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Impact of a Skin Model on the In Vitro Performance of a Zolmitriptan-Coated Adhesive Dermally Applied Microarray

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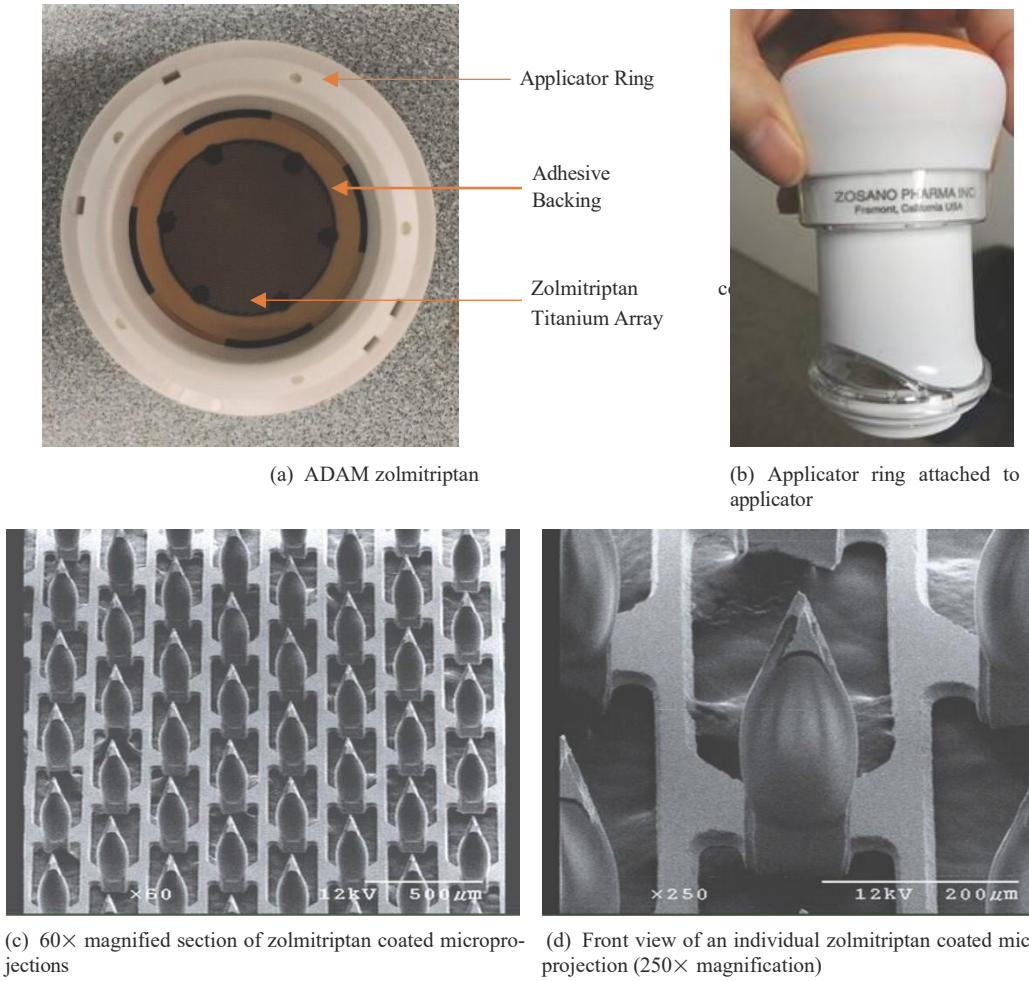
1. Introduction

