

RESEARCH ARTICLE

Optimisation of a dosing regime for a topical skin protectant (barrier cream)

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Abstract

Context: Topical skin protectants (barrier creams) have the potential to reduce or enhance the severity of dermal lesions following exposure to allergens or irritants. Therefore, it is essential that such products are subject to appropriate clinical evaluation prior to marketing. Consequently, it is important to accurately define a dosing regime in order to assess test products under appropriate conditions.

Objective: In this study, we extended the use of a standard rubefacient (methyl nicotinate; MN) assay to establish the optimum thickness and duration of action of a novel barrier cream (RD1433). White petroleum jelly (Vaseline®) was used as a comparator product.

Methods: The dermal response to MN was measured on the volar forearm skin of volunteers ($n = 12$; average age 47.5 years) using an array of biophysical instruments and visual scoring. When applied at a nominal thickness of 0.1 mm, RD1433 retained effectiveness against MN for up to six hours. In contrast, Vaseline® was relatively ineffective. Moreover, RD1433 provoked no measurable signs of irritation and so can be considered acceptable for further clinical evaluation.

Conclusion: Future clinical studies using RD1433 should be based on topical application of a 0.1 mm thickness layer every six hours.

Keywords

Clinical study, human volunteer, methyl nicotinate, rubefacient, topical treatment, white petroleum jelly

History

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Introduction

Topical skin protectants (barrier creams) may provide an effective means of mitigating the effects of dermal exposure to irritants^{1–4} and can complement skin hygiene protocols associated with other eczematous conditions such as incontinence-associated dermatitis^{5–11}. However, the use of barrier creams can also have detrimental effects^{12–15} and so a robust evaluation of clinical efficacy is required prior to use which, in turn, requires that treatments are applied according to an appropriate, evidence-based dosing regime.

The composition of barrier creams varies considerably¹⁶, although classic (oil-in-water or water-in-oil) emulsions or silicone-based products probably represent the two most common types of commercial product. Within the last twenty years, perfluorinated formulations have been developed which appear to offer greater protection against the dermal absorption of very toxic materials^{15,17,18}. Moreover, the amphiphobic nature of perfluorinated formulations may confer protection against a wider range of compounds than traditional products and so may have clinical utility in the prevention or treatment of skin conditions such as IAD.

One such formulation is RD1433, a mixture of perfluoroalkyl ether and micro-particulate polytetrafluoroethylene.

The purpose of this study was to ascertain the optimum dosing regime for RD1433 prior to clinical assessment. This was achieved using a standard rubefacient (methyl nicotinate) assay to assess the protective effect of RD1433 at (1) different thicknesses and (2) following different durations of wear.

Materials and methods

This study was approved by the UK's National Research Ethics Service (North East – Northern & Yorkshire; protocol reference 12/NE/0255) and the Medicines and Healthcare Products Regulatory Agency (study reference CI/2012/0033) and was performed in compliance of the International Conference on Harmonization (ICH) Tripartite Guidelines on Good Clinical Practice (GCP) and Medical Device Regulations 2002 (SI No 618), as amended by the Medical Device Regulations 2008 and the EU Medical Device Directive 93/42/EEC (as amended by Directive 2007/47/EC). The study was listed with the International Standard Randomised Controlled Trial Number Register (Trial Number 74608958).

The test product (RD1433; a chemically inert, two-phase polymer system comprising particulate polytetrafluoroethylene dispersed in a liquid perfluoroalkyl ether [Fomblin® Y 25])

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was supplied by Bracco Diagnostics (Princeton, NJ). The comparator product (Vaseline[®]; white petroleum jelly BP) was purchased from a local pharmacy store (Boots, Welwyn Garden City, UK). Methyl nicotinate (purity >99%) was purchased from the Sigma Chemical Company (Dorset, UK).

A total of twelve (six male, six female), fair skinned (Fitzpatrick Type I and II) individuals (average 47.5 years, range 27–81) who provided informed consent were enrolled in the study which was conducted between October and December (late autumn–early winter) 2012 at the University of Hertfordshire. The medical history and current health of each volunteer was evaluated by a qualified physician in order to exclude individuals with any contra-indicatory skin disease, medical condition or medication (specifically, non-steroidal anti-inflammatories). Each volunteer was instructed not to apply any topical formulations (creams, lotions, sprays, etc.) to their forearms at least 24 h prior to participating in the study and not to wash their arms on the day of the study. A sample size of twelve was derived from a power calculation (StatMate v2.00, GraphPad Software Inc., San Diego, CA) of data from a previous study¹⁹ and was determined to be sufficient to detect a difference between treatments of ~10% at a power of 90% and a probability of less than 0.05. The study was limited to Fitzpatrick skin types I and II in order to limit experimental variation caused by the interaction of skin pigments with optical measurements of skin function (such as skin reflectance spectroscopy).

