AAPS PharmSciTech (2022) 23:198
https://doi.org/10.1208/s12249-022-02352-3

RESEARCH ARTICLE

Evaluation of an Anhydrous Permeation-Enhancing Vehicle for Percutaneous Absorption of Hormones

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Received: 4 May 2022 / Accepted: 29 June 2022

Abstract

The efficiency and safety of hormone delivery through the skin partly depend on the appropriate choice of vehicle and the type of formulation. The present study reports the skin cytotoxicity, irritancy, and safety of a newly developed anhydrous permeation-enhancing base (APEB) and the percutaneous absorption of progesterone, testosterone, estriol, and estradiol in APEB formulations. Using the human skin EpiDerm model, cell death was not observed after 4 h of exposure to APEB and was 48% after 24 h, indicating its mild to non-irritating property. APEB did not change the expression level of skin cell proliferation markers including PCNA, MCL-1, iNOS, and NFκB proteins, and apoptosis was minimal after 8-h exposure. The *in vivo* skin irritation and sensitization evaluation of APEB using a Human Repeat Insult Patch Test showed no adverse reaction of any kind during the course of the study. These results indicate the safety of APEB on skin tissues. The hormone percutaneous absorption was performed using human cadaver abdomen skin tissues and the Franz diffusion system, and hormone concentrations were determined by ELISA. Absorption was observed as early as 2 h of application and accumulated after 24 h to 2851 ± 66 ng/cm^2, 2338 ± 594 ng/cm^2, 55 ± 25 ng/cm^2, and 341 ± 122 ng/cm^2 for progesterone, testosterone, estriol, and estradiol, respectively. A steady flux rate of absorption of the hormones was observed within 24 h of application. These results suggest that APEB can be used as a vehicle to deliver these hormones through the skin and into the bloodstream for hormone replacement therapy.

Keywords Anhydrous base · Hormone replacement therapy · Progesterone · Testosterone · Estrogen

Introduction

Hormones are body chemical messengers secreted by the endocrine glands directly into the bloodstream to the targeted organ/tissue. Hormone deficiency affects development, growth, metabolism, homeostasis, and sexual function among others [1]; hence, hormone replacement therapy (HRT) is used for management of its symptoms. Replacement therapies for progesterone, estrogen, and/or testosterone are commonly used to treat menopausal symptoms such as hot flashes, night sweats, bone loss and fracture, vaginal discomfort, and mood and depressive disorders. The efficiency and safety of HRT partly depend on the method of delivery including oral, injection, nasal spray, or topical [2].

The inherent limitations of oral and parenteral delivery of hormones are usually overcome by transdermal delivery through percutaneous absorption. The latter method is a noninvasive self-administration with predictable pharmacokinetics and potentially better bioavailability because it avoids first-pass metabolism by the liver with fast onset of action [3]. For example, transdermal administration of progesterone and estrogen reduces the risk of venous thromboembolism compared with the oral route [4]. Oral formulations of testosterone have been linked with liver toxicity and fluctuations in testosterone levels [5] whereas testosterone transdermal gels and liquids provide more consistent serum testosterone levels [6]. The guideline from the National Institute for Health and Care Excellence (NICE) suggests that transdermal HRT is more cost-effective and efficacious than oral HRT for hot flushes and night sweats [7]. A common adverse effect of these transdermal formulations includes

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Published online: 19 July 2022

application site reactions, which underscores the importance of developing compounding bases for these hormones with improved safety.

Custom-formulated/compounded hormone preparations have become an alternative to FDA-approved drug products because they are tailored to fit a unique need of a patient including avoidance of a possible allergic reaction to an inactive ingredient, provision of an exact dose that may not be commercially available, preference for a certain flavor and texture, and access to discontinued or out-of-stock medications. Drug compounding is a valuable treatment option to patients who do not have access to a commercial drug that meets their individual needs [8]. Recent reviews of the literature show the clinical and therapeutic values of compounded progesterone, testosterone, estrogen, and other hormones in HRT [9, 10]. A potential factor that contributes to the efficacy of these compounded HRT is the base composition.

In the search for an optimized vehicle for topical hormone delivery, an anhydrous permeation-enhancing base (APEB, also called PCCA VersaBase® Anhydrous HRT [11]) was selected to evaluate the percutaneous absorption of progesterone, testosterone, estriol, and estradiol. Progesterone has been shown to be percutaneously absorbed using a similar vehicle called VersaBase® Cream (VBC), a topical cream base that simulates the natural moisturizing barrier of the skin through its emulsion system [12–15]. Compared with VBC that contains water, APEB has a water activity below 0.6 (Aw < 0.6), which is considered an anhydrous base [11–13]. It uses a unique, patent-pending delivery system designed to improve the solubility of lipophilic molecules, such as hormones.

