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ORIGINAL RESEARCH

Sensory properties analysis of a calcipotriol and betamethasone dipropionate cream vehicle formulated with an innovative PAD Technology for the treatment of plaque psoriasis on the skin and scalp

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Abstract

Background: In psoriasis, poor treatment adherence is frequently related to low efficacy and limited cosmetic acceptability from the patients' perspective. This study aimed to characterize the sensorial attributes of a calcipotriol (CAL) and betamethasone dipropionate (BDP)-cream vehicle based on polyaphron dispersion (PAD) Technology and to compare them with the conventional ointment and oleogel formulations for psoriasis.

Methods: A panel of 16 experts assessed sensory properties at four different stages: appearance, pick up, rub out and afterfeel. Descriptive sensory analysis was used to evaluate relevant attributes. Each attribute was rated on a line scale (range 0–100%). Active ingredients were not used because panellists were healthy volunteers, and vehicle formulations needed to be used instead.

Results: CAL/BDP PAD-cream vehicle was evaluated as having a low stickiness, low grease behaviour, good wetness, and good spreadability. Ointment showed the least desirable behaviour regarding these properties. Moreover, once CAL/BDP PAD-cream vehicle was absorbed, the gloss disappeared quickly, leaving low stickiness and a low amount of residue. This afterfeel behaviour was not observed with ointment. The oleogel formulation had good sensory properties, similar to CAL/BDP PAD-cream vehicle, but with lower integrity of shape, lower wetness and higher greasiness.

Conclusion: Overall, CAL/BDP PAD-cream vehicle has the desirable requirements for a topical product for the treatment of psoriasis, with better sensory properties than ointment and easier manipulation than oleogel, which may lead to greater acceptance and adherence.

Keywords: betamethasone dipropionate, calcipotriol, perception, pharmaceutical technology, psoriasis, rheology, skin cream.

Citation

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Introduction

Poor adherence to topical treatments in psoriasis is a determining factor of therapeutic efficacy.[1] Given that poor adherence is often related to cosmetic acceptability, patient preferences should therefore be considered to improve adherence and clinical outcomes.[2] Patient preference for a product vehicle is important for proper treatment adherence.[3]

An increase in the patient satisfaction with the drug vehicle has the potential to result in significant clinical and patient benefits.[4] Vehicles formulated to provide a fast absorption and minimum residue, allowing the patient to dress shortly after application without staining clothes, are expected to increase satisfaction with topical therapy and consequently promote adherence. Simple dosing regimens, good skin tolerance and good moisturizing properties are also preferred attributes from patients' perspective.[2]

Topical treatments for psoriasis exist in a variety of formulations with different physical properties. Ointments are considered the least desirable vehicles due to their uncomfortable application, poor absorption and greasy character,[1] whilst gels and creams may offer greater ease of application due to their lower firmness, consistency and adhesiveness.[5] The ideal dosage form for topical treatment of psoriasis would be a formulation that allows patient satisfaction with the daily routine and has acceptable cosmetic properties (e.g. non-greasy and non-sticky). One of the most frequently reported reasons for non-adherence by patients with psoriasis are interference with daily activities,[5] ease of use and convenience of application.[6] Thus, considering the preferences of patients in the choice of formulation and delivery system of their topical treatment may improve acceptability of treatment in their daily routine.[7]

A fixed-dose combination of calcipotriol (CAL) and betamethasone dipropionate (BDP) is recommended as the first-line choice in the topical treatment of psoriasis due to its high efficacy and once-daily application.[8] However, some of the currently marketed therapeutic options with the CAL/BDP fixed-dose combination are restricted to non-aqueous oil-based or paraffin-based formulations, such as ointment, gel/topical suspension (TS) or foam, which cause a sticky or greasy feeling inconvenient to many patients.[2,3,9–11]

Polyaphron dispersion (PAD) technology is a novel oil-in-water topical formulation and drug delivery system consisting of oil droplets encapsulated in a multimolecular shell structure.[12] The utilization of PAD Technology to develop a combination of CAL and BDP aqueous cream (CAL/BDP PAD-cream) confers multiple benefits compared with alternative approaches. When compared with anhydrous ointments or suspensions, the presence of a continuous water phase in an oil-in-water cream significantly alters the rheological and sensory attributes that a patient will notice upon application. A switch to an aqueous cream system can be associated with sub-optimal efficacy and poorer chemical stability of the active ingredients.[4,13] However, PAD Technology has enabled the formulation of not only a chemically stable cream but also one that exhibits significantly greater efficacy compared with the commercially available anhydrous gel alternative.[9]