Study 1: Optimal thickness

Six skin exposure sites on the volar aspect of both forearms of each participant were marked with indelible ink (providing a total of 12 sites per volunteer). One site on each arm was untreated (control). The remaining five areas on each arm were treated with test products (either RD1433 or Vaseline[®]) applied at different nominal thicknesses (0.01, 0.02, 0.05, 0.1 or 0.2 mm). Thus, each volunteer was treated with five nominal thicknesses of Vaseline[®] and RD1433, with two (contralateral) controls. Each treatment (i.e. specific thickness of RD1433, Vaseline[®] or control) was assigned to a specific skin site using a pseudo-Latin square design. This ensured that no skin site received the same treatment and that the treatments were rotated around each available skin site to minimise the effects of anatomical variation²⁰. Treatment allocations were coded and randomly assigned to each participant. Application of treatments was performed by staff who did not take part in any other aspect of the study. The treatment code and allocations were not disclosed to the trial staff until all corresponding data had been analysed.

The volume (V) of test product required to achieve a nominal thickness (NT ; expressed in millimetres) was calculated according to Equation (1), where A was the surface area of the skin exposure site (3.8 cm^2). The resultant application volumes are given in Table 1.

$$V = \left(\frac{NT}{10} \right) \times A$$

Each test product was dispensed onto the appropriate skin site using a pre-weighed tip of a positive displacement pipette. The pipette tip was re-weighed after use to calculate the

amount of formulation delivered to the skin (dispensed dose). The formulation was then rubbed into the skin using a gloved finger; the finger glove was weighed before and after use to calculate the amount of formulation recovered from the skin surface (retained dose). The actual (as opposed to nominal) thickness of test product on the skin surface was calculated taking into account the difference between the “dispensed” and “retained” doses (assuming a density of 0.952 g cm^{-3} and 2.238 g cm^{-3} for Vaseline[®] and RD1433, respectively).

A baseline set of visual and biophysical measurements were taken 15 min before topical application of the test products. Visual measurements were scored according to a standard scale (Table 2). Biophysical measurements included laser Doppler imaging (LDI; Moor Instruments Ltd, Axminster, UK), infrared imaging (IRI; Model P620, FLIR, Ltd, West Malling, UK), tissue viability imaging (TiVi; TiVi 60, Wheelsbridge, Sweden), skin reflectance spectroscopy (SRS; 2600d, KonicaMinolta, Basildon, UK), pH (pH905, Courage and Khazaka, Cologne, Germany) and transepidermal water loss (TEWL; Aquaflux AF200, Biox Ltd, London, UK). The standardised use and operating principles of these instruments have been reviewed elsewhere^{21,22}. Further, non-contact measurements (visual scoring, LDI, IRI and TiVi) were acquired immediately after application of the test products. Skin contact measurements (i.e. SRS, pH and TEWL) were omitted at this stage in order to prevent interference with the physical integrity of the exposure sites (for example, displacement or removal of the test products).

Approximately 15 min after application of the test products, each site was exposed to a ($10\text{ }\mu\text{l}$) droplet of methyl nicotinate (MN; 5 mMol aqueous solution). The droplet of MN was left *in situ* for 20 min after which all skin sites were gently blotted with tissue paper to remove residual liquid. Visual scoring and non-contact biophysical measurements (LDI, IRI and TiVi) were then acquired from each site at regular intervals for up to 120 min. At the end of this period, the test products were physically removed from the skin surface using cotton-tipped sticks and the skin sites washed with warm water using a mild proprietary skin cleansing lotion and blotted dry with paper towels. The sites were then allowed to air dry for 60 min prior to a final set of visual and biophysical measurements.

Study 2: Optimal duration

The study was performed as described above on the same 12 volunteers (according to a randomised, double-blind design). However, the application of test products (applied at a nominal thickness¹ of 0.1 mm) was staggered (according to a pseudo-Latin square design) prior to MN exposure in order to establish a delay of 1, 2, 3, 4 or 6 h prior to the application of MN. During this time, volunteers were allowed to engage in activities requiring minimal physical activity such as reading, playing computer games or watching television. In order to minimise potential discomfort to the volunteers, the duration

¹A nominal thickness of 0.1 mm was determined following analysis of data arising from Study 1 and represented the minimum thickness of RD1433 which provided a significant protective effect against methyl nicotinate.