In the present study, the skin cytotoxicity, irritancy, and safety of APEB and the percutaneous absorption of progesterone, testosterone, estriol, and estradiol in this base were determined using an *in vitro* dermatomed skin model.

Materials and Methods

Compounded Topical Formulation

The compounded formulation used in this study contained either APEB or VBC with 10% progesterone USP (PCCA Special Micronized), 0.1% testosterone USP Micronized CIII (Yam, PCCA), or 0.1% estriol/0.1% estradiol USP micronized (PCCA).

Evaluation of Toxicity/Safety of APEB

Tissue Viability Assay

The three-dimensional *in vitro* human EpiDerm system (EPI-200) was purchased from MatTek (Ashland, MA). It is an *in vitro*–reconstructed human epidermis model that contains normal human-derived epidermal keratinocytes that has been validated by the European Union Reference Laboratory (EULR ECVAM) as an alternative to the standard Draize test [16, 17]. Cultures were maintained with the supplied culture media according to the manufacturer's instructions. The EpiDerm tissues were exposed to 100 µL of APEB for 1, 4, 17, and 24 h (h) at 37 °C. Each sample was duplicated. Triton X-100 1% solution was used as a positive control. Tissues left not dosed were used as a negative control. Following the exposure period, the dosing materials were removed, and tissues were analyzed for cell viability.

Tissue viability was determined by measuring the reduction of 3-[4, 5-dimethylthiazol-2-yl]2,5-diphenyltetrazolium bromide (MTT) as previously described [18]. The tissues were evaluated for their ability to reduce soluble-MTT (yellow) to formazan-MTT (purple). An MTT solution was prepared following the instruction of the MatTek MTT-100 kit. At each time point, after the media and dosing solution were removed from all wells of the EpiDerm tissue, the MTT solution was added to the basal side of each tissue and the tissues were incubated at 37 °C for 3 h. The purple formazan product was extracted using the provided extractant applied to both the apical and basal sides of the tissues. The optical density (OD) of the samples was measured at 570 nm and 650 nm (reference OD) with a plate reader. Tissue viability acquired by MTT assay was reported as relative viability compared to 100% of the untreated control.

Western Blot Analysis

EpiDerm tissues exposed to APEB or Triton X-100 for 8 h were homogenized with a pellet mixer for approximately 1 min on ice, and the lysates were centrifuged at 14,000 rpm for 10 min at 4 °C. The supernatant was saved for protein analysis. Protein concentrations were determined using a bicinchoninic acid (BCA) Protein Assay kit (ThermoFisher Scientific, Inc.). Western blot analysis was performed as previously described [19].

In vivo Irritation Test

A Human Repeat Insult Patch Test (HRIPT) was performed by BioScreen Testing Services, Inc. (Torrance, CA) in 55 human subjects to evaluate the skin irritation and sensitization of APEB. BioScreen is registered with the US Food and Drug Administration (Registration number 2027219) and the Drug Enforcement Agency and it is ISO 9001-certified (certification number CERT-0123096). An informed consent was obtained from each volunteer prior to initiating the study, describing reasons for the study, possible adverse effects, associated risks, and potential benefits of the treatment and their limits of liability. Panelists signed

and dated the informed document to indicate their authorization to proceed and acknowledge their understanding of the contents. The parties agreed to comply with applicable state and federal privacy laws for the use and disclosure of a subject's personal health information by taking reasonable steps to protect the confidentiality of this information. Patches containing APEB were affixed directly to the skin of the intrascapular regions of the back, and the subjects were dismissed with instructions not to wet or expose the test area to direct sunlight. Patches remained in place for 48 h after the first application. The subjects were instructed not to remove the patches prior to their 48-h scheduled visit. Thereafter, the subjects were instructed to remove the patches 24 h after application for the remainder of the study. This procedure was repeated until a series of nine consecutive, 24-h exposures had been made three times a week for three consecutive weeks. Prior to each reapplication, the test sites were evaluated by trained laboratory personnel. Test sites were evaluated 48 h and 96 h after application. In the event of an adverse reaction, the area of erythema and edema were measured. Edema is estimated by the evaluation of the skin with respect to the contour of the unaffected normal skin. The subjects were instructed to report any delayed reactions that might occur after the final reading.

The scoring scale and definition of symbols shown below were based on the scoring scheme to the International Contact Dermatitis Research Group scoring scale [20].