For the investigation of percutaneous absorption and the assessment of the pharmacokinetics of medications administered topically, the Franz in vitro human skin finite dose model has proven to be an invaluable resource. The model makes use of ex vivo human skin that is mounted in specially made diffusion cells, which enable the skin to be kept at a temperature and humidity that are similar to those found in vivo [1]. A limited amount of a formulation (for instance, 2–10 mg/cm2 of a semisolid or transdermal delivery system) is applied to the skin's outer layer and the pace at which the medication appears in the receptor solution that bathes the inner surface of the skin is used to quantify drug absorption. This model allows for the determination of data specifying skin content, absorption rate, and total absorption. The technique has a long history of correctly forecasting the kinetics of percutaneous absorption in vivo [2, 3]. Using ex vivo skin of different thicknesses as the diffusional barrier, the Franz cell has also been used to evaluate microneedle-mediated drug delivery [4–6]. Another potential substitute for ex vivo skin has been proposed: synthetic membranes like Silescol® [7, 8]. The alleged benefits of using synthetic membranes' accessibility, usability, and storage simplicity, as well as their potential to reduce the unpredictability related to the usage of ex vivo skin [9]. Unambiguous correlation to human stratum corneum barrier function has not yet been thoroughly investigated, especially for finite dose applications, despite the potential benefits of artificial membranes over human skin [10].
In the current work, we assessed the effects of zolmitriptan delivered percutaneously from a new drug-coated microprojections that target the epidermal/dermal layer for quick and effective administration on Strat-M (synthetic membrane), full thickness, and dermatomed ex vivo skin. An applicator and an array of titanium microneedles affixed to an adhesive backing that is seated in a retainer ring make up the Adhesive Dermally Applied Microarray (ADAM) system (Figure 1(a)). The retainer ring's adhesive backing is fastened to the applicator's bottom. The adhesive is separated from the retainer ring by spring tension, which activates the applicator (Figure 1(b)) and adheres the patch to the skin location. The dry drug coating is dissolved by the surrounding skin interstitial fluid as the drug-coated microneedles physically penetrate the stratum corneum and enter the epidermis and dermis.



(a) ADAM zolmitriptan

(b) Applicator ring attached to applicator

(c) 60× magnified section of zolmitriptan coated microprojections

(d) Front view of an individual zolmitriptan coated microprojection (250× magnification)

FIGURE 1: Adhesive Dermally Applied Microarray (ADAM) zolmitriptan. (a) 5 cm^2 adhesive backing with microprojection array (3 cm^2) in applicator ring. (b) Applicator ring press fit onto the bottom of the applicator, and applicator. (c) 60× magnification of zolmitriptan coated microprojections (725 microprojections/cm^2 and length 340 μm), zolmitriptan coated at 1.9 mg/3cm^2 array. (d) Front view of an individual zolmitriptan coated microprojection (250× magnification).

fluid. In a recent Phase 2 clinical investigation, the ADAM system was used to administer zolmitriptan to treat migraines [11]. Supplies and Procedures 2.1. Examine the articles. The test apparatus was made up of an ADAM with a 5 cm2 adhesive backing and a 3 cm2 titanium array with a nominal dose of 1.90 ± 0.05 mg of zolmitriptan (0.05 mg represents the standard deviation of the coated dose). An applicator ring with co-molded desiccant was put on top of the adhesive backing. The ADAM zolmitrip-tan was kept in a heat-sealed, nitrogen-purged pouch. Membrane Sources (2.2). Dermatomed human skin from the posterior trunk of three donors—two males and one female; two Caucasian and one African-American—who were between the ages of fifty and fifty-one years—was acquired from the New York Presbyterian Hospital Skin Bank (NY, NY). The testing facility received this skin in a water-sealed, cryopreserved, dermatomed state. impermeable bag that is kept at -70°C continuously. Every skin was utilized before the expiration date indicated on the label.

