

ORIGINAL ARTICLE

Reduced skin permeation and penetration of clobetasol propionate when Dermovate cream is applied at short time intervals with emollients

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Abstract

Background: Dermovate cream containing 0.05% clobetasol propionate is a very potent topical corticosteroid (TCS) used in the treatment of severe inflammatory dermatoses. Regular emollient therapy should continue alongside clobetasol propionate treatment, however, the impact on drug delivery to the skin when both products are applied at similar times is unknown.

Objectives: To assess whether application of emollients at similar times to Dermovate cream alter the delivery of clobetasol propionate to the skin.

Methods: This study was conducted using ex vivo human skin mounted in Franz cells. Dermovate cream was applied before or after three different emollients, Hydromol Intensive cream, Doublebase gel, and Diprobase ointment at 5- or 30-min intervals. Drug delivery to the skin was assessed up to 24 h using high-performance liquid chromatography.

Results: Significantly reduced clobetasol propionate delivery to the skin was observed when Dermovate cream was applied either before or after the three different emollients, compared to the application of Dermovate cream alone. The data suggest in situ formation of a mixed Dermovate cream and emollient layer which reduces clobetasol propionate delivery relative to the original product. Applying Dermovate cream after any emollient generally resulted in larger reductions in drug delivery to the skin, compared to when the steroid was applied first. This was attributed to the emollients forming an additional barrier to drug delivery at the skin-formulation interface.

Conclusions: These findings indicate that applying Dermovate cream at similar times as emollients can significantly reduce drug delivery to the skin and that separating the application of the two products by intervals of up to 30 min is not sufficient to mitigate this effect.

KEYWORDS

clobetasol propionate, emollient, order of application, skin permeation, time interval

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INTRODUCTION

Dermovate cream (0.05% wt/wt clobetasol propionate) is classified as a very potent topical corticosteroid (TCS) in the United Kingdom. Treatment with this TCS is typically only initiated in cases unresponsive to treatment with lower potency classes because of the increased risk of associated side effects such as hypothalamus pituitary adrenal axis suppression and skin atrophy.¹⁻⁴ Though TCSs are often prescribed alongside emollients, there is a lack of consensus for which product should be applied first, or the appropriate time interval between product applications owing to a paucity of evidence.⁵ Given that the prevailing approach to optimise drug delivery to the skin is through careful selection of drug content and excipients within a formulation to optimise drug release and absorption, in situ alterations in the levels of these when multiple products are applied to the skin may alter the expected drug delivery of TCSs to the skin. This is a particular concern for very potent TCSs which have a higher risk of associated side effects. Indeed, recent work has demonstrated that applying a potent TCS and various emollients to the skin at short time intervals (≤ 30 min) can significantly alter the TCS formulation design in situ and consequently the expected delivery profile of mometasone furoate to human skin.⁶ Dermovate cream contains 47.5% wt/wt propylene glycol, an excipient known to be a penetration enhancer and thus often crucial for achieving sufficient drug delivery to the skin and providing the expected pharmacodynamic skin blanching response.⁷ The concentration of this excipient in a formulation can have a large impact on drug delivery into the skin.⁸⁻¹⁰ However, the effect of applying emollients at similar times, which could effectively alter the formulation on the skin surface and the drug delivery performance of this type of formulation has not been previously elucidated. Performing clinical studies to evaluate these effects is prohibitively expensive and so here we have used Franz cells, mounted with ex vivo human skin to understand whether changes in drug absorption occur. This approach is widely used by the pharmaceutical industry to understand the impact of formulation composition on drug delivery to the skin or to evaluate bioequivalence between formulations and it can provide insight into the effect of emollients on clobetasol propionate absorption from Dermovate cream.¹¹ It has also been used to inform medical affairs answers to post approval questions on how to apply emollients when patients are being treated with the nonsteroidal phosphodiesterase 4 inhibitor, crisaborole.¹² Three marketed emollient products, Diprobace ointment, Doublebase gel, and Hydromol Intensive cream, which have different compositions were selected to provide an

indication of the effects different types of emollients may have when applied to the skin at short time intervals (≤ 30 min) with Dermovate cream.