The use of PAD Technology provides a chemically stable cream formulation of CAL and BDP, which are otherwise exposed to excessive hydrolytic degradation in normal aqueous cream systems, even if dissolved in an oil phase.[14] The CAL/BDP PAD-cream consists of a CAL-containing oil phase, a BDP oil phase and a non-solvent oil phase, which make up a relatively high proportion of the composition by weight and is significantly higher than technically possible in conventional oil-in-water creams (usually ~30% and rarely 50% or higher).[15] This is achieved with a surfactant-to-oil ratio of less than 1:40; a very low ratio compared with conventional creams that usually have significant excess surfactants and co-surfactants to help ensure physical stability and provide structure to the continuous phase. A more efficient use of the surfactant is enabled via careful selection of surfactant types and the processing steps associated with PAD Technology. During processing, the surfactants, together with oil and water, have been shown to form a complex non-crystalline shell-like structure at the interface of each droplet, accounting for several of the key attributes of the technology (Figure 1).

In the CAL/BDP PAD-cream, unlike gel and ointment alternatives, both the active pharmaceutical ingredients are incorporated in solution rather than in suspension, which maximizes their permeation potential. The active pharmaceutical ingredients are individually dissolved in blends of isopropyl myristate and medium-chain triglycerides. To help the aesthetic feel of the CAL/BDP PAD-cream, even in the presence of a relatively high oil level, the formulation composition is designed to give easy spreading on the skin, a light emollient feeling and be readily absorbed.

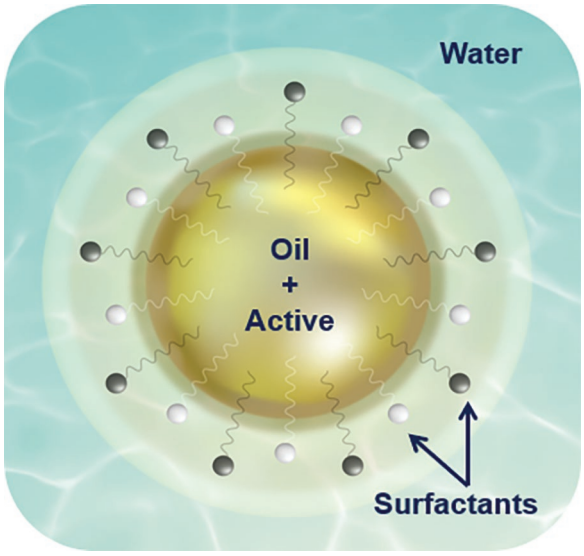
The objective of this study was to characterize the sensorial attributes of the CAL/BDP PAD-cream vehicle and to compare them with the sensorial attributes of conventional formulations for psoriasis such as an ointment and an oleogel product.

Methods

The sensory properties of CAL/BDP PAD-cream vehicle were evaluated by a panel of experts trained in sensory descriptive analysis and following the Standard Guide for Two Sensory Descriptive Analysis Approaches for Skin Creams and Lotions (ASTM E1490-11).[16] Sixteen trained experts of a sensory panel, composed of chemists, pharmacists, biologists, information technology specialists and analysts, amongst others, participated in the tests in two separate sessions. The expert panellists were chosen through a blind selection process of over 400 people according to the results of a selection test included in the ASTM E1490-11 guidelines[16] and receive continuous training in descriptive sensory analysis once a year.

The sensory parameters were evaluated by the panel at four different stages: appearance, pick up, rub out and afterfeel. Descriptive sensory analysis was used to assess relevant attributes on a line scale with values

Figure 1. Schematic structure of PAD Technology oil-in-water droplets.



A multimolecular layer of organized surfactant, oil and water forms a robust three-dimensional bicontinuous structure around the oil droplet. PAD formulations are manufactured with low levels of surfactant in the water and oil phases, in contrast to conventional emulsions that require a large excess of surfactant in the water phase to maintain physical stability.[12]

between 0% and 100%. Regarding sensory panel evaluations, words and definitions in sensory terms are highly relevant. The definitions and scores for each attribute are summarized in Table 1.

A sensory panel can only evaluate placebo or skin care formulations without active pharmaceutical ingredients. Therefore, CAL/BDP PAD-cream vehicle with all the components except the active ingredients was used for testing. CAL/BDP PAD-cream vehicle had the exact same properties as CAL/BDP PAD-cream due to the low concentration of active ingredients in the pharmaceutical product (0.005% CAL and 0.064% BDP w/w). For a more accurate determination, standards with a known value of each parameter were used as reference to determine CAL/BDP PAD-cream values. Samples were presented at an ambient temperature, and the tests were performed in a laboratory designed specifically for sensory evaluations (Figure 2).

