



Comparison of *In Vitro* Percutaneous Absorption of Compounded Medications in Liposomal vs Non-Liposomal Vehicles

Liposomes are a well-established transdermal vehicle for drug delivery across the skin barrier. This delivery method has been studied often in commercial drug products in which the active pharmaceutical ingredient is integrated into the vesicle during manufacturing.¹ This report seeks to examine if a similar effect can be observed in compounded preparations.

In pharmaceutical compounding, a pure drug powder is mixed into an inert vehicle such as a gel or cream base using methods such as a mortar and pestle, ointment slab or a high-shear method such as an EMP (Electronic mortar and pestle) machine.



If liposomes are an effective delivery system for compounded transdermal medication, enhanced penetration of the active ingredient would be observed with a liposomal vehicle when compared to a non-liposomal base. Two *in vitro* skin penetration studies were conducted by Dow Pharmaceutical Sciences Inc. to compare the abilities of a liposomal base vs a non-liposomal base to deliver a hormone and an anti-inflammatory to their respective target sites.

In both studies, the liposomal base did not

exhibit any improvement in penetration over the non-liposomal base. For Diclofenac Sodium, a PLO-based cream delivered more drug to the target site than the liposomal base, however the difference was not statistically significant. In the case of the Progesterone, both a proprietary oil-in-water emulsion as well as a PLO-based cream performed statistically significantly better than the liposomal base. Therefore, based on these studies, we cannot conclude that liposomes contribute any enhanced penetration to a compounded preparation. A likely explanation for these findings is that the drugs cannot be incorporated into pre-formed liposomes (such as those found in a liposomal compounding vehicle) and therefore they will have no impact on penetration level of the API.

Study #1: Local Target Site

Dow Pharmaceutical Sciences Inc. (DPSI) conducted an *in vitro* skin study which assessed the percutaneous absorption of Diclofenac Sodium from several vehicles, including a liposomal cream base. The main objective of this study was to achieve a certain degree of skin permeation and, in turn, determine the optimal vehicle that would reflect anticipated local effects. Diclofenac Sodium was selected for its common use as a non-steroidal anti-inflammatory drug (NSAID) and its low permeability through the skin.

Methods

This *in vitro* percutaneous absorption study was conducted using the Bronaugh flow-through diffusion cell method and

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ARE SUPPORTED BY:**

- ✓ Skin Studies
- ✓ Chemical Stability studies
- ✓ Preservative Efficacy Testing (USP <51>)

procedures adapted from the FDA and AAPS Report of the Workshop on Principles and Practices of *in vitro* Percutaneous Penetration Studies: Relevance to Bioavailability and Bioequivalence.² All evaluated formulations were prepared by incorporating 5% w/w Diclofenac Sodium, EP into formulation bases which were then spiked with radiolabeled (¹⁴C)-Diclofenac Sodium at a nominal 1.0 µCi/3.2 mg dose.

The clinically relevant dose of 5 mg/cm² was applied to dermatomed human abdominal tissue from a single donor obtained following elective surgery. Results from *in vitro* studies using this particular tissue preparation are typically less variable and more reproducible than *in vitro* studies using human cadaver skin preparations. The 54 flow-through diffusion cells were maintained at a constant temperature of 32°C by use of recirculating water baths and were left undisturbed for a 24-hour exposure period. Fresh receptor phase buffered solution was continuously pumped under the tissue at a flow rate of 1.0 mL/hr and collected in 6-hour intervals.



Results

Over the 24-hour period, liquid scintillation analyzing techniques were employed to quantify radioactivity thus determining tissue permeation and deposition results, while demonstrating local versus systemic delivery. Following a 24-hour period, a non-liposomal PLO-based vehicle delivered more (¹⁴C)-Diclofenac Sodium to the local target site relative to a liposomal cream base (1.82% of the applied dose.) See Figure 1.