MATERIALS AND METHODS

Materials

Micronised clobetasol propionate (Ph Eur) was provided by MedPharm Ltd (Guildford). Dermovate cream (0.05% wt/wt clobetasol propionate), Diprobace ointment, Doublebase gel, and Hydromol Intensive cream were acquired from the University of Hertfordshire Campus Pharmacy (Hertfordshire). Phosphate-buffered saline (PBS) tablets, acetonitrile (high-performance liquid chromatography [HPLC] grade), absolute ethanol (99+%) glycerol, liquid paraffin, isopropyl myristate, Arlatone G (castor oil), and propylene glycol were acquired from Fisher Scientific.

Quantitative analysis of clobetasol propionate

Quantitative analysis of clobetasol propionate was achieved using HPLC with an Agilent 1260 Infinity system, a Hypersil™ C₁₈ column (5 μ m particle size, 250 mm \times 4.6 mm; Phenomenex) and a UV detection wavelength of 235 nm. The sample injection volume, flow rate and column temperature were 20 μ L, 1 mL/min $21 \pm 2^\circ\text{C}$, respectively. The mobile phase composition was water (18.2 M Ω MilliQ) and acetonitrile (HPLC grade). Clobetasol propionate eluted at 15.9 min under the following gradient conditions: 35% acetonitrile from 0 to 5 min, 35%–95% acetonitrile from 5 to 17 min, 95%–35% acetonitrile from 17 to 19 min, 35% acetonitrile from 19 to 22 min. The HPLC method was fit for purpose with respect to linearity ($r^2 > 0.999$), precision ($< 2\%$ RSD), accuracy ($< 2\%$) and sensitivity (the limit of detection was 0.1 $\mu\text{g/mL}$ and the limit of quantification was 0.3 $\mu\text{g/mL}$), in accordance with current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

Solubility studies

The saturated solubility of clobetasol propionate in the main solvent systems of Dermovate cream, Diprobace ointment, Doublebase gel, and Hydromol Intensive cream was determined. The solvents were: water, glycerol, liquid paraffin, isopropyl myristate, Arlatone G

(castor oil), and propylene glycol. Saturated solutions were prepared as follows: adequate amounts of clobetasol propionate were added to the range of solutions until a suspension was formed (confirmed visually by the continued presence of drug particles in solution). Samples were stirred for 24 h at room temperature, filtered and appropriately diluted in mobile phase before drug quantification by HPLC UV analysis.

Skin preparation

Excised human scrotal skin was obtained with informed consent from gender reassignment surgeries following ethical approval from the South London Research Ethics Committee (ethics No. 10/H0807/51). Skin samples from six donors aged over 18 years old were removed from storage (-20°C) and left to thaw at ambient temperature, the subcutaneous fat was removed using a scalpel and samples were stored at -20°C until required.

Ex vivo finite dose percutaneous absorption and skin distribution studies: Clinical application protocols

Percutaneous absorption of clobetasol propionate

Individually calibrated upright unjacketed Franz diffusion cells (Soham Scientific) were used with an average volume of 3 mL and diameter of 1 cm. Skin samples were mounted between the donor and receiver chambers of Franz cells, the receiver chamber was filled with PBS and ethanol (7:3) and Franz cells were equilibrated in a water bath at 37°C for 0.5 h (to achieve a skin surface temperature of 32°C). Six replicates were performed for each formulation investigated with skin samples from different donors distributed across the different experiments to minimise any effect of skin donor variability on the data. Skin samples were dosed, using a calibrated positive displacement pipette, with $10\ \mu\text{L}$ of Dermovate cream alone or $10\ \mu\text{L}$ of Dermovate cream 5 min before an emollient (CAP1), 5 min after an emollient (CAP2), 30 min before an emollient (CAP3), or 30 min after an emollient (CAP4). The dose applied for each emollient (Diprobase ointment, Doublebase gel, or Hydro-mol Intensive cream) was $10\ \mu\text{L}$. To ensure contact with the membrane, the product was carefully spread over the surface of the skin with five clockwise, then anticlockwise, motions using the tip of a capillary piston. Samples of the receiver fluid were withdrawn

at intervals up to 24 h and replaced with fresh preheated receiver fluid. Drug quantification was achieved using HPLC-UV.

