

## In-Vitro Permeation Enhancement of Benzothiazole from Transdermal Drug Delivery Systems Utilizing Fatty Acid Derivatives

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### ABSTRACT

#### Purpose

To evaluate the delivery rate of molecule R053, a Benzothiazole, in a drug-in-adhesive Transdermal Drug Delivery System (TDDS) for permeation enhancement comparing an 18-carbon chain (C18) fatty acid to three C18 fatty acid derivatives.

#### Methods

Twelve drug-in-adhesive TDDS laminates were prepared. Unit design consists of an occlusive backing, drug-in-adhesive matrix and a protective release liner. The adhesive matrix contains 4% R053, 40.5% silicone pressure sensitive adhesive (PSA), 40.5% non-functional acrylic PSA, 10% Polyvinylpyrrolidone (PVP) and fatty acid or derivative enhancers at 5%, 7% or 10%. The silicone PSA was QS'd for the 7% and 10% fatty acid or derivative enhancer matrices. Formulation Set 1 was prepared with 5% fatty acid, while Formulations Sets 2 through 3 were prepared using 7% and 10% fatty acid derivatives of alcohol, amide and ester, respectively. Punched units from each laminate were utilized for the in-vitro permeation study using human cadaver skin. Drug delivery profiles were generated from HPLC R053 concentration results.

#### Results

Figures 1 through 3 clearly show that formulations containing the fatty acid derivatives produce significantly higher permeation rates in comparison to formulations containing the fatty acid component. This illustrates that structural functionality of enhancers can significantly impact the transdermal delivery of the R053 molecule. As enhancers are increased from 5 to 10%, it becomes evident that the alcohol and ester derivatives permeated slightly higher than the amide derivative.

#### Conclusions

This study shows that the C18 fatty acid derivatives of alcohol, amide and ester incorporated into TDDS matrices elevates the drug delivery of R053 over a one-day period in comparison to the fatty acid. Additionally, this study reveals that the chemical functionality of these derivatives have an effect on flux.

### I. EXPERIMENTAL METHODS

#### A. Formulations

##### Drug Permeation Profile/Study 1

Four amine-compatible silicone / non-functional acrylic formulations were prepared into a drug-in-adhesive TDDS matrix. A 10% PVP concentration was maintained to inhibit crystal growth and the drug concentration was held at 4%. Formulations 1 through 4 additionally contained a saturated fatty acid, an unsaturated fatty alcohol, an amide and an ester derivative respectively. Each dried laminate had a coat weight of 10 mg/cm<sup>2</sup>.

##### Drug Permeation Profile/Study 2

Study 2 mimics the formulation composition of Study 1 with the exception that 7% fatty acid and fatty acid derivatives and 8% PVP were used.

##### Drug Permeation Profile/Study 3

Study 3 additionally mimics the formulation composition of Study 1 with the exception that 10% fatty acid and fatty acid derivatives and 8% PVP were used.

#### B. In-Vitro Permeation Studies

Three Human Cadaver Skin Permeation Studies were performed to determine the delivery rate of the R053 molecule through the stratum corneum skin layer. Two different skin donors were used. Skin Donor 1 was used for Study 1 and Skin Donor 2 was used for Studies 2 and 3. Modified Franz diffusion cells with a defined receiving volume and delivery area were used for cadaver skin placement. The receptor solution was 7.5 mL of 0.9% NaCl and 0.01% NaN<sub>3</sub> in deionized water. The cells were maintained at 32°C and were magnetically stirred at approximately 300 rpm. Samples of the receptor solution were taken with complete replacement of the receptor phase at specified time points. The samples were quantified by HPLC. The results are graphically illustrated in Figures 1 through 3.

#### C. Transdermal Unit Preparation

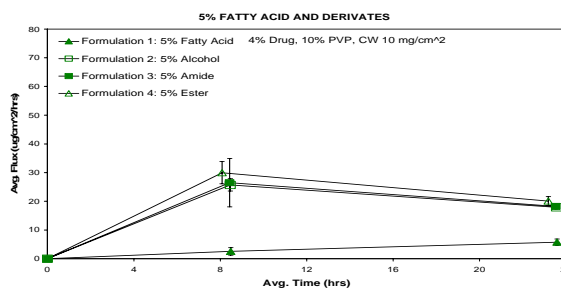
Formulations were prepared as a 1:1 ratio of amine-compatible silicone PSA and non-functional acrylic PSA. The homogeneous blends were cast with a wet gap applicator onto fluorinated polysiloxane coated polyester release liner. To remove solvents, the draw-downs were dried for 5 minutes at ambient room temperature and then for 5 minutes at 92°C in a convection air oven. The dried adhesive matrix was laminated to polyester/ethylene vinyl acetate backing.

