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Emollient product design: objective measurements of formulation structure, texture and performance, and subjective assessments of user acceptability

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Abstract

Background. The choice of prescribed emollients is usually based on cost and patient preference. Differences in formulations can affect user acceptability.

Aim. To compare the physical performance, user acceptability and various product design features of two emollient gels that are prescribed in the UK and alleged to be therapeutically interchangeable because their formulations are described as having the same contents of oily ingredients.

Results. We found that here are in fact significant measurable differences between the structure and performance of the two formulations, which materially affect their user acceptability. These differences are attributed to the use of different types of gelling agents and other ingredients of differing grades/quality and concentrations, and probably due to the formulations being made by different manufacturing processes. We also identified other product design features that are important to user appeal, including the type of container in which the formulations are presented, the type of dispensing devices provided, and the nature and form of the supplied user instructions.

Conclusion. Patients and prescribers should be aware that there can be important differences in performance and user appeal between emollients, even between products that, superficially, may appear to be very similar. These important performance aspects should be characterized for new emollient introductions to encourage better informed product selection.

Prescribers tend to recommend emollients based primarily on patient preference and cost.[1,2] Advanced and innovative emollients have been developed to optimize therapeutic performance and patient appeal. Recently, emollients have emerged on the UK market that are alleged to be interchangeable because, superficially, they appear to have similar oil compositions as the innovator products. However, owing to other important qualitative and quantitative differences between their ingredients, their physical performances and user appeal can nevertheless be very different.

We investigated this by comparing the structural and textural properties of an innovator licensed emollient gel [Doublebase Gel (DBG), PL 00173/0183; Dermal Laboratories, Hitchin, Hertfordshire, UK)] and a self-certified Class I medical device emollient gel [Zerodouble Gel (ZDG), T&R Derma, Linthwaite, Huddersfield, UK]. The well-established performance and therapeutic effectiveness of the innovator gel, DBG, stems from the special design of its formulation in its entirety, including the method of manufacture. One important feature is the manner in which the emulsion system breaks down irreversibly in contact with salts on the skin. This study therefore compared structural differences between the DBG and ZDG

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formulations in their normal states and after contact with salt. We also explored the perceived importance of various other differences between the designs of these two products that potentially might affect their user appeal and therapeutic usefulness.

Methods

Sample preparation

Salt-treated samples were prepared by sprinkling 2.0 ± 0.1 g of NaCl onto 20 ± 0.4 g of each formulation, and gently mixing by folding the formulation onto itself 10 times, using a spatula. The samples were then left to stand for 30 min. Untreated control samples for each emulsified gel were folded in the same manner without adding salt.

Microscopy

Approximately 20 mg of treated and control samples of each formulation were mixed with Nile Red fluorescent dye. The samples were then placed on microscope slides and pressed with coverslips for 5 s. After 1 h, the samples were viewed under a laser microscope (Eclipse 90i; Nikon Instruments Inc., Amsterdam, the Netherlands) at × 60 magnification.

Firmness/stiffness and stickiness by texture analysis

Aliquots (50 g) of treated and control samples of DBG and ZDG were weighed into a beaker and subjected to compression using a 35-mm diameter cylindrical probe (TA-HDplus; Stable Microsystems, Godalming, Surry) to measure firmness/stiffness and stickiness. The probe compressed the sample by 15 mm distance after an initial trigger force of 0.5 N at a rate of 0.5 mm/s. When the 15 mm target distance was reached, the probe returned to the starting position at 10 mm/s and recorded the force required to separate the probe from the sample. This force is an indicator of stickiness. Samples were analysed in triplicate.

Spreadability by texture analysis

Aliquots (1.1 ± 0.1 g) of treated and control samples were compressed between two glass plates using predetermined forces of 1, 5, 20, 40 and 50 N. At each force, the area of spread was recorded and calculated. Different samples were used for the measurements of spreadability at each force applied.

Product satisfaction questionnaire

With full ethics approval (University of Greenwich ethics committee), 67 adult participants completed a structured questionnaire asking whether they preferred either product or liked them both equally, in respect to various product design features addressing: (i) the physical appearance/look of the formulations, (ii) the suitability and performance of the containers and dispensing devices, (iii) the accompanying written instructions and medical advice, and (iv) the handling characteristics of the two gel formulations.