Skin distribution of clobetasol propionate

After 24 h, Franz cells were disassembled and the residual formulation was removed from the donor chamber and skin surface by three sequential wipes with cotton buds (a dry cotton bud, a cotton bud soaked in acetonitrile then a final dry cotton bud) and two tape strips (Scotch Tape strips, 3M Center) of the skin surface.

The epidermal and dermal layers of skin samples were heat separated by placing the skin in an oven set to 60°C for 1 min before carefully peeling the epidermis and dermis apart. The skin layers were then placed in individual vials and the drug was extracted in aliquots of acetonitrile. Vials containing the samples were sonicated for 20 min then placed on a roller mixer (Cole-Palmer) for 18 h. The extraction fluid was filtered and analysed using HPLC-UV.

Data treatment and statistical analysis

Scientist[®] 3.0 (Micromath Inc.) was used to calculate the apparent partition (Kh) and diffusion (D/h^2) parameters when the Laplace transformation solution to Fick's second law, under finite dose conditions, was fit to the experimental permeation datasets as described previously.¹³ The drug concentration in the formulation was set to 0.05% for the application of Dermovate cream alone and the clinical application protocols (where Dermovate cream is applied before of after and emollient) or 0.025% when Dermovate cream was applied in the premixed TCS and emollient systems. The pseudo steady state drug flux (J_{ss}) for drug permeation were estimated as previously described using Equation (1).

$$J_{ss} = \frac{D}{h^2} \times Kh \times C_v. \quad (1)$$

Statistical analysis was performed using Prism 8.0 (GraphPad, USA). The Shapiro-Wilk test was employed to determine the normality of all datasets. Nonparametric analysis for multiple comparisons was performed using Kruskal-Wallis and a Mann-Whitney test applied for post hoc analysis. Statistical differences were accepted at the 95% confidence interval ($p \leq 0.05$).

RESULTS AND DISCUSSION

The effect of emollients on clobetasol propionate delivery to the skin from Dermovate cream

Figure 1 shows clobetasol propionate delivery to the epidermis, dermis and the receiver fluid following the application of Dermovate cream alone and with three emollients according to the four investigated clinical application protocols to human scrotal skin. The total drug delivery (total drug content in the epidermis, dermis, and receiver fluid) was used for statistical analysis as an indication of the change in total clobetasol propionate absorption compared to the application of Dermovate cream alone. Across emollient groups, total drug delivery to the skin invariably decreased by up to circa 4.5-fold when compared to Dermovate cream alone, regardless of the clinical application protocol ($p < 0.05$). Dermovate cream premixed with the emollients immediately before application also significantly reduced drug delivery to the skin by approximately twofold to threefold compared to Dermovate cream alone ($p < 0.05$; Figure 1). Previous work has demonstrated that in situ mixing of a saturated TCS formulation with different emollients

resulted in a range of complex formulation changes which increased or decreased drug delivery to the skin to varying extents.⁶ Applying crisaborole ointment 15 min before an emollient was found to prevent the decreased absorption observed when the crisaborole ointment was applied after an emollient.¹² In this study, administration of Dermovate cream with Diprobace ointment, Doublebase gel, or Hydromol Intensive cream in situ across 5- or 30-min intervals or before application invariably reduced clobetasol propionate delivery to the skin.