In order to better understand the difference in sensory properties of CAL/BDP PAD-cream *versus* conventional formulations for psoriasis formulated as ointments and oleogels, a comparative study was conducted with a standard ointment based on petrolatum and a standard oleogel product, both skin care products, *versus* CAL/BDP PAD-cream vehicle. All samples were blind evaluated, with no information about the products provided to the panellists.

Results

The results of the sensory parameters evaluated for CAL/BDP PAD-cream vehicle, petrolatum ointment and an oleogel are shown in Figure 3 and main findings are summarized in Table 2. Statistical analysis and interpretation were provided for each sensory attribute to describe data and to ensure consistent criteria amongst the panel members.

Appearance

The attributes of the formulations were measured by the sense of vision and included immediate integrity of shape, the integrity of shape after 10 seconds and gloss. Petrolatum exhibited the highest integrity of shape, both immediate and after 10 seconds. The CAL/BDP PAD-cream vehicle had lower integrity of shape than petrolatum and similar gloss. The oleogel was rated as the glossiest product and the formulation with the lowest integrity of shape (Figure 3 and Table 2).

Pick up

The rheological attributes of the formulation were measured by manipulation between the fingers through the firmness, stickiness, cohesiveness and amount of peaking. Petrolatum was rated with the highest scores (i.e. less desirable) for all pick up attributes. The CAL/BDP PAD-cream vehicle and the oleogel revealed similar firmness, stickiness, cohesiveness and amount of peaking, though slightly better results were obtained for the oleogel (Figure 3 and Table 2).

Rub out

The physical and rheological attributes of the formulation on the skin, measured by rubbing the product on the skin to the point of its absorbency, as well as kinaesthetic sensations that may occur, were assessed. Petrolatum was considered the greasiest and thickest product and the one with less spreadability and wetness. The CAL/BDP PAD-cream vehicle was the least greasy product and the one with more wetness. Regarding the absorbency, similar results were observed between the CAL/BDP PAD-cream vehicle and petrolatum, and oleogel showed the lowest values. Thickness and spreadability were also similar between the CAL/BDP PAD-cream vehicle and oleogel (Figure 3 and Table 2).

Afterfeel

The physical and kinaesthetic attributes of the skin surface after using the formulations to include measurements of

Table 1. Definitions and values used for the evaluation of sensory attributes.

Stage of use	Sensory attribute	Definition	Values
Appearance	Integrity of shape	Degree to which product holds the given shape	0 = Flattens; 100 = Retains shape
	Gloss	Amount of reflected light from product	0 = Dull/flat; 100 = Shiny/glossy
Pick up	Firmness	Force required to fully compress product between thumb and index finger	0 = No force; 100 = High force
	Stickiness	Force required to separate fingertips	0 = Not sticky; 100 = Very sticky
	Cohesiveness	Amount sample strings rather than breaks when fingers are separated	0 = No strings; 100 = High strings
	Amount of peaking	Degree to which product makes stiff peaks on fingertips	0 = No peaks; 100 = Stiff peaks
Rub out	Wetness	Amount of water perceived whilst rubbing	0 = None; 100 = High amount
	Spreadability	Ease of moving product over the skin	0 = Difficult/drag; 100 = Easy/slip
	Thickness	Amount of product felt between fingertip and skin	0 = Thin, almost no product; 100 = Thick, lots of product
	Grease	Amount of grease perceived in the product during rub out	0 = None; 100 = Extreme
	Absorbency	Number of rubs at which the product loses wet, moist feeling and a resistance to continue is perceived (upper limit 100 rubs)	–
Afterfeel[a]	Gloss	Amount or degree of light reflected from product	0 = Dull/flat; 100 = Shiny/glossy
	Sticky	Degree to which fingers adhere to product	0 = Not sticky; 100 = Very sticky
	Slipperiness	Ease of moving fingers across skin	0 = Difficult/drag; 100 = Easy/slip
	Amount of residue	Amount of product on skin	0 = None; 100 = Large amount

[a]Immediate and after 10 minutes.
Adapted from ASTM E1490-11.[16]

product residues once absorbed were assessed immediately and at 10 minutes after application. Petrolatum was scored as the most glossy and sticky product as well as the one with the highest amount of residue. Oleogel was the formulation with the lowest amount of residue. Similar results were obtained between the CAL/BDP PAD-cream vehicle and oleogel regarding all other afterfeel attributes (Figure 3 and Table 2).

