPLC.

Results. The following table shows the cumulative skin permeation results for approximately 84 hours.

Formula	84-hr Cum. Permeation (ug/cm ²)
Methyl Ester	112.8
Ethyl Ester	64.5
Isopropyl Ester	40.5

Conclusions. Observed permeation rates indicate transdermal drug delivery of Ketoprofen esters is dependant on the molecular weight and polarity of the molecule. As the ester group increases in molecular weight, the derivative molecule increases in molecular weight and creates a more non-polar derivative molecule, which decreased the amount of drug delivered.

INTRODUCTION:

Transdermal drug delivery of Ketoprofen can be achieved with proper formulation into a drug-in-adhesive platform. In these formulations, drug delivery and wear properties can be compromised due to crystallization of the active drug, since high concentrations of the drug active are incorporated into each formulation. Low molecular weight (MW) Ketoprofen esters convert the physical form of Ketoprofen from a crystalline powder into a free flowing, high boiling point liquid. Transdermal drug delivery of liquid molecules can be difficult to formulate as well, but crystallization of the active drug is typically not a concern.

Esterification of active drugs to create pro-drugs is common practice to develop new drug products. The esterification of Ketoprofen with low MW alcohols was of interest to maximize drug delivery and alleviate challenges in formulation. Typically, pro-drugs convert back into the active form of the drug once absorbed into the skin and bloodstream.

Three esters of Ketoprofen were created to evaluate the effect on skin permeation. The three esters evaluated in this study included Methyl, Ethyl and Isopropyl esters of Ketoprofen. Purified Ketoprofen esters were isolated and incorporated into drug-in-adhesive formulations for evaluation.

METHODS AND MATERIALS:

Ketoprofen USP was utilized as the starting material for the chemical reaction along with one of the following alcohols: HPLC grade Methanol, Anhydrous Ethyl Alcohol (200 proof), or Isopropyl Alcohol USP. The esterification is carried out with the acid functional group of the Ketoprofen molecule reacting with the hydroxyl group of the alcohol under heat and an acid catalyst to drive the equilibrium reaction towards the ester. The methyl, ethyl and isopropyl alcohols were chosen due to their low molecular weight, availability, and purity. Purification of the products was performed using low pressure normal phase liquid chromatography. Thin Layer Chromatography (TLC) and High Performance Liquid Chromatography (HPLC) were the analytical techniques utilized to establish purity and potency of the esters. Since, standards of the ester materials were not available, a response factor of 1:1 was assumed and the potencies were based on the Ketoprofen reference standard.

TABLE I: Ketoprofen Ester Modification:

Active Drug	Molecular Weight	Calculated Log K _{ow} *
Ketoprofen	254.29	3.00
Ketoprofen Methyl Ester	268.31	3.65
Ketoprofen Ethyl Ester	282.34	4.14
Ketoprofen Isopropyl Ester	296.37	4.56

* Calculated by EPI Suite Software, KOWWIN v1.67, ©2000.

Blend to Laminare Production:

Formulations were made with the individual, purified Ketoprofen Esters in equivalent concentrations, Silicone PSA and Acrylic PSA. All blends are in an ethyl acetate solvent system to create homogeneous polymer blends. The homogeneous blends were cast with a wet gap applicator bar onto fluoropolymer coated polyester release liner. The draw-downs were dried for 5 minutes at ambient room temperature under a hood and for 5 minutes at 92° C in a convection air oven. Upon completion of drying, the dry adhesive was laminated to the ethylene/vinyl acetate side of a polyester/ethylene vinyl acetate backing. The end product had a dry coat weight of approximately 10 mg/cm².

Human Cadaver Skin Permeation Study:

A Human Cadaver Skin Permeation Study was performed to determine the drug delivery rate of Ketoprofen/Ketoprofen Ester through the stratum corneum barrier layer. The stratum corneum was obtained from split thickness, cryo-preserved cadaver skin by the heat separation technique. 5/16" diameter samples were cut from the laminate, in triplicate, and mounted onto 1/2" diameter pieces of the stratum corneum, then placed on modified Franz diffusion cells. The receptor phase was 7.5 mL of 0.9% NaCl and 0.01% Na₂S₂O₃ in deionized water. The cells were maintained at 32°C and were magnetically stirred at approximately 300 rpm. Samples of the receptor phase were taken with complete replacement of the receptor phase at specified time points. The samples were quantified by HPLC. Since standards of the Ketoprofen Esters were not available, the concentrations of the Ketoprofen Esters were determined by derivation of the Ketoprofen

RESULTS AND DISCUSSION:

Tables and Graphs:

FIGURE 1: Cumulative Skin Permeation Graph

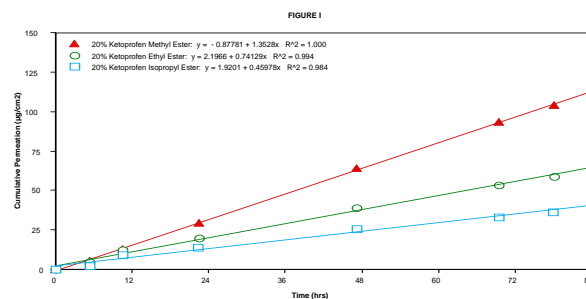


Table 1 presents the Cumulative Permeation for total Ketoprofen/Ketoprofen Ester delivered through the *Stratum Corneum* layer of human cadaver skin. Total drug delivered is higher for the Methyl ester than the Ethyl Ester, which is higher than the Isopropyl Ester. This is indicative of the polarity of the molecule and/or the size of the pendant ester group. Methyl > Ethyl > Isopropyl.

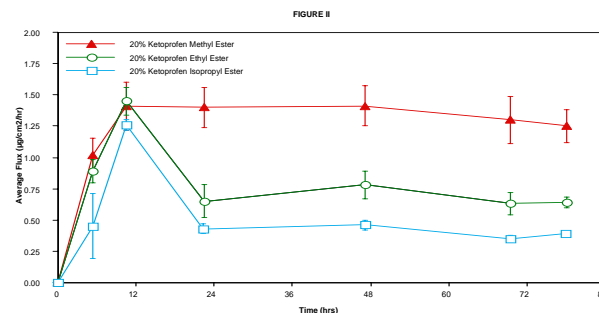


FIGURE 2: Average Skin Permeation (Flux) over 84-hours

Table 2 exhibits the average permeation of the Ketoprofen Esters over an approximate 84-hour time period. After 12 hours, the Methyl Ester delivers a more sustained drug delivery profile. The Ethyl Ester and Isopropyl Ester have a significant drop in skin permeation rate after 12 hours of delivery. This reduction in skin permeation after 12 hours is possibly indicative of the molecule converting back into the Ketoprofen free acid. This formulation was not developed to deliver the free acid, Ketoprofen. In this formulation, the free acid form would crystallize within the matrix hindering the drug from permeating the skin as observed.

CONCLUSION:

The incorporation of Ketoprofen Esters in a DIA matrix TDS is feasible. The use of Ketoprofen Esters potentially alleviates the difficult formulation aspects for adhesion and drug delivery of the crystalline, free acid Ketoprofen. Further development work is needed to properly identify the appropriate ester group which demonstrates the optimal skin permeation rate and profile while maintaining stability of the active molecule.

Future development work for a Ketoprofen Ester TDS includes optimizing the esterification of Ketoprofen to ensure the drug delivery rate, stability of the active, and adhesion are maintained for the duration of the wear period and shelf life of the product.