The skin permeation of clobetasol propionate from Dermovate cream alone or when applied with emollients is presented in Figure 2 and show permeation profiles typical of finite dose experiments.¹⁴ Consistent with the skin penetration studies, total drug permeation (Q_{24}) was greatest following the application of Dermovate cream alone, with 65% of the applied dose delivered to the receiver fluid over 24 h. Dermovate cream applied with either Diprobace ointment, Doublebase gel, or Hydromol Intensive cream resulted in significantly lower Q_{24} compared to Dermovate cream alone (14%–50% of the applied dose; $p < 0.05$). The Laplace transformation solution to Fick's second law was fitted to the skin permeation data as previously described¹³ and provided mechanistic insight into how clobetasol propionate

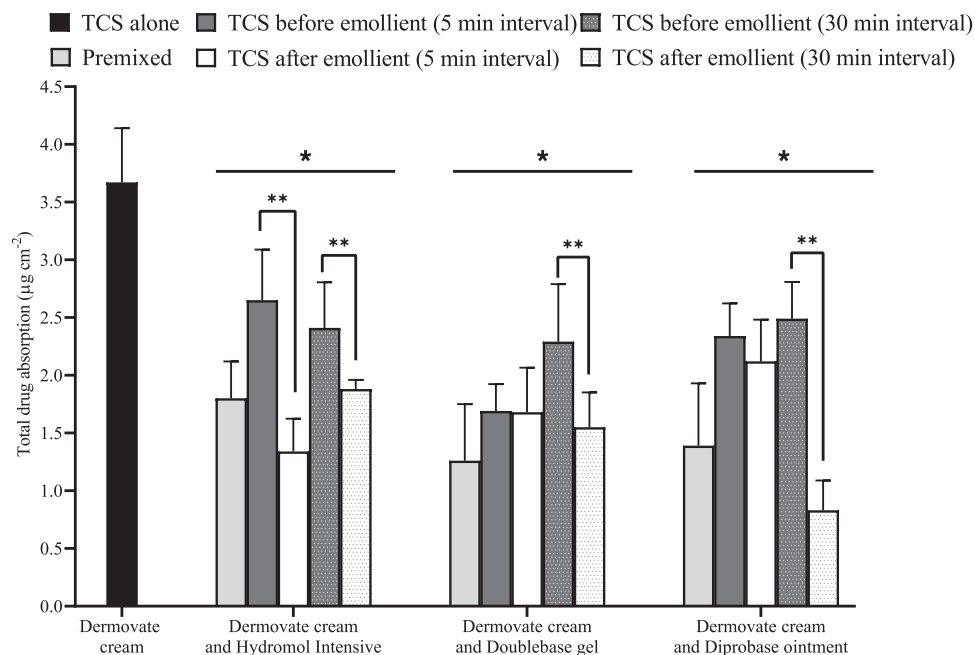


FIGURE 1 Skin distribution and percutaneous absorption of clobetasol propionate. Drug delivery to the epidermis, dermis and receiver fluid from a finite dose of Dermovate cream alone, Dermovate cream premixed with an emollient (1:1), and Dermovate cream applied according to a clinical application protocol (CAP). CAP1: TCS 5 min before an emollient, CAP2: TCS 5 min after an emollient, CAP3: TCS 30 min before an emollient, CAP4: TCS 30 min after an emollient. The emollients were Hydromol Intensive cream, Doublebase gel and Diprobace ointment. Data are shown as mean \pm SD ($n = 6$). * $p < 0.05$ when compared to the total drug recovered from Dermovate cream alone. ** $p < 0.05$ when comparing the effect of the order of application on total drug delivery to the skin (CAP1 with CAP2 or CAP3 with CAP4).