### II. RESULTS AND DISCUSSION

#### A. DRUG PERMEATION PROFILE/ STUDY 1: Skin Donor 1

Figure 1 illustrates that Formulations 2 through 4 containing fatty acid derivatives produced significantly higher permeation rates in comparison to Formulation 1 containing the fatty acid. Structurally, the fatty acid contains a carboxylic functional group (-COOH) whereas; the fatty acid derivatives contain -COOH groups that have been substituted with a functional alcohol (-OH), amide (-NH<sub>2</sub>) and ester (-COOR) group, respectively. Thus, the results demonstrate that the structural functionality of these enhancers contribute to drug delivery for R053. On average, the flux of Formulations 2, 3 and 4 containing fatty acid derivatives is 4 times greater than the formulation with the fatty acid component, Formulation 1. In this study, comparing flux performance for the fatty acid derivatives, neither enhancer was identified as significantly outperforming the other.

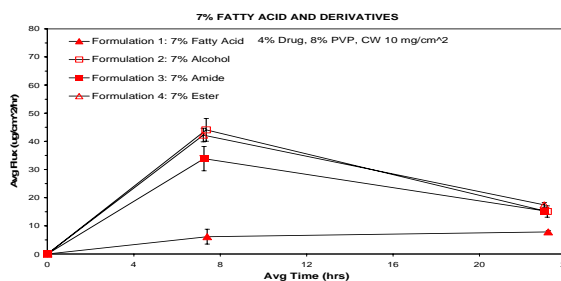
FIGURE 1



#### B. DRUG PERMEATION PROFILE/ STUDY 1: Skin Donor 2

Based on the results of Study 1, Study 2 was conducted to investigate the permeation rate of molecule R053 when incorporating the same drug-in-adhesive matrix with increased enhancement from 5 to 7%. In this study, Figure 2 illustrates that Formulations 2 through 4 containing fatty acid derivatives fluxed on average 3 times greater than Formulation 1, which contained the fatty acid component. Specifically, Formulations 2 and 4 containing the alcohol (-OH) and ester (-COOR) functional derivatives respectively, fluxed slightly higher than the amide (-NH<sub>2</sub>) functional derivative.

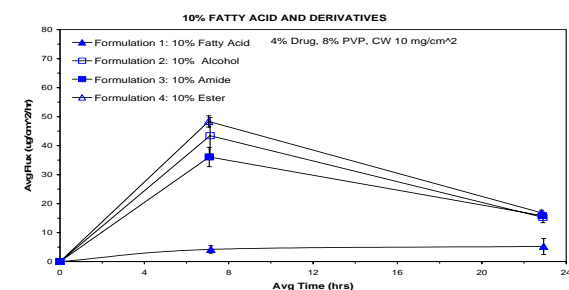
FIGURE 2



#### C. DRUG PERMEATION PROFILE/ STUDY 3: Skin Donor 2

Figure 3 illustrates the same drug-in-adhesive matrix Formulations 1 through 4 utilized in Studies 1 and 2, with an increase in enhancement concentration to 10%. In this study, Formulations 2 through 4 containing the fatty acid derivatives on average resulted in the enhancement of 5 times Formulation 1 containing the fatty acid component. In this study, Formulation 4 containing the ester (-COOR) derivative fluxed higher than Formulation 2 containing the alcohol (-OH) derivative that in turn fluxed higher than Formulation 3 containing the amide (-NH<sub>2</sub>) functional derivative.

FIGURE 3



### III. CONCLUSION

The results of the three permeation studies indicate that the in-vitro skin permeation rate of molecule R053 can be greatly enhanced by the use of fatty acid derivatives with alcohol (-OH), amide (-NH<sub>2</sub>) and ester (-COOR) functionality in comparison to a fatty acid enhancer with carboxylic functionality (-COOH). In general, these studies show that R053 is functionally sensitive to specific functional groups for in-vitro permeation enhancement. These results additionally indicate that the skin flux rate of molecule R053 can be manipulated by varying the concentration of the specified functional enhancer, thus making delivery controllable.

### IV. REFERENCES

[1] Li, Chensheng; Composition and Methods for Transdermal Delivery of Acid Labile Drugs; US Patent 6,024,974.