1 no reaction (negative)
2 erythema throughout at least ¾ of patch area
3 erythema and induration throughout at least ¾ of patch area
4 erythema, induration, and vesicles
5 erythema, induration, and bullae

In Vitro Permeation Test of Hormones Compounded in APEB

Skin Preparation

Percutaneous absorption was measured using human cadaver abdomen skin tissue from Caucasian donors purchased from BioIVT (Westbury, NY, USA). The obtained dermatomed skin samples were stored at − 20 °C in tightly sealed plastic bags. Prior to use, the samples were defrosted and soaked in diffusion medium for at least 30 min at room temperature. The samples were visually checked for any significant damages, such as cuts or holes. Skin tissues from 3 donors and 3 replicates were used for each compounded formulation. No skin tissue was re-frozen to avoid the contributions of freeze–thaw to cell death.

Franz Cell Diffusion

The Franz diffusion system (surface area of 1.77 cm^2) was used in the study as previously described [12]. The diffusion cells were mounted in the diffusion apparatus, and the physiological diffusion medium was added to the receptor compartment. A skin integrity test was performed using a Precision LCR meter set at low voltage alternating current, and any skin sample exhibiting an electrical resistance < 4 kΩ was rejected and replaced. The electrical resistance cut-off value was derived from published data [21] as 4.0 kΩ corresponds to a tritiated water permeability coefficient of 4.5×10^{-3} cm/h [22]. The finite dose, approximately 5 mg/cm^2 of the compounded formulation, was applied on each skin sample using a positive displacement pipette and a pellet pestle to spread the product across the skin surface. Hank's balanced salt solution (HBSS #14,175–079, 25 mM HEPES, #15,630–080, and 50 µg/mL gentamicin, #15,750–060, Gibco) was used as diffusion medium to maintain the skin integrity during the experiment. The diffusion medium was stirred magnetically, and the skin surface temperature was maintained at 32 ± 1 °C. During the exposure period, samples of the diffusion medium (1 mL) were removed at predetermined time points: 2, 4, 6, 8, 12, and 24 h after applying the compounded formulations.

Hormone Quantification

The levels of progesterone, testosterone, estriol, and estradiol in the diffusion medium were determined by ELISA (Cayman, Ann Arbor, MI, USA) according to the manufacturer's instructions. The samples collected from the diffusion medium were diluted with ELISA buffer and adjusted later while calculating the concentrations. All samples were run in duplicate and mean values for each sample were used in the analysis. The sensitivities for progesterone, testosterone, estriol, and estradiol assay were 10 pg/ml, 6 pg/ml, 4 pg/ml, and 20 pg/ml, respectively. No samples were below the sensitivities.

Statistical Analysis

A two-way ANOVA was used to determine statistical differences among mean values of cumulative amount of permeant transported through the skin at each time point across test formulations and skin donors. Statistical analyses were performed using Analysis ToolPak in 2016 Excel. *P* values less than 0.05 were considered statistically