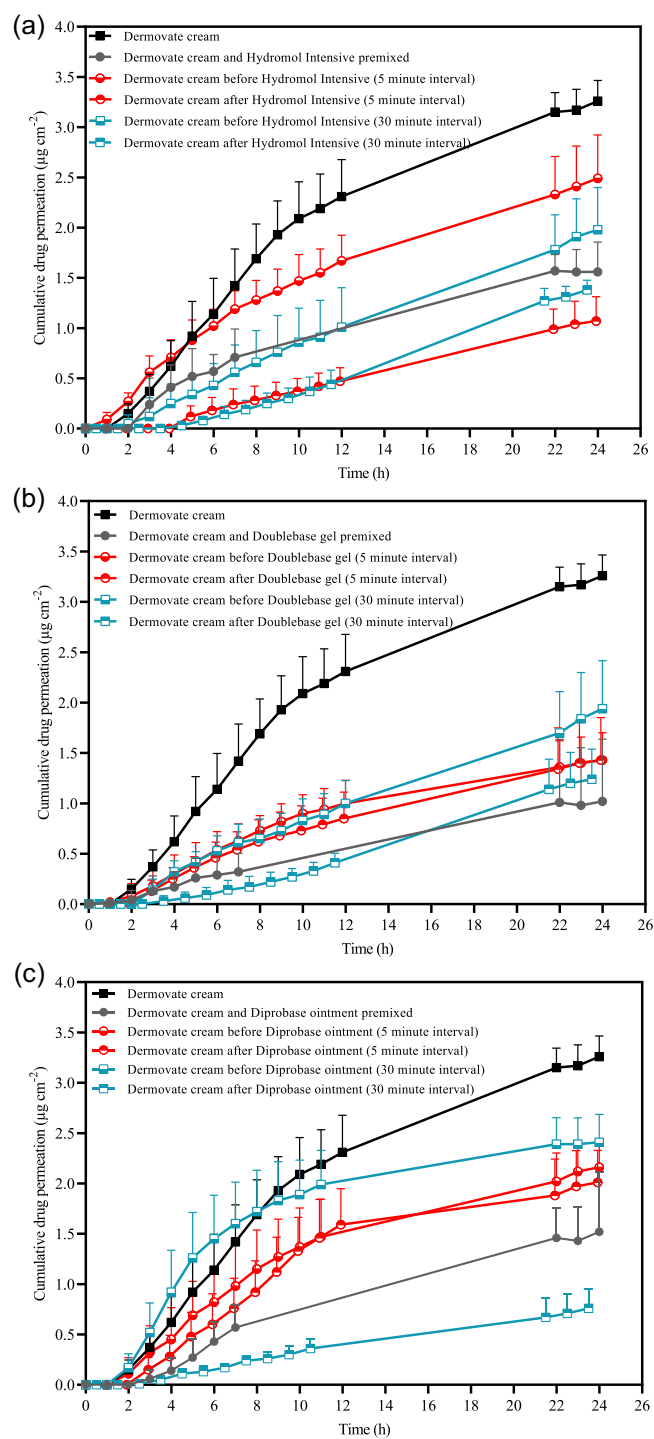


FIGURE 2 Clobetasol propionate permeation across ex vivo human skin. The cumulative amount of clobetasol propionate ($\mu\text{g}/\text{cm}^2$) permeated over 24 h across human skin from Dermovate cream when a finite dose was applied alone (\blacksquare), in a premixed system (1:1; \bullet); 5 min before an emollient (\ominus), 5 min after an emollient (\oplus), 30 min before an emollient (\square) or 30 min after an emollient (\boxplus). The emollients were (a) Hydromol Intensive cream, (b) Doublebase gel, (c) Diprobase ointment. Data are shown as mean + SD ($n = 6$).