One male, Caucasian, 40-year-old donor's upper outside arm was used to obtain full thickness human skin from Science Care in Phoenix, Arizona. The testing facility received this skin fully excised and sealed in a water-impermeable bag for ongoing storage at -20°C.
Strat-M, a synthetic membrane with a nominal thickness of 300 μm and a diameter of 47 mm, was acquired from Mil-lipore Sigma (Burlington, MA).
2.3. Medium of Receptor. The diffusion cells were initially mounted and the skin barrier integrity test was conducted using normal phosphate buffered saline (pH 7.4 ± 0.1) with 0.008% gentamicin sulfate (PBSg) solution. The reservoir solution was completely substituted with 0.1x phosphate buffered saline (pH 7.4 ± 0.1) with 0.008% gentamicin sulfate (0.1x PBSg) during the barrier integrity test. The receptor medium had a capacity of 25 milliliters. 1.1. Preparing the Diffusion Cell. The Franz finite dose method was used to quantify absorption in vitro. Before being used, the skin was thawed in water at 37 °C and cleaned with deionized water to get rid of any clinging blood or other substances. Each donor's skin was divided into several smaller pieces that were big enough to fit on static Franz diffusion cells with a 7 cm2 nominal dosage area. A Digital Pocket Thickness Gauge was used to measure each skin section's real thickness three times. After that, each skin segment was placed on a diffusion cell. PBSg was poured into the cutaneous receptor compartment until it was full. The epidermal chamber was exposed to the surrounding laboratory conditions without any obstructions. After that, the cells were put within a rack system and connected to a water circulation system, which allowed the receptor solution to be magnetically agitated at about 600 RPM while maintaining a temperature that

32 ± 1∘C is the skin's surface temperature.
Without any changes or modifications, the Strat-M synthetic membrane was mounted straight onto the diffusion cell. After that, the cells were put inside a rack system and connected to a water circulation system. The receptor solution was then magnetically agitated at about 600 RPM and kept at a temperature that reached 32 ± 1∘C for the skin's surface.
1.2. Test for Barrier Integrity. Each skin section's water absorption was assessed for transepidermal water loss (TEWL) in order to guarantee the integrity of its barrier. After activating and applying a Delfin VapoMeter (Surrey, UK) probe to the skin's surface, the TEWL value was noted. It was deemed appropriate to mount skin in diffusion cells when the TEWL was less than 25 g/m2/h. If necessary, skin portions deemed unsuitable for dosing might have served as non-dosed negative sample control cells. The receptor solution was swapped out for the specified stock receptor solution of 0.1x PBSg following the completion of the barrier integrity test.
1.3. Administration of Doses and Gathering of Samples. A predose (0 hour) sample was taken before the ADAM zolmitriptan was administered to the skin and membrane sections. The entire volume of the receptor solution was removed, and an approximate 5 mL aliquot of the collected sample was saved for further analysis. The authorized stock receptor solution of 0.1x PBSg was used in place of the receptor solution. The epidermal surface was then fully accessible once the skin was momentarily removed from the Franz diffusion cell. The skin-ADAM combination and the donor compartment (chimney) were immediately transferred to the receptor compartment of the Franz diffusion cell after ADAM zolmitriptan was applied. An approximate 5 mL aliquot of the collected sample was saved for further analysis. The receptor solution was completely removed and replaced with stock receptor solution at the prearranged sampling time points (3, 5, 10, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270, and 300 minutes). A 5 mL aliquot was lyophilized using vacuum centrifugation (Savant SpeedVac) and reconstituted in 0.25 mL of deionized water for sample analysis. Following the collection of the final receptor sample, the ADAM zolmitriptan was extracted and evaluation. Two consecutive refluxing washes of deionized water were used to wash the skin's surface. There were at least ten refluxes every wash cycle. For each diffusion cell, a single surface wash sample was created by combining the two wash volumes from each donor cell. The

skin was let to dry for at least ten minutes after the surface wash. The stratum corneum was then removed and collected by tape-stripping the skin with up to 10 consecutive tapes (3M Transpore® tape). At room temperature, tape strips were removed throughout the entire night in deionized water using a horizontal mixer set at 60 rpm. After being removed from the cell, the skin was manually dissected into the epidermis and dermis for further extraction and examination. Overnight, at room temperature, skin pieces were removed using a horizontal mixer running at around 60 rpm in deionized water. At room temperature, strat-M and the ADAM zolmitriptan array were extracted overnight in deionized water using a horizontal mixer set to 60 rpm.