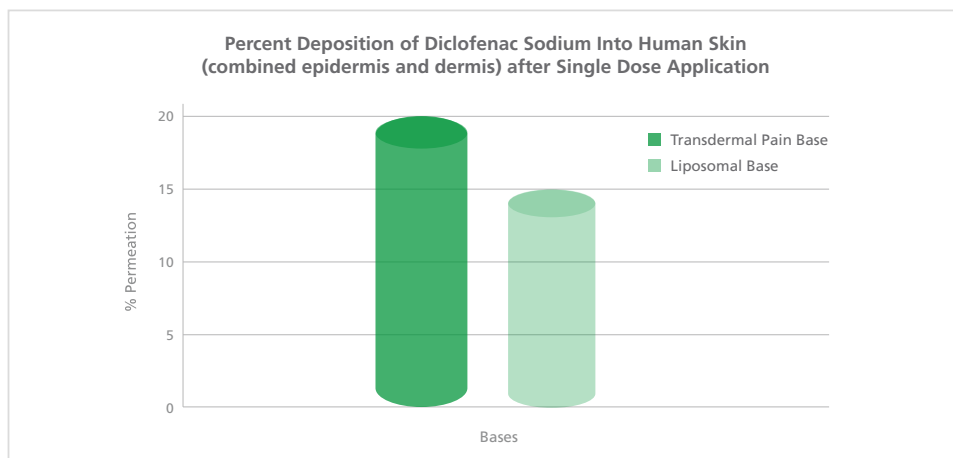


Figure 1. Non-liposomal cream (Transdermal Pain base) delivered more (¹⁴C)- Diclofenac Sodium into the dermis + epidermis in comparison to a liposomal base.

Study #2: Systemic Target Site

DPSI also studied the *in vitro* percutaneous absorption of (¹⁴C)-Progesterone from various transdermal delivery vehicles, including one liposomal cream base. The study was conducted by using the Bronaugh flow-through diffusion cell method and human excised skin from a single Caucasian female donor following elective abdominal surgery, thus reducing the potential for variability.

Methods

All formulations evaluated in this study were equally spiked with sufficient (¹⁴C)-Progesterone to achieve a nominal formulation dose of 1.0 µCi/3.2 mg per diffusion cell, which corresponds to a topical application of 5 mg formulation per cm² of tissue.

This clinically relevant dose was dispensed onto dermatomed skin tissue (0.028 ± 0.004 inches), and was left undisturbed for a 24-hour exposure period. The 54 flow-through diffusion cells were maintained at a constant

temperature of 32°C by use of recirculating water baths. Fresh receptor phase buffered solution was continuously pumped under the tissue at a flow rate of 1.0 mL/hr and collected in 6-hour intervals. Over the 24-hour period, the amount of (¹⁴C)-Progesterone residing in the receptor phase samples was quantified using liquid scintillation analyzing techniques to determine the cumulative permeation of (¹⁴C)-Progesterone.

Results

Following a 24-hour period, the liposomal base did not exhibit improved penetration over a proprietary oil-in-water base (VersaPro™ cream) or a PLO-based cream. The amount of (¹⁴C)-Progesterone to reach the receptor phase was statistically significantly greater with VersaPro™ cream vs a liposomal base (p < 0.01). See Figure 2.

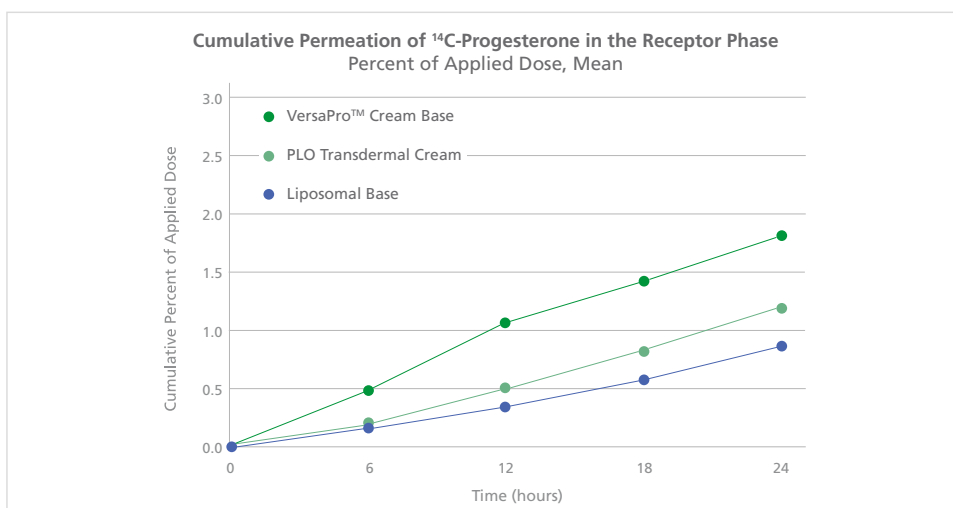


Figure 2. Non-liposomal cream base (VersaPro™ Cream) delivered statistically significantly more (¹⁴C)-Progesterone into the receptor fluid in comparison to a liposomal base.

References

- 1 Akbarzadeh, Abolfazl et al. "Liposome: Classification, Preparation, and Applications." *Nanoscale Research Letters* 8.1 (2013): 102.
- 2 Skelly et al. "FDA and AAPS Report of the Workshop on Principles and Practices of In Vitro Percutaneous Penetration Studies: Relevance to Bioavailability and Bioequivalence." *Pharmaceutical Research* 4(3)(1987): 265-267.