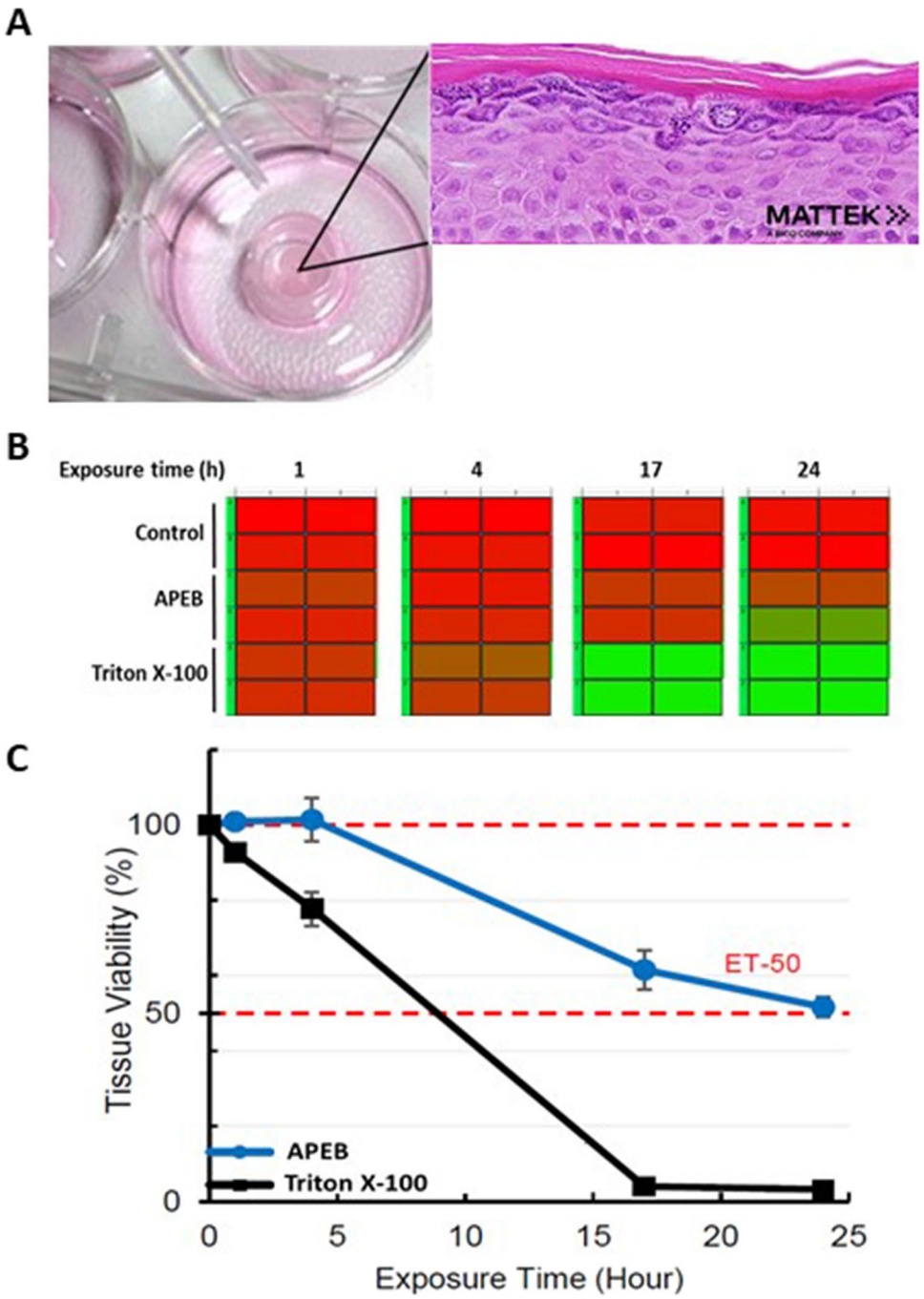

Fig. 1 Effects of APEB on skin cell viability and irritancy. **A** Illustration of the 3D tissue model of EpiDerm used in the study (with permission from MatTek Corporation). The tissue was exposed to APEB or 1% Triton X-100 (positive control), and cell proliferation was analyzed by the MTT assay after the indicated time points and results are presented as color-coded signals **B** and in graphical form **C**. ET-50 indicates the exposure time that results in 50% cell survival

significant. All results are expressed as mean ± SD of treatments in triplicates.

Results

APEB is Non-cytotoxic

Vehicles used to deliver drugs percutaneously should be non-irritating and non-toxic in order to minimize adverse effects and patient discomfort. We, therefore, sought to determine the cytotoxicity of APEB on the EpiDerm skin model (Fig. 1A). The application of APEB to EpiDerm did not affect cell proliferation after 4 h of exposure as suggested by the MTT assay (Fig. 1B, C). This was followed by a slow decline of tissue viability, and 48% cell death was observed after 24 h of base exposure. In contrast, 1% of Triton X-100, considered as a moderate-to-mild skin irritant and previously used positive control [18], caused 22% and 97% skin cell death after 4 h and 24 h of exposure, respectively (Fig. 1C).

The observed ET50 value of more than 24 h for APEB in EpiDerm tissues indicates that APEB can be classified very mild to non-irritating, equivalent to a baby shampoo, as suggested by MatTek Corporation (Table 1).

To further confirm the non-cytotoxic property of APEB, total cell extracts from treated EpiDerm were analyzed by Western blotting for changes in the level of some molecular protein markers commonly used for skin tissues. Exposure of EpiDerm to APEB for 8 h did not significantly affect the protein level of proliferating cell nuclear antigen (PCNA) relative to the control. In contrast, exposure of EpiDerm to Triton X-100 obliterated the expression of PCNA (Fig. 2). A similar status of MCL-1, a pro-survival protein, was observed. The effects of APEB on the status of inducible nitric oxide synthase (iNOS), which is important for keratinocyte proliferation and epidermal permeability barrier homeostasis [23], were also examined. APEB did not change the level of iNOS whereas Triton X-100 inhibited its expression after 8 h (Fig. 2). A similar lack of effect of APEB on the level of proliferation-related protein NFκB [24] was observed.