Statistical analysis

A binomial test was carried out to identify statistical differences between any preferences between the products. This test was carried out separately for each design feature, with a null hypothesis of equal preference for the two emollients. The tests were performed using the PROBBNML() function from an SAS data step, so they are exact binomial probabilities. The *P* values were all very much smaller than the cut-off of 0.05.

Results

Gross characteristics of gels

On visual inspection, there were noticeable differences between the surface characteristics and consistencies of the two emulsified gels. DBG has a smooth and homogeneous structure, whereas ZDG is lumpy and

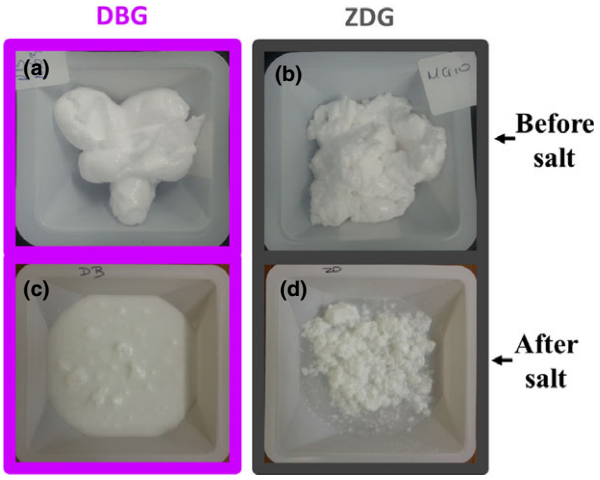

Figure 1 (a–d) Structural behaviour of Doublebase gel (DBG) and Zerodouble gel (ZDG) in the presence of salt.

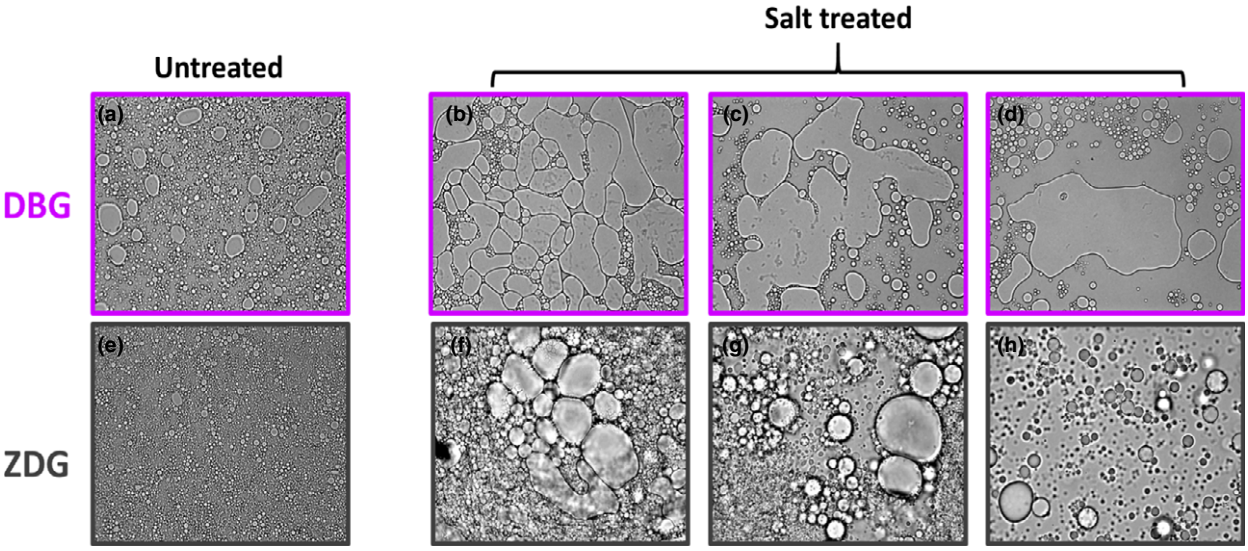

Figure 2 (a–h) Laser microscopy images of different areas of Doublebase gel (DBG) and Zerodouble gel (ZDG) samples before and after salt treatment obtained at × 60 magnification.

heterogeneous. Figure 1a–d shows the appearance of the two gel structures before and after coming into contact with salt. The DBG structure (Fig. 1a) largely broke down into a liquid (Fig. 1c) after contact with salt, whereas the ZDG structure (Fig. 1b) did not break down, and in fact appeared to curdle and become firmer (Fig. 1d).

