

Transdermal Drug Delivery of Polar Derivatives of Ketoprofen Free Acid Through Human Cadaver Skin

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ABSTRACT:

Purpose. To evaluate the difference in polarity and molecular weight of derivatives of Ketoprofen for skin permeability through human cadaver skin in transdermal drug delivery systems (TDDSs). This experiment focused on the evaluation of a polar derivative of Ketoprofen compared to the non-polar derivatives. **Methods.** Ketoprofen USP was esterified to produce three different ester forms of Ketoprofen (mono-glycerol, ethyl and isopropyl esters). These esters were incorporated into DIA matrices. Identical blends of silicone pressure sensitive adhesives (PSAs) and acrylic PSAs were utilized in the 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 calculated Log Kow (octanol-water coefficients) indicates the mono-glycerol ester is more polar, and the ethyl and isopropyl esters are less polar than the parent molecule. The following table shows the cumulative skin permeation results for approximately 72 hours.

Formula	MW	Calculated Log Kow	72-hr Cum. Permeation (ug/cm ²)
Glycerol monoester	328	2.04	214.4
Ketoprofen	254	3.00	1110.0
Ethyl ester	282	4.14	169.7
Isopropyl ester	296	4.56	61.2

Conclusions. In previous work, it was observed the skin permeation of less polar esters of Ketoprofen was dependant on the molecular weight and polarity of the molecule. As the ester group increases in molecular weight, the parent molecule increases in molecular weight and creates a less polar parent molecule, which decreased the amount of drug delivered. This work suggests the skin permeation rate of the derivative is weighted more towards polarity than molecular weight as the more polar ester, glycerol, delivered more total drug than the less polar derivatives, ethyl and isopropyl.

INTRODUCTION:

Previous work (Hartwig et al., AAPS 2005 Poster) demonstrated the calculated octanol/water coefficient (Log Kow) and molecular weight (MW) affected the rate of transdermal drug delivery rate of Ketoprofen through human cadaver skin. The derivations prepared were Ketoprofen Methyl, Ethyl and Isopropyl esters which are decreasing in polarity (higher Log Kow) compared to the parent molecule, respectively. This study showed that increasing the molecular weight and decreasing the polarity of the molecule decreased the drug delivery rate. It was proposed that more polar derivatives of Ketoprofen would increase the rate of the transdermal drug delivery of Ketoprofen. The proposed polar derivative of Ketoprofen was the mono-glycerol ester. This polar group was selected because it significantly decreases the Log Kow and the de-esterification of the molecule in the body converts the ester into Ketoprofen and Glycerin, a pharmaceutically safe excipient. The main drawback to this group is the increase in the molecular weight by approximately 30% compared to the parent molecule. This study evaluates the potential of the larger, more polar ester of Ketoprofen for transdermal drug delivery.

Three esters of Ketoprofen were created to evaluate the effect on skin permeation. The three esters evaluated in this study included Mono-Glycerol, Ethyl and Isopropyl esters of Ketoprofen. Laboratory 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: Glycerol (99.5%), Anhydrous Ethyl Alcohol (200 proof), or Isopropyl Alcohol USP. The esterification is carried out by refluxing Ketoprofen and the alcohol under heat and an acid catalyst to drive the equilibrium reaction towards the ester. Purification of the products was attempted 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 Monoglycerol Ester	328.37	2.04
Ketoprofen	254.29	3.00
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 Laminate Production:

Formulations were made with the laboratory purified Ketoprofen Esters in equivalent concentrations of Silicone PSA and Acrylic PSA to specifically target only the drug's potential to deliver through human cadaver skin. Unfortunately, it was found after the formulations were made different concentrations of the derivatives, due to purity, were added to the formulations. This prevents evaluating a true comparison of the actual drug delivery based on the derivative only. 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 and Ketoprofen Esters 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% NaN₃ 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 USP standard.

RESULTS AND DISCUSSION:

Tables and Graphs: FIGURE I Average Flux of Ketoprofen Non-Polar Esters

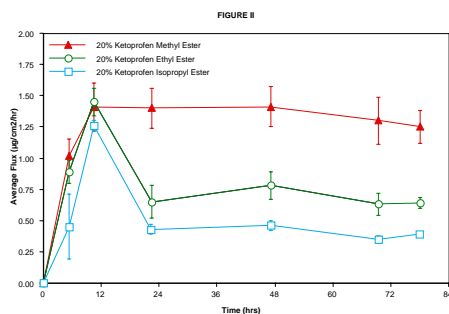


Figure I exhibits the average flux of the Ketoprofen Non-Polar Esters over an approximate 84-hour time period. The drug delivery profiles are consistent with the hypothesis that the more polar the derivative the more total drug or derivative is delivered, i.e. the Methyl ester delivered more drug than the Ethyl ester which delivered more than the Isopropyl ester.

FIGURE II: Average Flux of Ketoprofen, Polar and Non-Polar Derivatives

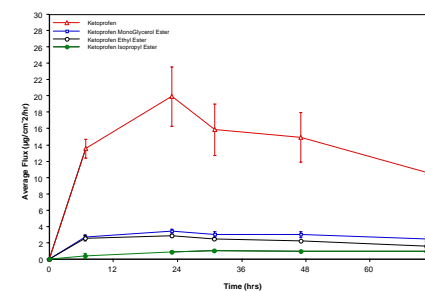


Figure II exhibits the average flux of the polar and non-polar esters as well as Ketoprofen. As can be observed the parent molecule permeates the highest compared to the polar and non-polar derivatives. Comparing the derivatives the mono-glycerol ester delivers at a higher rate than the two non-polar derivatives. The hypothesis that the more polar the molecule delivers more holds true to the extent that the molecular weight and/or molecular volume and/or Total Polar Surface Area inhibit the delivery of the derivative.

CONCLUSION:

The incorporation of Ketoprofen and ester derivatives in DIA matrices was performed to evaluate the efficiency and potential of drug release from TDDSs. The use of Ketoprofen Esters potentially alleviates the difficult formulation aspects for adhesion and drug delivery of the crystalline, free acid Ketoprofen. Ketoprofen derivatives have proven to permeate the skin, but not as well as the parent molecule. It was presumed the decrease in permeation was due to polarity of the molecule. This was not the case as less polar molecules, Methyl, Ethyl and Isopropyl esters permeate significantly less than Ketoprofen. It was then proposed the molecular weight inhibited permeation. This experiment evaluated a more polar derivative of Ketoprofen, the mono-glycerol ester. The mono-glycerol ester permeates more than the non-polar derivatives, but not the parent molecule. This poses difficulty in optimizing the molecule for transdermal drug delivery, unless the free acid is the best selection for transdermal drug delivery. Further work to be performed includes derivatives with molecular weight and polarity, i.e. Log Kow, between the monoglycerol ester and the free acid. If non-polar derivatives significantly decrease drug delivery rate, and significantly more polar derivatives decrease the drug delivery rate as well, then the only option is the parent molecule. A derivative closer in molecular weight to the parent molecule with more polarity is the goal of further research.