Table 1 ET50 values used for grouping irritancy responses obtained using EPI-200 tissues

ET50 (h)	Expectedinvivo irritancy	Examples
< 0.5	Strong/severe, possible corrosive	Nitric acid
0.5–4	Moderate	1% sodium dodecyl sulfate
4–12	Moderate to mild	1% Triton X-100
12–24	Very mild	Baby shampoo
24	Non-irritating	10% Tween 20

Permission to use the data was granted by MatTek Life Sciences

The effects of APEB on the activation of apoptosis were then examined by determining changes in the level and modification of known molecular death markers. Cleavage of caspase 3 (Casp 3) is known to trigger a cascade of events leading to apoptosis [25]. Exposure of EpiDerm to Triton X-100 for 8 h markedly induced the cleavage of caspase 3, which was not observed in the APEB-treated tissue (Fig. 2). This activation by cleavage of Casp 3 is known to lead to cleavage of PARP1 [26]. APEB slightly induced cleavage of PARP1 after 8-h exposure. On the other hand, Triton X-100 significantly induced cleavage of PARP1 after 8 h and further cleavage to shorter peptide was observed (Fig. 2).

To evaluate the *in vivo* skin irritation and sensitization activity of APEB, an HRIPT was performed. There were 55 subjects who completed the study, and no adverse reaction of any kind was observed during the course of the screening (Table 2). There were seven subjects with a grade 1 reaction, four subjects with a delayed grade 1 reaction, and two subjects with a delayed grade 2 reaction to the positive control (2.0% sodium lauryl sulfate solution). No subject showed any signs of reaction to deionized water (negative control). These results indicate that APEB is safe to human skin and has no potential to elicit dermal irritation.

Progesterone in APEB is Percutaneously Absorbed

We previously showed that the water-containing vehicle VBC facilitated penetration of progesterone through full-thickness skin following topical application using an in vitro model [12]. We sought to compare the progesterone absorption in formulations containing VBC and the anhydrous APEB using human cadaver abdomen skin tissues and the Franz diffusion system. Percutaneous absorption of progesterone was detected as early as 2 h after skin application, which continued to increase until the 24-h time point. After 24 h, the cumulative percutaneous absorption of progesterone facilitated by APEB was 2851 ± 66 ng/cm^2, which was significantly higher than 1867 ± 125 ng/cm^2 by VBC (Fig. 3A). A two-way ANOVA revealed that there was a statistically significant interaction ($P < 0.05$) between the effects of applied formulations (progesterone respective in APEB and VersaBase Cream) and time (2–24 h). A simple main effect analysis showed that progesterone respective in two formulations did have a statistically significant effect on the skin permeation of progesterone ($P < 0.001$). A simple main effect analysis showed that time did have a statistically significant effect on skin permeation ($P < 0.001$).

In order to understand what led to the significant difference in the absorption of progesterone, the rate of absorption (flux rate) was determined. The rate of percutaneous absorption showed a rapid penetration upon application, and the maximum flux was achieved at approximately 7 h post-application in both formulations, followed by a slow decline (Fig. 3B). The mean flux profiles of progesterone were similar in both compounded formulas, except for the absorption rate, which declined slower in APEB than VBC after 12 h. The flux rate of progesterone in VBC decreased between 10 and 18 h after application. In contrast, the flux rate of progesterone in APEB did not change between the same periods. These results indicate that APEB can maintain a steady flux rate, resulting in a higher total percutaneous absorption of progesterone.

Testosterone Has Similar Absorption Profiles in APEB and VBC Formulations

Comparison of the rate of testosterone absorption in the two compounded formulations showed rapid penetration upon application (Fig. 3C), and the maximum flux rate was achieved at approximately 4–6 h post-application, followed by a slow decline (Fig. 3D). After 24 h, the percutaneous