Table 1. Volumes of test products applied to skin to achieve nominal thickness.

Nominal thickness (mm)	Volume of product applied (μ l)
0.2	83.1
0.1	41.5
0.05	20.8
0.02	8.3
0.01	4.2

Volumes were calculated using Equation (1).

Table 2. Visual scoring system for assessing skin lesions.

Score	Appearance
0	None
1	Very slight
2	Well-defined
3	Moderate/Severe
4	Severe/eschar

over which the MN exposure was performed was reduced from 120 min to 60 min, as it was observed in Study 1 that the response to methyl nicotinate was generally complete within an hour.

Data for visual scoring, LDI, IRI and TiVi were initially plotted as a function of time and corresponding area under the curve (AUC) calculated using a proprietary software package (GraphPad Prism 6, version 6.03, San Diego, CA). Comparisons between treatments and control(s) were performed using one factor repeated measures ANOVA (where parametric assumptions were met), with Bonferroni-corrected *post-hoc* pairwise comparisons (where the ANOVA outcome was significant). Where one of the parametric assumptions was not met (as indicated by a sphericity assumption violation), the Greenhouse-Geisser corrected ANOVA was performed. Statistical analysis was performed using IBM SPSS Statistics v20 (Portsmouth, UK).

Results

Nominal and actual test product application thickness

There was a consistent disparity between the intended (nominal) thickness of test products and the actual thickness achieved when applied to the volunteers. On average, the actual thickness of Vaseline[®] and RD1433 was $73 \pm 5\%$ and $80 \pm 7\%$ lower, respectively, than the nominal thicknesses.

Determination of optimal application thickness

The thickest layer of Vaseline[®] (0.2 mm) was significantly more effective than that applied at 0.05 and 0.01 mm in reducing blood flow (Figure 1; horizontal bars). However, only the thickest (0.2 mm) layer of Vaseline[®] had a significant ($p < 0.05$) effect when compared to untreated (control) skin. In contrast, RD1433 was significantly effective for thicknesses ≥ 0.05 mm (Figure 1; asterisks) and blood flow at RD1433 treated skin sites was significantly lower ($p < 0.05$) than those treated with Vaseline[®] when compared at the same

thickness. The thinnest layer (0.01 mm) of RD1433 was significantly less effective than the three thickest layers (0.05, 0.1 and 0.2 mm) and the 0.02 mm layer was significantly less effective than 0.1 and 0.2 mm.

Vaseline[®] was ineffective at reducing visual erythema following exposure to MN when compared to control (untreated) skin (Figure 2). However, the thickest layer (0.2 mm) was statistically more effective ($p < 0.05$) than the thinnest layer (0.01 mm). Visual erythema was significantly reduced ($p < 0.01$) at the three thickest layers of RD1433 (Figure 2). The two thickest layers were significantly more effective than the three thinner layers ($p < 0.01$). Visual erythema at sites treated with RD1433 was significantly lower than skin treated with Vaseline[®] when compared at the same thickness ($p < 0.01$).

Vaseline[®] was only effective at preventing MN-induced erythema when applied at a thickness of 0.2 mm ($p < 0.05$; Figure 3) when compared to untreated (control) skin. Within treatments, the thickest layer was statistically more effective than the three thinnest layers (0.01, 0.02 and 0.05 mm). There was also a statistically significant ($p < 0.05$) difference detected between the 0.01 and 0.05 mm layers of Vaseline[®]. The three thickest layers of RD1433 significantly reduced erythema (Figure 3; $p < 0.01$) and these treatments were significantly more effective than the two thinnest treatments ($p < 0.01$). When measured using TiVi, erythema at sites treated with RD1433 was significantly lower than skin treated with Vaseline[®] when compared at the same thickness ($p < 0.01$).

There were no statistically significant treatment-related effects on skin temperature (IRI), skin reflectance spectroscopy (SRS) L^* , a^* and b^* parameters, skin surface pH or transepidermal water loss (TEWL).

Overall, RD1433 was significantly effective at reducing the rubefacient effects of MN at a thickness of 0.05 mm or greater (Table 3). In contrast, Vaseline[®] was relatively ineffective, only having an effect at a thickness of 0.2 mm. When compared at the same nominal thickness, RD1433 was consistently and significantly ($p < 0.05$) more effective in reducing the effects of methyl nicotinate than Vaseline[®].