1.4. The dosage. Using a handheld, reusable applicator, the ADAM zolmitriptan systems were applied to the substrate (Strat-M membrane or cadaver skin) with a total energy of 0.26 J. Using a previously published approach, the ADAM zolmitriptan was linked to the applicator, which was then pressed on the substrate to release the patch and administer it with a preset force [12]. The substrate containing the attached ADAM zolmitriptan was promptly placed onto a Franz diffusion cell after dosage.

1.5. Analysis of the Sample. A thoroughly verified HPLC method was used to quantify the amount of zolmitriptan in the samples that were collected. A Shimadzu Series LC System was used to analyze the samples. For the analysis of zolmitriptan, the HPLC/UV method employed a solvent system that included a mobile phase gradient made up of (Solvent A) 0.1% ammonium acetate with 0.1% acetic acid in water and (Solvent B) methanol. The solvent system was run through a Phenomenex Luna C18(2) column (100 x 4.6 mm, 3 μ) at a flow rate of 0.5 mL/min. The temperature of the column was kept at 40°C.

1. 6. Analysis of Statistics. Each key parameter's standard deviation was determined by averaging the duplicates within skin donors (2 replicates/donor). Averages within the donor population were then compiled, and the mean with standard error for the entire donor population was determined. Six replicates of Strat-M were used, averaged, and the standard deviation was computed.

2. Outcomes

The in vitro bioavailability and bioequivalence of topical semisolid formulations and transdermal systems are typically evaluated using Franz cell studies. Optimizing formulations to improve percutaneous distribution is one significant use [13]. Therefore, an approximation of in vivo percutaneous absorption should be possible due to drug penetration through ex vivo skin. However, because there is no circulatory system in an ex vivo setting, the gap between the stratum corneum and its interaction with the receptor medium may contain extra

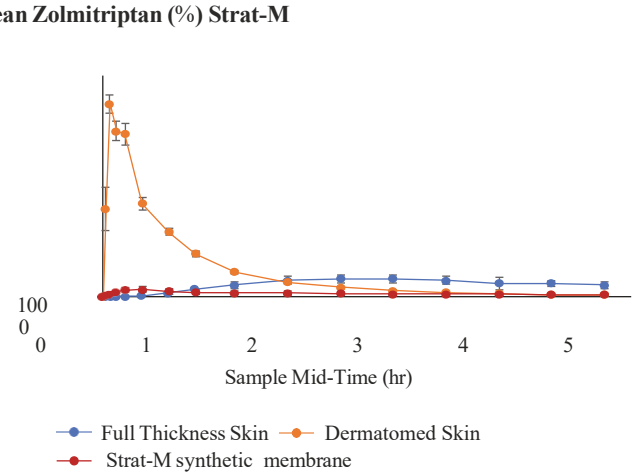


FIGURE 1: Comparison of mean flux (μg/cm²/hr) from full thickness, dermatomed skin, and Strat-M synthetic membrane.

unstirred barriers to drug permeation for some molecules. In an *in vivo* model the distance is 200-400

μm from the stratum corneum to the dermis, where the greatest amount of drug is systemically absorbed via the capillaries [14]. Thus an essential attribute of an *ex vivo* percutaneous absorption experiment is a prudent deliberation of the membrane utilized to model *in vivo* skin conditions [13].

To evaluate the effect of the skin model on microprojec- tion facilitated delivery, full thickness skin (0.70 ± 0.09 mm thickness), dermatomed skin (0.46 ± 0.09 mm), and Strat-M (0.30 ± 0.01 mm thickness) were utilized. Figure 2 compares the percutaneous absorption of zolmitriptan through full thickness, dermatomed *ex vivo* human skin, and Strat-M synthetic membrane over five hours.