absorption was influenced in the presence of emollients. Representative model fittings of the data are shown in the Supporting Information S1. The apparent partition coefficient (Kh), apparent diffusion coefficient (D/h^2) and pseudo steady state drug flux (J_{ss}) for clobetasol propionate permeation from Dermovate cream alone, premixed systems or clinical application protocols are presented in Table 1. Across all clinical application protocols and premixed systems, decreases in drug flux were largely attributed to reductions in Kh from the formulations towards the skin, ranging from 2.3- to 7.2-fold when compared to Kh for Dermovate cream alone ($p < 0.05$). Dermovate cream is formulated with 47.5% wt/wt propylene glycol, a penetration enhancing solvent, known to be important for its delivery to the skin.⁷ The solubility of clobetasol propionate in propylene glycol and other solvents contained within Dermovate cream and the emollients are shown in Table 2. Drug delivery to and across the skin is typically a slow process and application of the Dermovate cream at short time intervals with the emollients may potentially form a mixed vehicle on the skin surface that could behave similarly to the premixed formulation. The lower absorption observed with the premixed formulation was also observed when the emollients were applied separately at short time intervals, even though the same dose of clobetasol propionate was applied to the skin as Dermovate cream alone. The effects of dilution of TCS formulations on drug delivery are known to be unpredictable, particularly if the diluent used is dissimilar to the TCS base.^{15–17} Considering the relatively high solubilising capability of propylene glycol for clobetasol propionate (8.4 mg/mL; Table 2) it is reasonable to assume that clobetasol propionate is present in a dissolved, thus subsaturated, state in Dermovate cream. In the presence of the emollients the saturation level of the drug in the mixed formulation on the skin surface, which provides the driving force for drug release from the formulation and into the skin would be expected to be altered relative to that of Dermovate cream. Some of the excipients contained within the emollients, such as isopropyl myristate (Doublebase gel and Hydromol Intensive cream) and Arlatone G (hydrogenated castor oil in Hydromol Intensive cream) are reasonably good solvents for clobetasol propionate (1.4 and 10.0 mg/mL, respectively) whereas others such as water and liquid paraffin are poor solvents (0 and 1.4 $\mu\text{g}/\text{mL}$, respectively) (Table 2). Thus it is difficult to estimate the effect of the emollients on the drug saturation in the mixed formulation as the emollients contain typically unreported amounts of different solvents with considerable

TABLE 1 Skin permeation parameters for clobetasol propionate when employing various clinical application protocols.

Time interval	Product 1	Product 2	D/h^2 (cm)	Kh (h ⁻¹)	J_{ss} (μg cm ⁻² h ⁻¹)
N/A	Dermovate cream alone		7.26E-02 ± 1.23E-02	1.46E-02 ± 1.64E-03	5.40E-05 ± 1.55E-05
Premixed Dermovate cream and Hydromol Intensive			1.54E-01^a ± 3.19E-02	2.60E-03^a ± 1.34E-04	1.01E-05^a ± 2.42E-06
5 min	Dermovate cream	Hydromol Intensive	1.44E-01 ^{a,b} ± 2.82E-02	6.02E-03 ^a ± 4.45E-04	4.34E-05 ^b ± 8.55E-06
	Hydromol Intensive	Dermovate cream	3.11E-02 ^{a,b} ± 5.56E-03	6.31E-03 ^a ± 3.63E-04	9.75E-06 ^{a,b} ± 1.52E-06
30 min	Dermovate cream	Hydromol Intensive	8.28E-02 ^b ± 2.01E-02	3.17E-03 ^{a,b} ± 3.02E-04	1.34E-05 ^a ± 4.29E-06
	Hydromol Intensive	Dermovate cream	1.93E-02 ^{a,b} ± 2.68E-03	1.66E-02 ^b ± 1.39E-03	1.60E-05 ^a ± 2.61E-06
Premixed Dermovate cream and doublebase gel			8.76E-02 ± 3.64E-02	2.66E-03^a ± 3.41E-04	5.86E-06^a ± 2.78E-06
5 min	Dermovate cream	Doublebase gel	7.18E-02 ± 1.59E-02	3.07E-03 ^{a,b} ± 1.45E-04	1.11E-05 ^a ± 2.81E-06
	Doublebase gel	Dermovate cream	9.30E-02 ± 2.90E-02	2.10E-03 ^{a,b} ± 1.81E-04	9.98E-06 ^a ± 3.80E-06
30 min	Dermovate cream	Doublebase gel	8.17E-02 ^b ± 1.48E-02	3.05E-03 ^{a,b} ± 1.73E-04	1.25E-05 ^a ± 2.53E-06
	Doublebase gel	Dermovate cream	1.74E-02 ^{a,b} ± 1.97E-03	1.62E-02 ^b ± 6.60E-04	1.41E-05 ^a ± 1.95E-06
Premixed Dermovate cream and Diprobase ointment			7.38E-02 ± 2.82E-02	7.23E-03^a ± 1.20E-03	1.39E-05^a ± 6.70E-06
5 min	Dermovate cream	Diprobase ointment	1.01E-01 ^a ± 1.04E-02	4.76E-03 ^a ± 1.03E-03	2.42E-05 ^a ± 5.98E-06
	Diprobase ointment	Dermovate cream	9.10E-02 ^a ± 1.44E-02	5.53E-03 ^a ± 1.91E-04	2.53E-05 ^a ± 4.87E-06
30 min	Dermovate cream	Diprobase ointment	1.94E-01 ^{a,b} ± 4.12E-02	2.42E-03 ^{a,b} ± 1.64E-04	2.33E-05 ^{a,b} ± 4.22E-06
	Diprobase ointment	Dermovate cream	4.46E-02 ^{a,b} ± 6.16E-03	2.03E-03 ^{a,b} ± 1.82E-04	4.52E-06 ^{a,b} ± 7.93E-07