Determination of optimal application frequency

When compared to control (untreated) skin, Vaseline[®] did not produce a statistically significant effect on MN-induced blood flow for any duration of application (Figure 4). Application of RD1433 significantly reduced blood flow following exposure to MN in comparison to control (untreated) skin sites (Figure 4). The level of significance was very significant ($p < 0.01$) for application durations of 1–3 h (prior to exposure of MN) and significant ($p < 0.05$) for the 4 and 6 h duration of application. No statistically significant effects were measured for RD1433 between different application durations. Blood flow in skin treated with RD1433 was significantly lower than skin treated with Vaseline[®] for all application durations ($p < 0.01$).

Vaseline[®] did not produce a statistically significant effect on MN-induced visual erythema for any duration of application (Figure 5). Application of RD1433 significantly reduced visual erythema following exposure to MN in

Figure 1. Blood flow (expressed as percentage of control area under the curve measured by laser Doppler imaging) at skin sites exposed to methyl nicotinate 15 min after topical application of Vaseline® or RD1433 at a nominal thickness of 0 (control), 0.01, 0.02, 0.05, 0.1 or 0.2 mm. Each value represents average $\pm$ standard error of mean acquired from $n = 12$ volunteers. Horizontal bars indicate significant ($p < 0.05$) difference within treatments. Asterisks indicate value is significantly different ($p < 0.05$) to corresponding control.

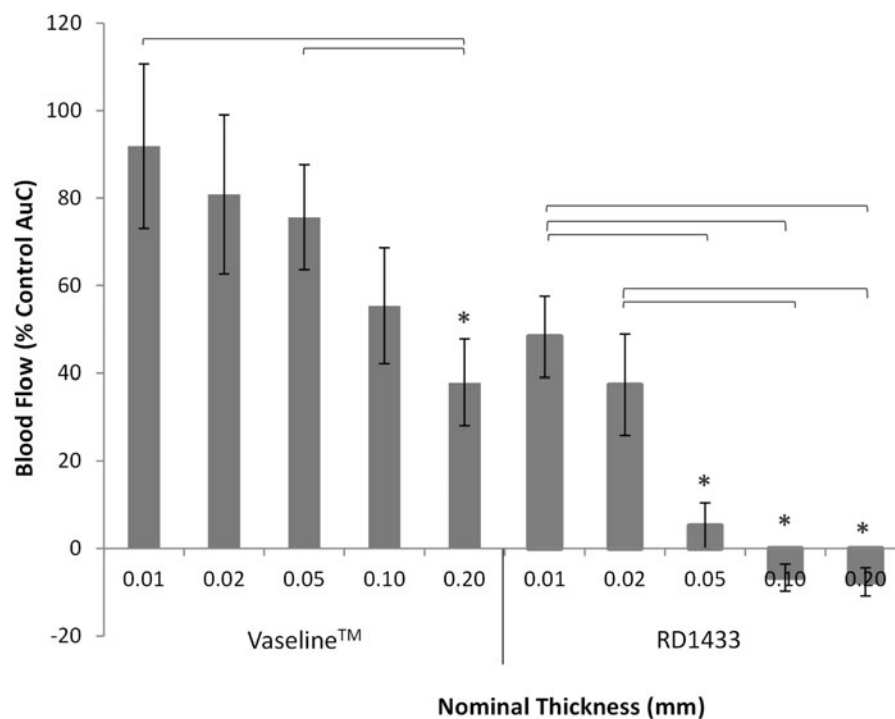


Figure 2. Erythema (expressed as percentage of control area under the curve measured by visual scoring) at skin sites exposed to methyl nicotinate 15 min after topical application of Vaseline® or RD1433 at a nominal thickness of 0 (control), 0.01, 0.02, 0.05, 0.1 or 0.2 mm. Each value represents the average $\pm$ standard error of mean acquired from $n = 12$ volunteers. Horizontal bars indicate significant ($p < 0.05$) difference within treatments. Asterisks indicate value is significantly different ($p < 0.05$) to corresponding control.