The absorption of zolmitriptan from the two skin sources is markedly different. The time to maximum flux was much slower with the full thickness skin in comparison to the dermatomed skin. The time to maximum flux and the shape of the curve for the full thickness skin substrate are in stark contrast to what has been reported by Kellerman et al. [15] in a Phase 1 clinical study of ADAM zolmitriptan, where the median time to maximum drug plasma concentration was 20 minutes. The difference in the time to peak flux is that with *in vivo* skin, the tips of the microprojections would be very close to the capillary plexus of the dermis allowing for immediate release of drug into the blood stream. Full thickness i*n vitro* skin lacks the blood flow, resulting in the drug having to diffuse through the full dermis to the receptor solution. Utilization of dermatomed skin, where the lower region of the dermis, at the capillary bed, has been removed, is a better *in vitro* skin model as when the drug reaches that area, it finds the receptor solution rather than the capillary blood flow, which, in either case, provides sink conditions. The results indicate that the utilization of dermatomed skin resulted in the greatest extent of intracutaneous delivery in comparison to full thickness skin. That data suggests that the diffusion of zolmitriptan across the full thickness skin demonstrates how the dermis, without capillary flow, will result in a rate limiting step in absorption of microprojection mediated drug delivery [16] attributable to the increased

	Dermatomed Skin	
Receptor	85.46 ± 1.36	10.55 ± 6.15
Dermis	0.50 ± 0.04	---
Epidermis	0.43 ± 0.16	---
Stratum Corneum	0.13 ± 0.04	---
Surface Wash	2.57 ± 1.09	---
Strat-M Extraction	----	39.76 ± 19.75
Ti Array	3.27 ± 0.36	52.79 ± 29.28
Total Recovery	92.35 ± 2.48	103.1 ± 9.2

diffusional path length associated with the utilization of full thickness skin [17].

Figure 2 compares the percutaneous absorption of zolmitriptan through Strat-M synthetic membrane with that through dermatomed *ex vivo* human skin over five hours.

Though the Strat-M membrane and the dermatomed skin share a similar permeation curve profile, the peak flux for the Strat-M is significantly lower than that for the dermatomed skin. This phenomenon of very low absorption across synthetic membranes has been reported elsewhere and was attributed to the high elasticity of the synthetic membrane causing the microprojection to retract, such that microprojections do not reside within the created conduits [8]. In addition, adsorption of the zolmitriptan to compo-

nents of the synthetic membrane, *ca.* 40% of the applied dose recovered in the membrane versus <1% in the epidermal and dermal layers of the dermatomed skin, may also be a contributing factor. Consequently, the utilization of Strat-M membrane does not accurately depict the absorption *in vivo* and may lead to a significant underestimation of the drug release profile.

Table 1 shows the mass balance of 1.9 mg ADAM zolmitriptan that was administered to dermatomed skin and to the Strat-M membrane. In this case, for the skin, the total recovery was 92%, and the total absorbed zolmitriptan through the dermatomed skin to the receptor solution was found to be 85%.

Negligible amount of drug was found on the stratum corneum and on the titanium array after administration.

In stark contrast to the skin data presented in Table 1, the amount found in the receptor media for the Strat-M condition was *ca.* 11% of the nominal 1.9 mg zolmitriptan dose. The majority of the dose resided on the titanium array (*ca.* 53%), whilst the remainder was on the surface or within the Strat-M membrane (*ca.* 40%).

2. Conclusions

This study confirmed the influence of choice of *in vitro* experimental conditions on the rate and extent of permeation

of ADAM zolmitriptan. The results of the present study suggest that synthetic membranes such as Strat-M should be employed with caution when evaluating drug release from coated microprojections that are designed to deposit their drug locally *via* dissolution. Dermatomed skin may be not only a more representative measure of *in vivo* performance for drug-coated metallic microprojections, but also a more representative approach for most *in vitro* absorption studies.

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