Microscopic characteristics of gels

Microscopic examination also revealed differences between the two emulsion gels, both in their normal states (Fig. 2a,e) and following salt exposure. For DBG, the structural matrix stabilizing the oil droplets broke down completely (Fig. 2b–d), releasing the oil from the emulsion. For ZDG, however, microscopic examination suggests that the emulsion structure did not break down to the same extent and manner as DBG (Fig. 2f–h).

Firmness/stiffness and stickiness using texture analysis

Considerable differences were observed between the two untreated formulations in terms of firmness and stickiness. ZDG appeared to have a significantly firmer (Fig. 3a) and stickier polymeric structure than thatof DBG (Fig. 3b). Upon treatment with salts, the polymeric structure of DBG readily broke down, resulting in extensive loss of firmness, whereas under the same conditions the firmness of ZDG scarcely changed

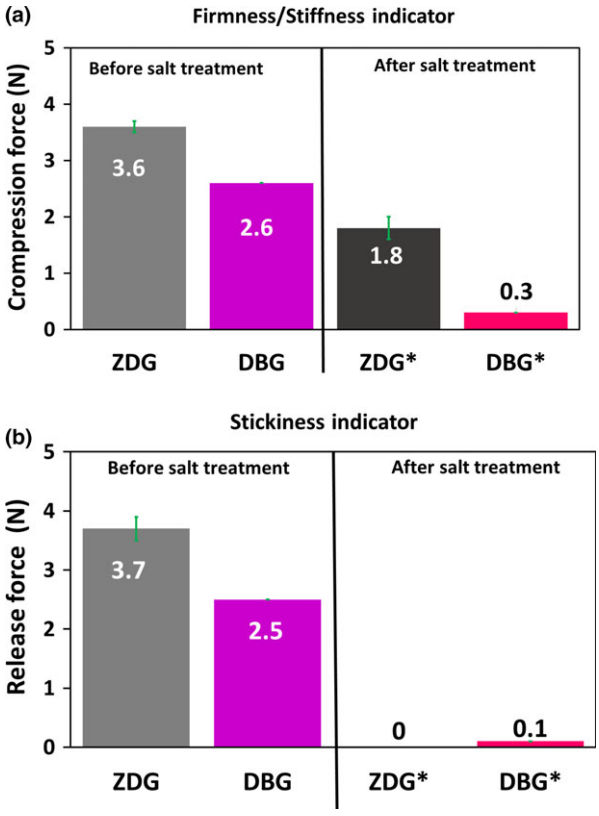

Figure 3 (a) Firmness/stiffness and (b) stickiness indicators of Doublebase gel (DBG) and Zerodouble gel (ZDG) before and after exposure to salt. ZDG* and DBG* indicate salt-treated samples.

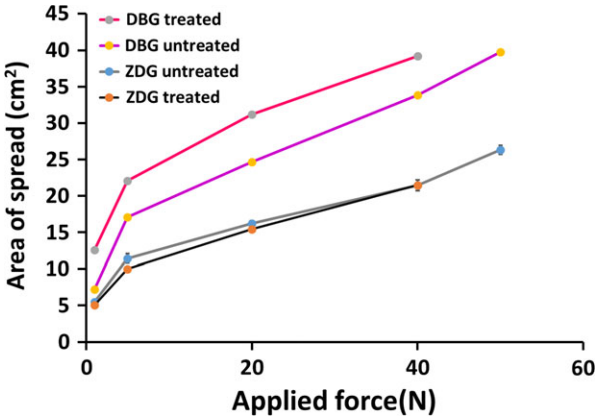

Figure 4 Spreadability of Doublebase gel (DBG) and Zerodouble gel (ZDG) before and after exposure to salt.

(Fig. 3a). Both gels appeared to lose their stickiness once exposed to salt.

Spreadability

Notable differences were observed between the two gels in terms of spreadability (Fig. 4). DBG spread more easily than ZDG, and even more so after exposure to salt. Interestingly, no such effect was observed for ZDG, as there was no substantial difference between ZDG samples before and after salt treatment.