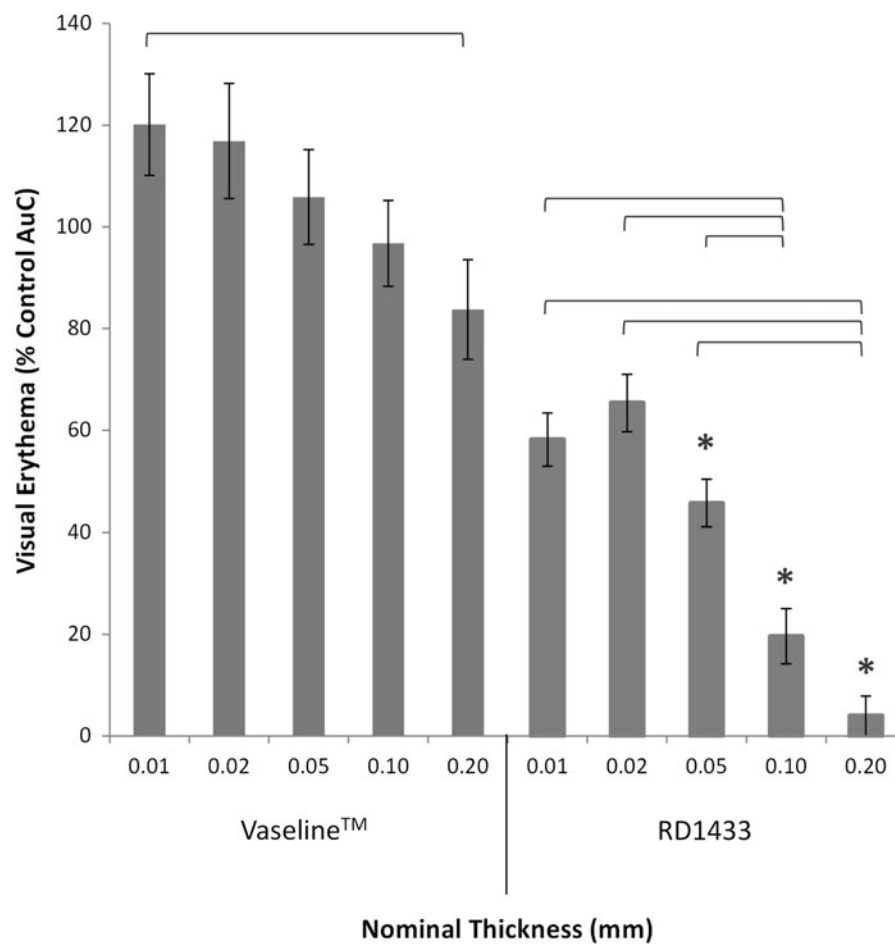


Figure 3. Erythema (expressed as percentage of control area under the curve measured by tissue viability imaging) at skin sites exposed to methyl nicotinate 15 min after topical application of Vaseline® or RD1433 at a nominal thickness of 0 (control), 0.01, 0.02, 0.05, 0.1 or 0.2 mm. Each value represents average ± standard error of mean acquired from *n* = 12 volunteers. Horizontal bars indicate significant (*p* < 0.05) difference within treatments. Asterisks indicate value is significantly different (*p* < 0.05) to corresponding control.

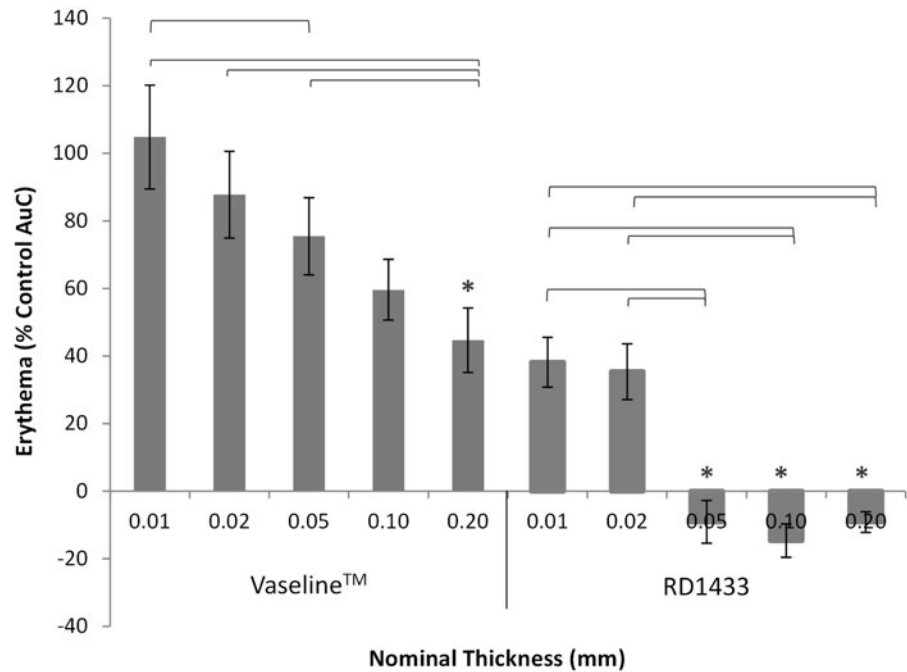


Table 3. Summary of performance of RD433 and Vaseline® (at five thicknesses) in reducing the rubefacient effects of methyl nicotinate (MN).