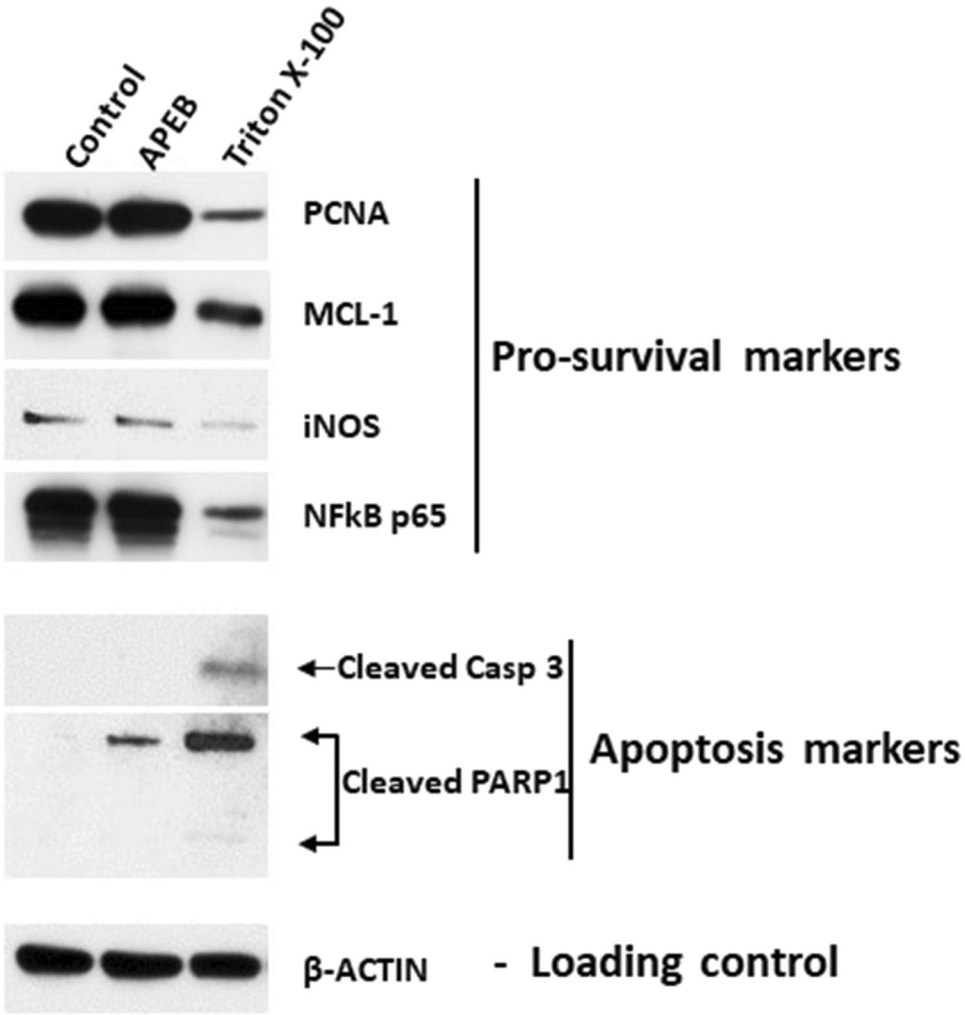

Fig. 2 Western blot analysis of skin cells exposed to APEB and Triton X-100. EpiDerm tissues were exposed to either APEB or Triton X-100 and homogenized after 8 h. Total protein concentration was determined and lysates were analyzed by Western blotting

absorption of testosterone was 2338 ± 594 ng/cm^2 with APEB and 1901 ± 506 ng/cm^2 with VBC. A two-way ANOVA revealed that there was no statistically significant interaction ($P > 0.05$) between the effects of applied formulations (testosterone respective in APEB and VersaBase Cream) and time. A simple main effect analysis showed that testosterone respective in two formulations did not have a statistically significant effect on the skin permeation of testosterone ($P > 0.05$). A simple main effect analysis showed that time did have a statistically significant effect on skin permeation ($P < 0.001$). No statistically significant difference was observed in the single main effect of testosterone respective in two formulations, suggesting that the two bases have comparable capabilities in delivering testosterone into the skin.

APEB Facilitates Absorption of Estriol and Estradiol

The percutaneous absorptions of estriol and estradiol in APEB and VBC formulations were compared. Both estriol and estradiol were detected across the dermis as early as 2 h after skin application, and the amount continued to increase; after 24 h, the cumulative absorptions of estriol facilitated by APEB and VBC were 55 ± 25 ng/cm^2 and 16 ± 5 ng/cm^2, respectively (Fig. 3E). The 24-h absorption of estradiol was six times higher in APEB (341 ± 122 ng/cm^2) than in VBC (157 ± 28 ng/cm^2) (Fig. 3G). There was no statistically significant interaction between the effects of applied formulations (APEB and VersaBase Cream) and time for both estradiol and estriol using a two-way ANOVA. A simple main effect analysis showed that time did have a statistically significant effect on skin permeation for both estriol and estradiol formulations ($P < 0.05$ for estriol and $P < 0.001$ for estradiol). A simple main effect analysis showed that estriol respective in two formulations did have a statistically significant effect on the skin permeation of ($P < 0.05$) but did not have a statistically significant effect for estradiol formulations ($P > 0.05$).