Product satisfaction questionnaire

Of the 67 participants who were screened and completed the study, 26 were men and 41 were women. Most participants (77.6%) were in the 18–30 age group. The product satisfaction questionnaire results are presented in Table 1. The results showed that > 88% of subjects reported that the look of the DBG formulation was smoother/more uniform, appeared to be of a better quality and looked more appealing to use, while 89.6% said they would prefer the DBG formulation for long-term use and > 79% of subjects felt that the DBG pump presentation looked more convenient, more hygienic, easier to use and more suitable for medicinal products of this sort than the squeeze-bottle presentation used by ZDG. When asked which user instructions encouraged the most patient benefit from using the product and contained the most helpful advice on how to look after dry skin, over 68% of subjects favoured the information leaflet supplied with DBG rather than the 'peel and read' label supplied with ZDG. In addition, 74.6% reported that they preferred the handling characteristics of the DBG formulation. All the binomial tests were highly statistically significant ($P < 0.001$).

Discussion

Emollients are available in various formulation types, including emulsified creams, ointments, lotions and gels.[3] They perform a crucial role in the treatment and management of dry skin conditions such as eczema and psoriasis.[4]

The sensory profile of leave-on emollients has to be cosmetically acceptable in order to encourage patients to use them properly, and emulsified gel formulations

Table 1 Product Satisfaction Questionnaire summary table.

	DBG		ZDG		Both	
Question and options	*n*	%	*n*	%	*n*	%
(1) Physical appearance/look of the two formulations						
(a) Which one do you prefer?	61	91.0	1	1.5	5	7.5
(b) Which one looks like it has a smoother, more uniform appearance (i.e. less lumpy)?	65	97.0	1	1.5	1	1.5
(c) Which one looks the best quality?	59	88.1	1	1.5	7	10.4
(d) Which one looks the most appealing to use?	62	92.5	1	1.5	4	6.0
(e) Over a long period of time which one would you prefer to use?	60	89.6	3	4.5	4	6.0
The suitability and performance of their containers and dispensing devices						
(a) Which bottle and dispenser looks the most convenient to handle in use?	60	89.6	6	9.0	1	1.5
(b) Which bottle and dispenser looks the most hygienic?	53	79.1	11	16.4	3	4.5
(c) Which bottle and dispenser looks the easiest to use?	60	89.6	5	7.5	2	3.0
(d) Which bottle and dispenser looks the most suitable for a medicinal product?	56	83.6	9	13.4	2	3.0
The written instructions and medical advice supplied with the products						
(a) Which leaflet is likely to encourage the most patient benefit from using the emollient?	46	68.7	12	17.9	9	13.4
(b) Which leaflet includes the most helpful healthcare advice on how to look after dry skin?	61	91.0	4	6.0	2	3.0
The handling characteristics of the two formulations						
(a) Which cream would you prefer to use?	50	74.6	7	10.4	10	14.9

Table 2 Composition of Doublebase and Zerodoublegels.

Function	DBG	ZDG
Emollients	Isopropyl myristate 15%; liquid paraffin 15%	Isopropyl myristate 15%; liquid paraffin 15%
Preservative	Phenoxyethanol	Phenoxyethanol
Humectant	Glycerol	Glycerin
Emulsifier	Carbomer	Acrylates
Emulsifier/ SWA	Sorbitan laurate	Sorbitan laurate
pH modifier	Triethanolamine	Triethanolamine
Water base	Purified water	Purified water

DBG, Doublebase gel; SWA, surface-wetting agent; ZDG, Zerodouble gel.

such as those tested here are popular because of their relatively nongreasy feel.[3] It is very important that emollients are formulated to ensure they are appealing for patients to use properly and thus achieve their full clinical benefit.[5,6]

Oil-in-water (O/W) emulsions of the sort studied here use various types of gelling agents. Carbomers provide both gelling and emulsifying properties,[7,8] and thereby confer appropriate structure/viscosity to make the formulation convenient to dispense, and to physically stabilize dispersion of the oil droplets. In addition, some types of carbomer have a high propensity to deconstruct once applied to the skin, and this property can provide important performance advantages for the formulation.[9] The breakdown of the carbomer gel structure is influenced by both the shear forces applied when spreading it over the skin and by the interaction of the formulation with salts on the skin.[7] Ideally, this deconstruction both reduces the viscosity of the gel and results in separation of the oil and aqueous phases, allowing the emollient (oily) ingredients to be spread easily and form a uniform occlusive barrier over the skin surface.[10] In addition, if the phase separation is irreversible, this also serves to prolong emollient retention on the skin by rendering the oily ingredients more resistant to re-emulsification when washing/bathing.[11,12]