Parameter	Nominal treatment thickness (mm)									
	RD1433					Vaseline®				
	0.01	0.02	0.05	0.10	0.20	0.01	0.02	0.05	0.10	0.20
Laser Doppler imaging		***	***	***	***					*
Visual erythema		***	***	***	***					
Tissue viability imaging		***	***	***	***					*

Shading indicates a statistically significant reduction in dermal response to methyl nicotinate (in comparison to controls) as indicated by asterisks (**p* < 0.05 and ****p* < 0.005). Absence of asterisk indicates no statistically significant effect.

comparison to control (untreated) skin sites at durations of 1, 2 and 4 h (Figure 5). No statistically significant effects were measured for RD1433 between different application durations. Erythema in skin treated with RD1433 was significantly lower than skin treated with Vaseline® for all application durations (*p* < 0.01).

Vaseline® did not produce a statistically significant effect on MN-induced erythema measured by TiVi for any duration of application (Figure 6). Application of RD1433 significantly reduced visual erythema following exposure to MN in comparison to control (untreated) skin sites for all application durations (Figure 6). The one hour application of RD1433 was statistically significant to three, four and six hours, and the two hours application was significantly different to the six hours duration. Erythema in skin treated with RD1433 was significantly lower than skin treated with Vaseline® for all application durations (*p* < 0.01).

There were no statistically significant treatment-related effects on skin temperature (IRI), skin reflectance spectroscopy (SRS) L*, a* and b* parameters, skin surface pH or transepidermal water loss (TEWL).

In summary, RD1433 was significantly effective at reducing the effects of exposure to methyl nicotinate at a thickness of 0.1 mm for up to 6 h (Table 4) when measured by

LDI, visual scoring and TiVi. In contrast, Vaseline® was ineffective at all time points. When compared at the same nominal thickness, RD1433 was consistently and significantly more effective in reducing the vasodilatory effects of methyl nicotinate than Vaseline® (*p* < 0.01).

Discussion

Topical application of methyl nicotinate (MN) is an established and relatively safe method for producing localised, reproducible skin inflammation²³ and has been previously used to assess skin barrier function following topical application of healthcare formulations²⁴. In this study, we extended the use of this rubefacient assay to assess the optimal application thickness and duration of effectiveness of a new barrier cream, RD1433, using an array of biophysical instruments and a visual scoring index. Vaseline® (white petroleum jelly BP) was included in the study as a comparator product due to its known effects as a barrier and emollient²⁵.

The optimal dose of RD1433 was pre-determined to be the minimum thickness at which no further, statistically significant improvement in barrier performance could be measured. Thus, while the 0.05 mm application was the thinnest layer which resulted in a significant reduction in

Figure 4. Blood flow (expressed as percentage of control area under the curve measured by laser Doppler imaging) at skin sites exposed to methyl nicotinate following topical application of Vaseline® or RD1433 at a nominal thickness of 0.1 mm for a duration of 0 (control), 1, 2, 3, 4 or 6 h. Each value represents average $\pm$ standard error of mean acquired from $n = 12$ volunteers. Asterisks indicate value is significantly different ($p < 0.05$) to corresponding controls.