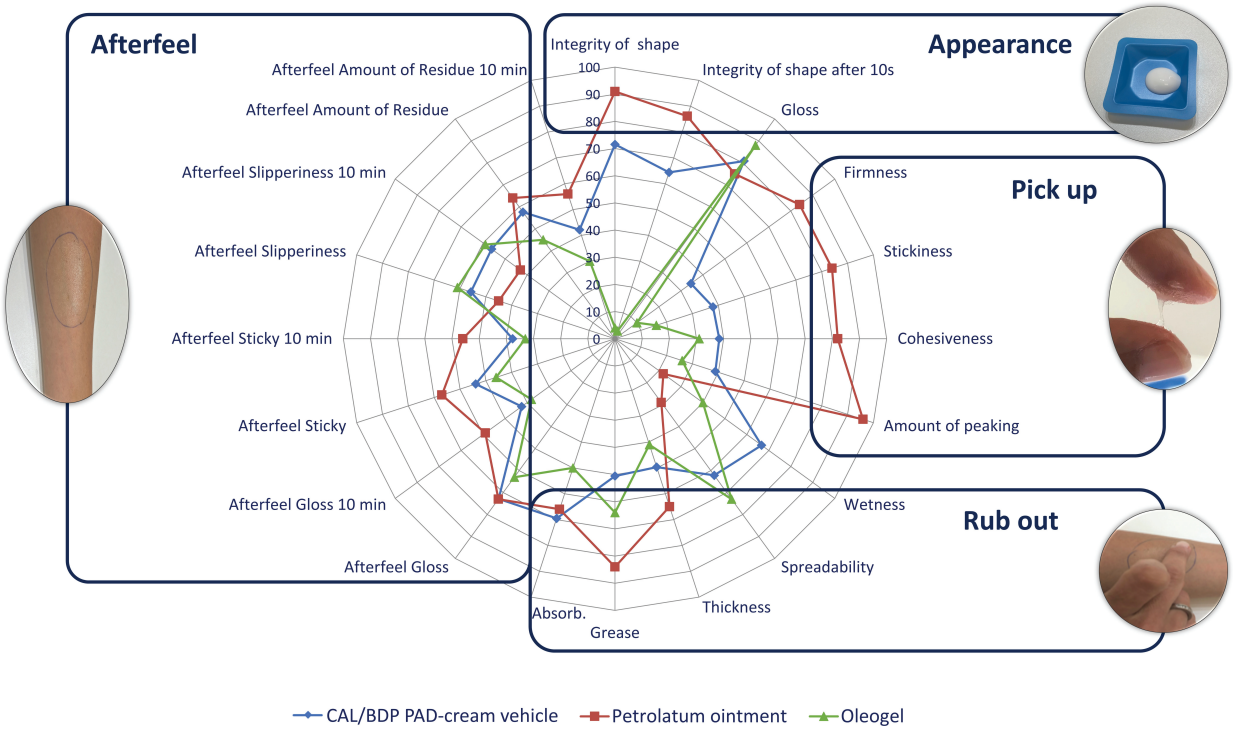
Discussion

Limited cosmetic acceptability is one of the main factors of poor adherence in dermatology, which is often associated with less efficacy.[1,2] Thus, organoleptic and application characteristics, such as spreadability and stickiness, are of extreme importance.[18]

A CAL/BDP cream formulation was developed using PAD Technology to separate and stabilize CAL and BDP and to provide emollient properties similar to those of an ointment whilst maintaining the feeling and spreadability of a light cream. The good emollient properties of CAL/BDP PAD-cream were demonstrated by the results of the questionnaires of two phase III clinical trials on CAL/BDP PAD-cream (NCT03308799 and NCT03802344), which evaluated the preference between the CAL/BDP PAD-cream and CAL/BDP gel/TS through the Psoriasis Treatment Convenience Scale (PTCS). The PTCS is a novel and validated patient-reported outcome scale consisting of six disease-specific, self-reported questions rated on a 1–10 scale, and has been shown to be a reliable, sensitive and valid scale to evaluate the preference of topical treatment for psoriasis.[19] The mean PTCS at week 8 for

Figure 2. Almirall R&D room set up as sensory panel laboratory that complies all the requirements for sensory evaluations according to Meilgaard et al.[17]

Figure 3. Radar diagram of the sensory evaluation of CAL/BDP PAD-cream vehicle *versus* petrolatum ointment and an oleogel regarding parameters, including in the terms of appearance, pick up, rub out and afterfeel.



Absorb., absorbency; BDP, betamethasone dipropionate; CAL, calcipotriol; PAD, polyaphron dispersion.