Analysis of the rate of estrogen absorption showed rapid penetration and maximum flux of absorption 6–8 h post-application. Steady flux was observed until 24 h, with the two bases showing similar trends although APEB delivered

Table 2 Population demographics and reactions of subjects enrolled in HRIPT

Number of subjects enrolled	60
Number that completed the study	55
Age range (yrs)	19–65
Sex	
Male	7
Female	48
Fitzpatrick skin type*	
1—always burns, does not tan	3
2—burns easily, tans slightly	7
3—burns moderately, tans progressively	22
4—burns a little, always tans	23
5—rarely burns, tans intensely	0
6—never burns, tans very intensely	0
Subjects with no reaction to APEB	55
Subjects with reaction to 2% SDS	
Grade 1	7
Delayed grade 1	4
Delayed grade 2	2

*Agache P, Hubert P. Measuring the skin. Springer-Verlag, Berlin, Heidelberg, 2004, p. 473

Discussion

The demand for efficacious, safe, and convenient topical HRT continues to increase. In this study, APEB developed specially for topical hormone delivery is characterized. The results suggest that APEB is safe for dermal application, and the base facilitates the percutaneous permeation of the hormones, suggesting that despite the anhydrous property of the vehicle, the lipophilic hormones are released from the base and permeate through the skin.

The correlation between in vivo and in vitro irritancy response can be extrapolated by the ET50 values (exposure time with 50% cell survival) as suggested by MatTek Corporation [29] and shown in Table 1. Based on this correlation, the observed ET50 of ~ 24 h for APEB (Fig. 1C) indicates that skin tissues exposed to this base were above the irritation classification threshold and it is considered non-irritating. These results are supported by the patch test in human volunteers; no adverse reaction was observed among the 55 subjects tested.

This non-irritating property of APEB is consistent with the observed minimal change in the levels of molecular protein markers of cell proliferation and apoptosis in cells exposed to the base (Fig. 2). Specifically, the status of pro-

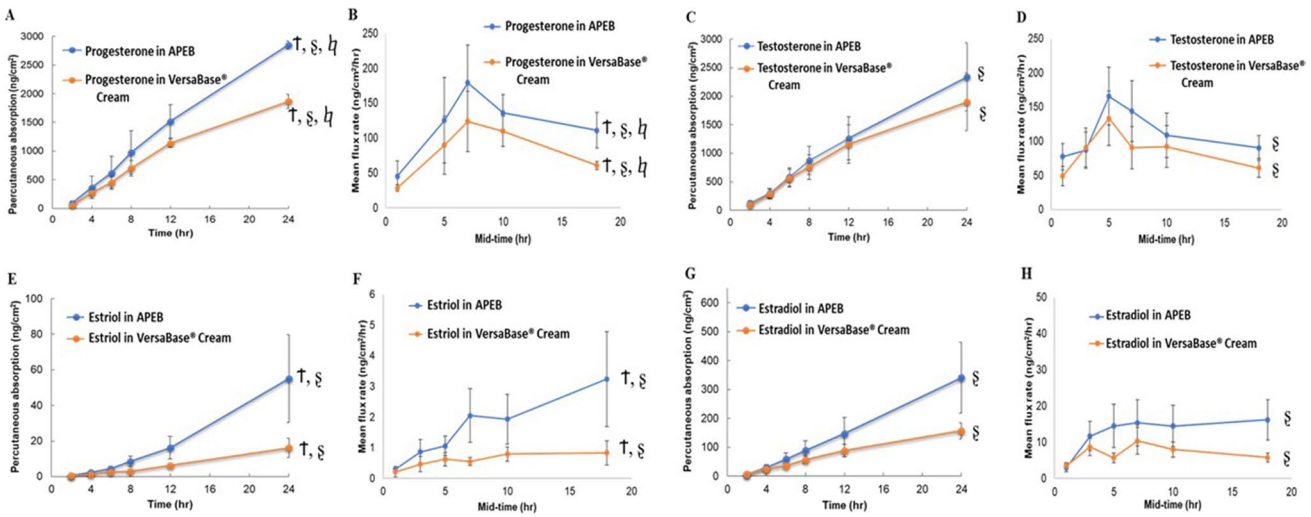

Fig. 3 Comparison of skin absorption of hormones in APEB and VBC compounded formulations. The percutaneous absorption and mean flux rate of progesterone **A**, **B**, testosterone **C**, **D**, estriol **E**, **F**, and estradiol **G**, **H** were determined as described under "Materials and Methods". ŧ, ş, and ɧ indicate $P < 0.05$ for main single effect of formulations, and time, and the interaction effect of formulation and time, respectively

more estrogens than VBC, but not in a statistically significant manner (Fig. 3F, H). The total amount of percutaneous estrogen absorption and flux rate observed in this study are consistent with previously published data [27, 28] and suggest the relevance of APEB as a base for estrogen formulations for topical application.