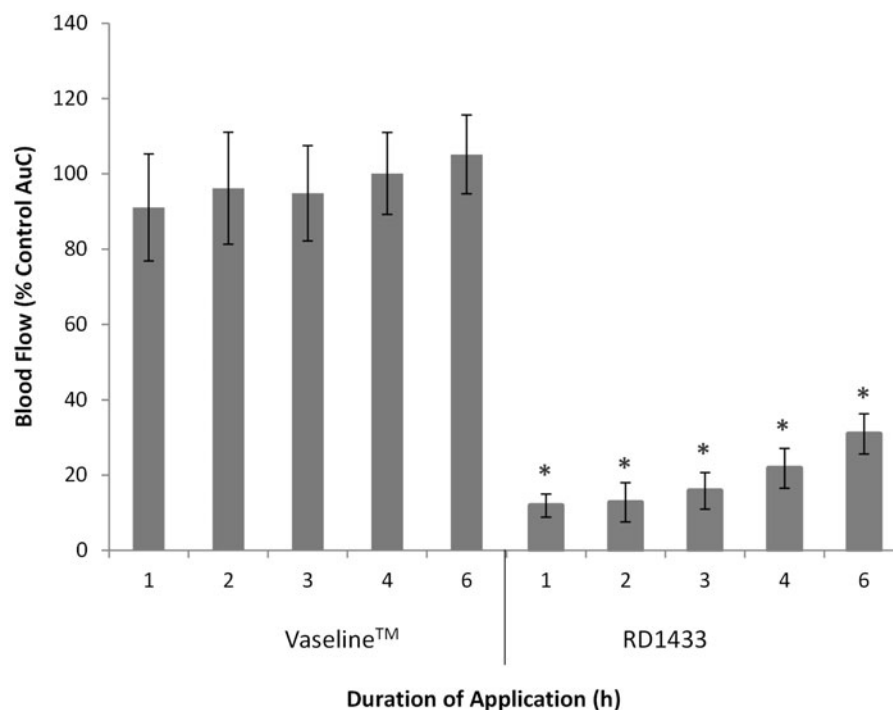
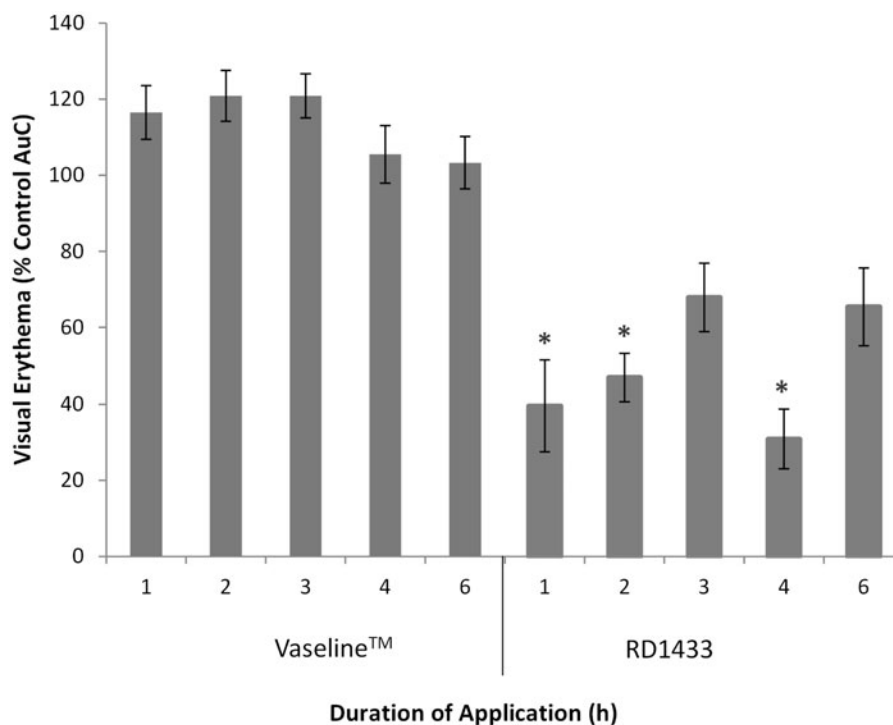


Figure 5. Erythema (expressed as percentage of control area under the curve measured by visual scoring) at skin sites exposed to methyl nicotinate following topical application of Vaseline® or RD1433 at a nominal thickness of 0.1 mm for a duration of 0 (control), 1, 2, 3, 4 or 6 h. Each value represents the average $\pm$ standard error of mean acquired from $n = 12$ volunteers. Asterisks indicate value is significantly different ($p < 0.05$) to corresponding controls.



blood flow and erythema (when compare to controls), only the 0.1 and 0.2 mm thicknesses were consistently equipotent. Therefore, a nominal thickness of 0.1 mm was deemed representative of the optimum dose of RD1433. Accounting for loss of material during topical application, this equated to an actual thickness of 80 μ m ($\pm 8\%$).

The duration of effectiveness of a topical skin protectant is an important practical parameter which dictates the frequency of topical application required to maintain an effective dose

on the skin. In this study, performed under non-active conditions, no statistically significant loss of barrier function was measured over the six hours application period when compared to control (untreated) skin. However, both blood flow and erythema (TiVi) data indicated a trend for RD1433 barrier function to decrease with time, indicating a progressive loss in performance presumably due to the natural sloughing of the stratum corneum²⁶. For the purpose of establishing a dosing regime for future clinical studies

Figure 6. Erythema (expressed as percentage of control area under the curve measured by tissue viability imaging) at skin sites exposed to methyl nicotinate following topical application of Vaseline® or RD1433 at a nominal thickness of 0.1 mm for a duration of 0 (control), 1, 2, 3, 4 or 6 h. Each value represents average ± standard error of mean acquired from *n* = 12 volunteers. Horizontal bars indicate significant (*p* < 0.05) difference within treatments. Asterisks indicate value is significantly different (*p* < 0.05) to corresponding controls.