Note: Data are shown as mean ± SD ($n = 6$).

Abbreviations: D/h^2 , estimated apparent diffusion coefficient; J_{ss} , pseudo steady state drug flux; Kh , apparent partition coefficient.

^aDenotes a significant difference when D/h^2 , Kh , and J_{ss} values were compared to the respective permeation parameters for Dermovate cream alone ($p < 0.05$).

^bDenotes a significant difference ($p < 0.05$) when comparing the effect of the order of application, within the same time interval, on permeation parameters.

TABLE 2 The solubility of clobetasol propionate in liquid excipients of investigated formulations.

Solvent	Solubility (μg/mL)
Water	0 ^a
Liquid paraffin	1.45 (0.38)
Glycerol	79.94 (8.14)
Isopropyl myristate	1468.40 (64.61)
Propylene glycol	8426.42 (128.36)
Castor oil	10,035.09 (321.73)

Note: Data are presented as mean of three replicates. The range is denoted in brackets.

^aNo drug detected on analysis.

differences in solubility for the clobetasol propionate. Propylene glycol is often employed as a co-solvent in formulations to alter both drug solubility in the vehicle and partitioning into the skin; the latter of which is thought to be achieved by the propylene glycol entering the stratum corneum and increasing drug solubility within this membrane.^{9,18} A strong concentration/saturation dependent effect of propylene glycol on drug permeation across human skin has been established.⁸⁻¹⁰ Thus, a decrease in propylene glycol concentration/saturation in a newly formed emollient and Dermovate cream mixed layer is likely to have contributed to the pattern of reduced drug delivery observed across emollient groups.

Comparisons of clinical application protocols: The impact of the order of product applications

Within emollient groups, the order in which the products were applied further impacted the magnitude to which drug delivery to the skin was reduced. As a general trend, applying Dermovate cream after a particular emollient resulted in significantly less drug delivery to the skin compared to the application of Dermovate cream before the same emollient. This decrease in drug delivery ranged from 1.3-fold when comparing Dermovate cream applied 30 min before and after Hydromol Intensive cream, to threefold when comparing Dermovate cream applied 30 min before and after Diprobace ointment (Figure 1; $p < 0.05$). This trend held for all application protocols with the exception of Dermovate cream applied five minutes before Doublebase gel or Diprobace ointment compared, respectively, to Dermovate cream applied 5 min after Doublebase gel or Diprobace ointment (Figure 1; $p > 0.05$).

Modelling of the permeation profiles largely attributed these further decreases in drug delivery to significant reductions in the apparent diffusion coefficient of the drug by up to 4.6-fold, when compared to Dermovate cream applied before the respective emollient within the same time interval ($p < 0.05$; Table 2). When Dermovate cream was applied to the skin after the emollients, it is likely that a residual layer of the emollient remained at the skin-formulation interface, above which a new 'mixed' formulation layer formed. Presence of this residual emollient layer may have created an additional barrier to drug permeation across this skin. This has been previously postulated as a reason to apply corticosteroids before emollient ointments.¹⁹ However, the data here does not provide support for the associated reasoning that TCS should be applied after emollient creams as these do not provide such a barrier.