survival proteins PCNA, MCL-1, iNOS, and NFκB did not change in the skin model exposed to APEB. PCNA protein is a well-accepted marker of cell proliferation; it associates with various proteins to facilitate DNA replication [30]. MCL-1, on the other hand, is a pro-survival mitochondrial

protein, which interacts and antagonizes pro-apoptotic proteins [31]. The inducible NOS (iNOS) catalyzes the synthesis of nitric oxide, which regulates cutaneous functions through stimulation of keratinocyte proliferation [23], and although NFκB is involved in inflammatory and immune responses, it also plays a pivotal role in skin cell proliferation [32, 33]. The lack of change in the expression of these proteins in this skin model (Fig. 2) indicates that APEB does not inhibit skin cell proliferation. These results are consistent with the effects of APEB on pro-apoptotic proteins. Caspase 3 and PARP1 proteins were cleaved within 8 h of exposure of skin tissue to Triton X-100 in contrast to APEB exposure (Fig. 2).

After showing the safety of APEB on skin cells, its possible application on HRT was then determined. The percutaneous permeation mean flux rate for progesterone and testosterone peaked after 5–7 h, and started to decline and reached ~ 100 ng/cm^2/h after 18 h (Fig. 3B, D). A similar trend was observed for the percutaneous absorption of estriol and estradiol, and their mean flux rate continued to increase albeit at a slow pace within 18 h (Fig. 3E, H). The systemic effectiveness of these formulations in producing therapeutic hormonal effects is outside the scope of this study and remains to be determined.

Previous in vitro and in vivo studies have shown that VBC can efficiently deliver progesterone, testosterone, estriol, and estradiol through the skin [12–15]. Results of this study show that APEB is a better vehicle than VBC for percutaneous absorption of hormones used in HRT. The ingredients phosphatidylcholine and jojoba esters in APEB, which are not present in VBC, may have permeation-enhancing effects [34, 35]. As an anhydrous base, APEB provides a better solubility for lipophilic hormones and an unfavorable environment for microbial growth and, therefore, allows extended default beyond-use dates (BUDs) without compromising drug delivery capabilities.

The study has its own limitations including the number of samples used in the in vitro evaluations and the number of human subjects in the HRIPT analysis. Better statistical power and more significant results are obtained with greater numbers. In vitro evaluations cannot fully reproduce the complexity of biological systems, and the results are considered only a prediction of the in vivo skin absorption [36]. Moreover, anatomical site, skin hydration, and age of the person are important factors that may affect the skin absorption of hormones compounded in APEB [37].

Although a clinical trial for hormone delivery using APEB as a vehicle is warranted, compounding pharmacists and physicians will now have a better option in using APEB for compounded topical hormones for HRT. Based on the need of the pharmacy compounding industry to focus on the role of water activity in establishing beyond-use dates for compounded medications, the described efficient percutaneous absorption of progesterone, testosterone, estriol, and estradiol in APEB formulations indicates that this base can be used to maximize efficiency.

Conclusions

The in vitro and in vivo results of this study suggest that APEB is non-toxic to human skin cells and can be used as an effective vehicle for topical hormone delivery. APEB facilitates the percutaneous absorption of progesterone, testosterone, estriol, and estradiol without quick peaking or declining, which is one of the desired characteristics for an ideal hormone delivery base. Based on the presented results, APEB could provide a reliable option to compounding pharmacists, and practitioners may also consider these formulations as a viable route of hormone administration for patients undergoing HRT.

Acknowledgements The authors would like to thank BioScreen Testing Service, Inc. (Torrance, CA) for conducting HRIPT for skin irritation and sensitization.

Author Contribution G. Song, K. Ip, H. Song, and B. Valdez contributed to the conception and design of the study and analysis and interpretation of data. G. Song, Y. Liu, and B. Valdez wrote the manuscript. D. Banov and A. Bassani were responsible for the research approach, funding, analysis of data, and critical revision of the article. All of the authors contributed to the final version of the manuscript.

Funding This work was supported by Professional Compounding Centers of America (PCCA), the manufacturer of APEB and VersaBase Cream.

Declarations

Conflict of Interest The authors G. Song, D. Banov, H, Song, Y. Liu, K. Ip, and A. Bassani are employees of PCCA, the manufacturer of the proprietary bases VersaBase® Cream (VBC) and anhydrous permeation-enhancing base (APEB).

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