Table 2. Summary of the sensory evaluation of CAL/BDP PAD-cream vehicle *versus* petrolatum ointment and an oleogel.

	CAL/BDP PAD-cream vehicle	Petrolatum ointment	Oleogel
Relevant parameters	Meets desirable requirements for a topical psoriasis product [2]: • Low stickiness • Low greasiness • Good feeling of wetness • Good spreadability	Opposite behaviour than CAL/BDP cream vehicle: • High stickiness • High greasiness • Bad feeling of wetness • Bad spreadability	Good properties but these disadvantages: • Low integrity of shape • Higher greasiness • Low wetness
Once absorbed (afterfeel)	The gloss practically disappears, low afterfeel stickiness and low amount of residue	More gloss, stickiness and higher amount of residue than CAL/BDP PAD-cream vehicle	Good afterfeel behaviour, similar to CAL/BDP PAD-cream vehicle

BDP, betamethasone dipropionate; CAL, calcipotriol.

CAL/BDP PAD-cream was statistically significantly higher than CAL/BDP gel/TS (40.4 *versus* 37.0; $p<0.0001$). Individual results of the PTCS questions revealed that the greater preference for CAL/BDP PAD-cream was mainly due to the gel/TS being a greasier formulation.[20] The CAL/BDP PAD-cream was developed with the aim of obtaining a cream with the desirable properties for a topical product for psoriasis, reflected by the results of the sixth question of the PTCS (i.e. 'Overall, how satisfied were you with the medical treatment?'). Patients expressed a higher satisfaction in favour of CAL/BDP PAD-cream compared with CAL/BDP gel/TS ($p<0.0001$).[9]

The cosmetic nature of CAL/BDP PAD-cream is intended to generate greater acceptance and adherence to treatment regimens, seeking to offer a better patient experience with topical treatments. Many patients are averse to ointments on aesthetic grounds because of the difficulty in rubbing-in the medication as well as greasiness and sticking to clothes;[1] according to the results herein, this issue can be solved with the use of CAL/BDP PAD-cream. CAL/BDP PAD-cream vehicle has the desirable requirements for a topical product for psoriasis being a formulation with low stickiness, low grease behaviour, good wetness and good spreadability. These properties are much better than those in petrolatum ointment. Moreover, once the formulation is absorbed, the gloss disappears very quickly, leaving minimal stickiness and residue, an afterfeel behaviour that is not observed with petrolatum ointment. The oleogel formulation had good sensory properties, but the low integrity of shape may complicate its manipulation. The low wetness and higher greasiness of oleogel than of CAL/BDP PAD-cream vehicle may explain the preference for the CAL/BDP cream over the gel seen in the phase III trials mentioned above.

Although there is no one topical drug formulation that suits everyone, the generally preferred topical treatments for psoriasis are those with formulations that are less sticky, cosmetically acceptable, easily absorbed, easy to apply, and with a pleasant scent.[10] These sensory properties have been significantly improved with CAL/BDP PAD-cream vehicle compared to ointment and oleogel formulations, which needs to be considered in the process of shared decision-making between patients and physicians. The differences in the sensory properties observed between the CAL/BDP PAD-cream vehicle, petrolatum ointment and oleogel may also be of importance to the pharmaceutical industry, guiding the development of more patient-centred products, such as the CAL/BDP PAD-cream, that could improve treatment satisfaction and adherence, which is particularly relevant in psoriasis.

Limitations

The main limitation of this study is that active ingredients could not be used because the panellists were healthy volunteers, therefore only allowing assessment of vehicle formulations. Furthermore, since it was a study with a panel of experts, the data were obtained from a small group of panellists, unlike market studies, which provide results from a larger non-expert population. However, the panel met all the requirements of the ASTM guidelines.[16]

Conclusions

The complete characterization of CAL/BDP PAD-cream vehicle shows highly adequate properties in relation to appearance, pick up, rub out and afterfeel for use in psoriasis treatment. CAL/BDP PAD-cream is a formulation with low stickiness, low greasiness, good wetness and good spreadability compared with ointment and reveals an easier manipulation than oleogel products, which may lead to greater cosmetic acceptability and adherence.

Contributions: Conceptualization: JG, NG and PG; data curation: NG and PG; formal analysis: NG and PG; funding acquisition: JG; investigation: NG and PG; methodology: NG and PG; project administration: JG, NG and PG; resources: NG and PG; supervision: JG, NG, PG, NC, MP, LI and TT; validation: JG, NG, PG, NC, MP, LI and TT; writing – original draft preparation: NG and PG; writing – review and editing: JG, NG, PG, NC, MP, LI and TT. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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