When compared in their normal states, the DBG formulation looked smoother and more homogeneous, and was less firm and sticky compared with ZDG. In addition, after coming into contact with salts, the DBG emulsion broke down more readily and substantially, became less firm and spread more readily than ZDG. These contrasting characteristics and performances, both in their normal state and in contact with salts, amply demonstrate that the structures of these two gels are indeed very different. These measured differences also translated into the DBG formulation being significantly more appealing to most of the testing panel.

As explained above, the observed differences in performance may be partly attributed to the differing gelling agents used, as different grades of carbomer behave differently (Table 2). The differences are also likely to be influenced by the product formulation, if they contain other ingredients of differing grades/quality and concentrations. They are almost certainly made by different manufacturing processes, and it is known that even the order in which ingredients are added can influence product performance. Other researchers have observed that for topically applied dosage forms, small changes in the formulation or manufacturing process can significantly affect both quality and efficacy.[13–16] Performance differences have also been attributed to other factors such as occlusivity, pH, viscosity, droplet size, partition coefficients and the ionic nature of ingredients. Bearing in mind that emollients are designed to produce an oily, partially occlusive film over the surface of the skin and fill the interstices between the desquamating corneocytes abundant in dry skin conditions, their occlusivity is bound to be influenced by the viscosity, molecular weight and spreading characteristics of the formulation.[17] Changes in viscosity, for example, can alter occlusivity and skin retention of the dosage form and even percutaneous absorption.[15] Another important consideration is the effect of the formulation on skin pH. Some formulation excipients can increase the pH of the skin, resulting in skin barrier damage,[18] whereas other ingredients can have beneficial effects by decreasing skin pH[19] and promoting the skin's acid mantle. For example, the skin's innate antimicrobial properties are optimal at acidic pH, as *Staphylococcus* and other pathogenic bacteria favour neutral pH and are inhibited in an acidic environment.[20] Additionally, in an acidic environment, normal desquamation of the stratum corneum is a controlled process regulated by the enzymes kallikreins 5 and 7.[21] However, at higher pH, desquamation of skin cells can run out of control, damaging the stratum corneum barrier.[20]

For topically applied licensed medicines, there is universal acceptance that two ostensibly similar formulations cannot be assumed to be therapeutically equivalent. Indeed, this important principle explains why regulatory authorities require generic manufacturers to demonstrate that their products are indeed bioequivalent to the innovator formulation. This is very important for topically applied dosage forms, as differing physicochemical characteristics are known to

render ostensibly similar formulations therapeutically nonequivalent.[16] The performance differences reported here confirm this important principle. In stark contrast, however, for self-certified Class I medical devices, there is no independent regulatory assessment of their quality, safety or effectiveness, and the important matter of therapeutic equivalence can be completely ignored. This is something that regulatory authorities, healthcare professionals, prescribers and patients should take into consideration, because important performance differences do exist, even between formulations that, superficially, may seem to be very similar.

In addition to these important formulation differences, other product design features were found to significantly influence the user appeal and acceptability of DBG and ZDG. The DBG pump pack presentation was significantly more popular than the ZDG squeeze bottle, in terms of convenience, hygiene and ease of use. Although not tested in our study, leachates from certain types of plastic containers are also known to affect the biocompatibility of topical dosage forms, especially for patients with sensitive skin. It is also notable that two-thirds of users felt that the more comprehensive style of patient instruction leaflet supplied with DBG was likely to encourage the most patient benefit.

Conclusion

By combining both objective instrumental measurements and users' subjective assessments of product performance and acceptability, we have demonstrated important differences between two prescribed emollient gels that are alleged to have the same oil content and apparently comparable lists of ingredients. It is therefore important to recognize that emollients from different manufacturers are not the same as one another, and for prescribing purposes should not be grouped into a 'class' and regarded as being interchangeable. When choosing between gel emollients, patients and prescribers should be aware that there can be important performance differences, even between products that, superficially, may appear to be very similar. The performance of new emollient introductions should be properly characterized in order to inform product selection.

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