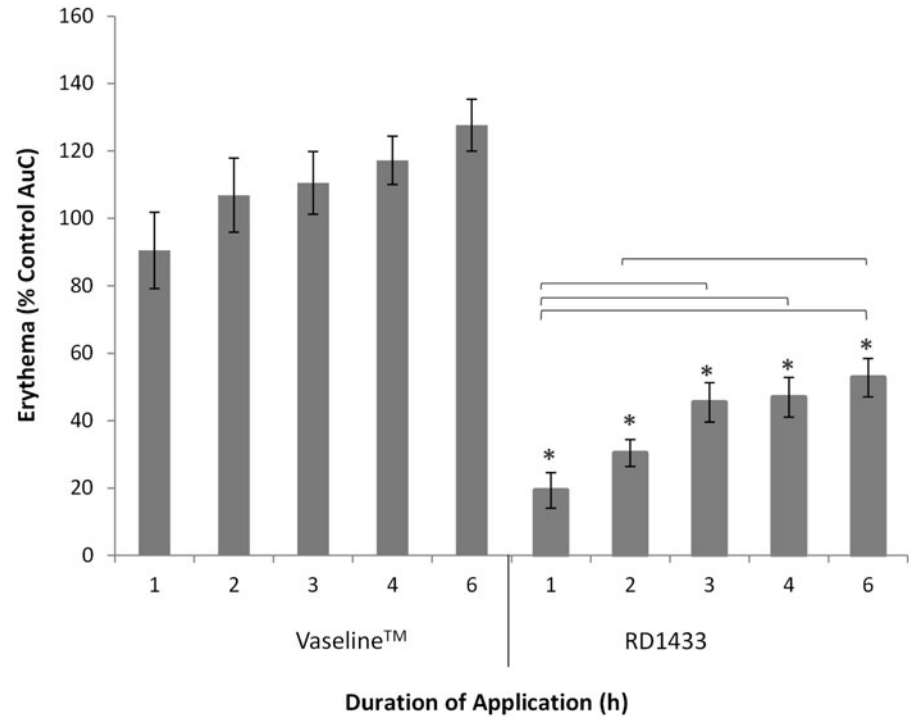


Table 4. Summary of performance of RD433 and Vaseline® (at five durations; 1–6 h) in reducing the rubefacient effects of methyl nicotinate (MN).

Parameter	Treatment duration (h)				
	RD1433				
	1	2	3	4	6
Laser Doppler imaging	***	***	***	*	*
Visual erythema	**	**		**	
Tissue viability imaging	***	***	***	***	***

Shading indicates a statistically significant reduction in dermal response to methyl nicotinate (in comparison to controls) as indicated by asterisks (**p* < 0.05; ***p* < 0.01 and ****p* < 0.005). Absence of asterisk indicates no statistically significant effect.

performed under identical (sedentary) conditions, a single daily application of RD1433 would seem appropriate. However, further studies are required to measure the duration of effect under more realistic conditions of use.

The experimental work utilised a number of biophysical instruments in order to objectively measure skin function, many of which failed to detect a significant response to MN. This may have been due to delaying “contact” measurements until one hour after washing of skin sites exposed to MN. The contact measurements included skin reflectance spectroscopy (SRS), skin surface pH and transepidermal water loss (TEWL), all of which require intimate contact with the skin to produce a valid measurement. In order to prevent interference at the skin exposure sites (particularly those treated with RD1433 or Vaseline®), contact measurements were delayed until one hour after removal of the topical formulations at which point the dermal response to MN had subsided. Hence, it is not surprising that these measurements did not indicate any treatment-related effects. However, the inclusion of such measurements provided pharmacovigilance

data: the absence of any measurable skin reaction following (up to 6 h) dermal application of RD1433 indicates that the formulation is not contraindicated for further clinical study.

Overall, this study has demonstrated that RD1433 can provide significant levels of protection at a nominal thickness of 0.1 mm for a duration of six hours. In contrast, Vaseline® was relatively ineffective at preventing methyl nicotinate-mediated skin inflammation.

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Declaration of interest

The authors have no relevant declarations of interest to report.

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