In contrast to the prevailing pattern in the data, when Dermovate cream was applied 5 min before Hydromol Intensive cream, or 30 min before Diprosone ointment the drug flux at early time points was higher than that of Dermovate cream alone, despite a significant total decrease in drug delivery to the skin after 24 h. Nonlinear modelling of the permeation data attributed this to a significant circa twofold increase in the apparent diffusion parameter compared to Dermovate cream alone (D/h^2 ; $p < 0.05$). It is likely that that applying Dermovate cream before particular emollient products may result in an occlusive effect on drug permeation. This has the potential to increase the permeation rate of clobetasol propionate that had already started to be absorbed

into the stratum corneum before the relatively poor partitioning of the drug from the mixed TCS and emollient formulation layer reduces the permeation rate and overall delivery to the skin. This occlusive effect may also contribute to the observed differences in drug absorption resulting from different sequence of administration of the TCS and emollient. Occlusion by an emollient is thought to enhance permeation by increasing the hydration of the stratum corneum by reducing transepidermal water loss.²⁰ This causes the stratum corneum to swell, which can decrease its barrier properties to the permeation of drugs.

The work presented here has used human scrotal skin as a model membrane. The scrotum may be affected by atopic dermatitis and has been used previously for permeation studies.^{6,21,22} Scrotal skin is histologically similar to skin from other body regions, although it is typically more permeable to drugs.²³ The tissue still presents a barrier to drug penetration and although drug absorption may be relatively high, the insight gleaned from its use would be expected to be relevant for other body sites.²¹ The findings indicate that the application of an emollient with a very potent TCS, Dermovate cream, has the potential to significantly reduce drug delivery to the skin compared to Dermovate cream alone, regardless of the order in which the product are applied or whether 5- or 30-min time intervals are left between product applications. The data suggest a mixed layer of Dermovate cream and emollient was formed in situ which altered the formulation performance on the skin surface reducing drug delivery. Applying Dermovate cream after any emollient largely decreased drug delivery to the skin to a greater extent when compared to the application of Dermovate cream before the emollient with the same time interval. These effects are likely to result from the emollient providing an additional barrier to drug absorption if applied before the TCS and potentially providing an occlusive effect if applied afterwards. Leaving intervals of 30 min between product applications was not sufficient to mitigate formulation interaction effects on drug delivery. The clinical efficacy of Dermovate cream may be significantly reduced if patients apply the TCS at similar time intervals as emollients. Consideration could instead be given to leaving longer time intervals between applications of the different products, perhaps applying the TCS once a day to minimise the potential for any interaction between the different products.²⁴

AUTHOR CONTRIBUTIONS

M. T. Beebejaun: Conceptualisation; methodology; formal analysis; investigation; visualisation; writing—original draft. **M. B. Brown:** Conceptualisation;

supervision; writing—review and editing. **V. Hutter:** Conceptualisation; supervision **L. Kravitz:** Conceptualisation; supervision. **W. J. McAuley:** Conceptualisation; project administration, supervision, writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

W. J. McAuley: Received funding or support from GSK Consumer Healthcare (now Haleon), MedPharm Ltd., and Pangaea Laboratories. Other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Datasets related to this article can be found at <https://www.research.herts.ac.uk/admin/editor/dk/atira/pure/api/shared/model/researchoutput/editor/contributiontojournaleditor.xhtml?scheme=&type=&id=27886507> hosted at the University of Hertfordshire Research Archives. Datasets related to this article can be found at <https://www.research.herts.ac.uk/admin/editor/dk/atira/pure/api/shared/model/researchoutput/editor/contributiontojournaleditor.xhtml?scheme=&type=&id=36911445>.

ETHICS STATEMENT

The human skin used in this study was obtained with informed consent from surgical operations with ethical approval granted by the South London Research Ethics Committee (ethics no. 10/H0807/51).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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