

In-Vitro Comparison of Excipients for the Permeation Enhancement of Diclofenac Potassium

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ABSTRACT

Three excipients, oleic acid, methyl laurate and Labrasol®, were compared in an in-vitro permeation study to determine which is the most effective at permeating diclofenac potassium in a transdermal delivery device. Results of this study showed that the formula with oleic acid had the highest diclofenac potassium flux rate.

INTRODUCTION

Diclofenac is known as a nonsteroidal anti-inflammatory drug (NSAID). NSAIDs produce their therapeutic activities through inhibition of cyclooxygenase (COX), the enzyme that makes prostaglandins (PGs). COX-1 makes PGs that protect the stomach and kidneys. COX-2 produces PGs that cause pain and inflammation. Diclofenac is a non-selective NSAID that inhibits both types of COX enzymes¹.

Currently, diclofenac is administered by capsules, tablets, rectal suppositories, intramuscular injections and eye drops. Topical applications include gels, gel patches, transdermal patches and a cutaneous solution applied to the skin.

The objective for this study is to develop a multi-day, single-dose transdermal delivery device. Oleic acid, methyl laurate and Labrasol®, which is a caprylocaproyl macrogolglyceride, were evaluated for the enhancement of diclofenac potassium permeation. All three excipients are pharmaceutically acceptable for topical use.

Diclofenac potassium has a molecular weight of 334.24 daltons.

MATERIALS

The following materials were obtained from the indicated vendors:

Diclofenac Potassium – Farma-Lepori SA
Acrylic Pressure Sensitive Adhesive (PSA) – Cytec
BIO-PSA® Silicone – Dow Corning Corp.
Kollidon® 30, USP – BASF Corp.
Dipropylene Glycol – Dow Chemical Co.
Oleic Acid, NF – Cognis Canada Corp.
Methyl Laurate – Cognis Corp.
Labrasol® – Gattefossé
Scotchpak™ 9732 backing – 3M™
Scotchpak™ 1022 release liner – 3M™

EXPERIMENTAL METHODS

Patches were formulated with a drug concentration of 14%. The data was collected from an in-vitro permeation study utilizing modified Franz cells with stratum corneum obtained from human cadaver skin by the heat separation technique. The receiver solution for this study was 0.9% NaCl with 0.01% NaN₃ in deionized water. Franz cells were maintained at ~32°C for the duration of this study. Flux samples were analyzed by HPLC.

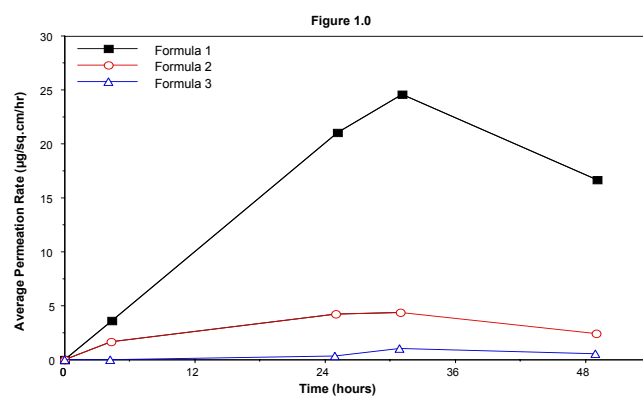
A non-reactive/non-functional acrylic PSA and a standard silicone PSA were utilized in the adhesive system for this experiment.

RESULTS AND DISCUSSION

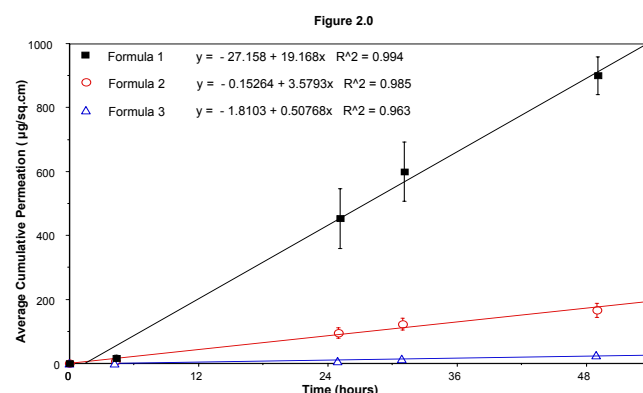
The following table gives a detailed description of each formula evaluated in this study.

Components	Formula 1	Formula 2	Formula 3
Diclofenac Potassium	14	14	14
Kollidon® 30	12	12	12
BIO-PSA® Silicone	50	50	50
Acrylic PSA	8	8	8
Dipropylene Glycol	4	4	4
Oleic Acid	12	0	0
Methyl Laurate	0	12	0
Labrasol®	0	0	12

Figure 1.0 shows the average permeation rates for the three formulas described in the table above. It is evident that oleic acid is the most promising excipient to enhance the permeation of diclofenac potassium in this drug delivery platform.



It is not surprising that an oleic acid / glycol combination shows positive permeation results. Mixtures of permeation enhancers have been evaluated for many years. Synergistic effects have been demonstrated for a variety of these combinations including oleic acid and glycols².



RESULTS AND DISCUSSION cont.

Utilizing the data in Figure 2.0, which illustrates the average cumulative permeations over the two day study, the formulas were compared to a commercially available estradiol transdermal product, Vivelle-Dot®. Please see the table below.

Drug	Rate (µg/cm ² /hr)	Label Claim (µg/cm ² /hr)	% of Label Claim	Dose (mg/day)	Patch Size (cm ²)
Vivelle-Dot® (Estradiol)	0.501	0.417	120%	0.1	10
Oleic Acid (Formula 1)	19.168	n/a	n/a	10	26
Methyl Laurate (Formula 2)	3.579	n/a	n/a	10	140
Labrasol® (Formula 3)	0.508	n/a	n/a	10	> 950

The table above clearly describes the effect that each excipient has on diclofenac potassium. Based on permeation rate, Formula 1 fluxes five-times higher than Formula 2 and over 30-times higher than Formula 3.

CONCLUSION

Diclofenac potassium was found to permeate through the skin at the highest rate when combined with oleic acid and dipropylene glycol. Methyl laurate showed a higher permeation rate when compared to Labrasol®, but it is clear that the oleic acid effects far exceed the other two excipients that were evaluated.

Based on the data presented, a transdermal delivery device containing 14% diclofenac potassium with 12% oleic acid should deliver 10 mg/day out of a ~26 cm² unit in vivo.

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