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Vehicles for atopic dermatitis therapies: more than just a placebo

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ABSTRACT

A topical vehicle is a 'carrier system' for an active pharmaceutical (or cosmetic) substance, referred to hereafter as the drug, but a vehicle may also be used on its own as an emollient to ameliorate dry skin. It is well established that the vehicle plays an important role in determining the bioavailability of a given drug at its ultimate target within the skin. Yet in the treatment of atopic eczema/dermatitis (AD), wherein the structure and function of the skin's outer barrier play a pivotal role in the development and course of the condition, the interaction of the vehicle with this barrier carries a particular importance. It is now clear that the often-considered inert excipients of a vehicle bring about changes within the skin at the molecular level that promote barrier restoration and enhance innate immune defenses with therapeutic value to AD patients. Moreover, the vehicle control in randomized controlled trials (RCTs) increasingly displays significant efficacy. In light of this, we consider the implications of vehicle design in relation to AD pathophysiology and the role vehicles play as controls in RCTs of new drug treatments for this condition.

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Atopic dermatitis and the skin barrier

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory disease of the skin, which is characterized by xerosis, pruritus, and erythematous lesions. The prevalence of AD is high, affecting 15% to 30% of children and 2% to 10% of adults (1). It is a disease that can cause enormous suffering at a crucial time in a child's development (2). A key event in the development of AD is breakdown of the skin barrier, formed by the intact stratum corneum (SC) (3). Skin barrier breakdown in AD can also occur as a result of the pro-allergic inflammatory state, characterized by high levels of T-helper type 2 (Th2) cytokines including interleukin (IL)-4 and IL-13 (4).

The structure of the skin barrier is often compared to that of a brick wall (Figure 1). The bricks represent the corneocytes, which are terminally differentiated keratinocyte cells. The mortar around the brick represents the lipid lamellae, a highly ordered arrangement of lipids that restricts water movements between the corneocytes (5). The functional integrity of these lipids, as a barrier to water, is dependent on the balance between the three constituent lipid types: ceramides, fatty acids and cholesterol. The corneocytes, which are themselves coated in an insoluble layer of protein (water-proofing), harbor a collection of water binding molecules (humectants) referred to as natural moisturizing factor (NMF). NMF accounts for 20% to 30% of the SC by weight, and helps keep the skin hydrated (6). Together this two-compartment system (bricks and mortar) creates an effective permeability barrier. This barrier provides essential protection from dehydration (inside-outside water permeation) and from irritants and allergens in the environment (outside-inside permeation) (3).

The skin barrier of patients with AD is defective, allowing water to escape, and predisposing the skin to dryness (7). The defect arises due to abnormalities affecting both the bricks and the mortar. Broadly, altered differentiation of keratinocytes culminates in an abnormal formation of the insoluble protein layer around the corneocytes and reduced production of NMF contained within them. This reduces the skin's capacity to retain moisture (6). Broad defects in lipid production, trafficking and processing culminates in a similarly defective lipid matrix around the corneocytes (5). This increases the permeability of the SC to water.

Disruption of the skin barrier triggers an abnormal response in patients with AD that favors pro-allergic inflammation (8). Innate defense mechanisms, such as the production of antimicrobial peptides and skin barrier repair mechanisms are inhibited under these conditions (9). The microbiome on the skin changes, and the opportunistic pathogen *Staphylococcus aureus* frequently takes hold, which can subsequently aggravate the inflammatory response (10,11). Damage to the skin barrier permits the penetration of irritants and allergens, which subsequently triggers immune system hyper-reactivity. In this way the

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structure and function of the skin barrier plays a pivotal role in both the development and fluctuating persistence of AD (3).

The role of vehicles

The role of the vehicle is to sustainably deliver the active pharmaceutical substance (i.e. drug) to the target site within the skin at an appropriate level to provide a pharmacological effect (12,13).

Currently, the most commonly used topically delivered pharmaceutical drugs for the treatment of AD are corticosteroids (14). Topical corticosteroids (TCSs) exhibit broad anti-inflammatory effects that have proven effective in suppressing inflammatory lesions of AD. To exert a pharmacological effect, corticosteroids must reach the viable epidermis and dermis where they target the glucocorticoid receptor (GR) expressed by infiltrating immune cells, keratinocytes and fibroblasts. There are several technically challenging barriers that stand between the active drug within the vehicle and the target site (Figure 1) (15).

To overcome these barriers a vehicle must:

1. maintain the solubility and stability of the active drug;
2. release the active drug, depositing it on the skin with even distribution;
3. enable penetration into and permeation through the SC/skin barrier;
4. facilitate partitioning from the SC into and diffusion through the viable epidermis;
5. sustain the active drug at the target site for a sufficient duration to provide a pharmacologic effect; and
6. limit systemic absorption.

Drug delivery

The rate-limiting step in topical drug delivery is often partitioning into and permeation across the SC, which forms the skin barrier. From a drug delivery perspective, the SC can be seen as a two-compartment structure of hydrophilic cells (bricks) within a hydrophobic matrix (mortar). Inevitably this highly effective natural barrier creates a significant obstacle for the delivery of active drugs. To permeate through the SC (transdermal delivery) a drug must take 1 of 2 direct paths: (1) the intercellular path through the continuous hydrophobic lipid compartment or (2) the transcellular path through the discontinuous polar (hydrophilic) environment of the corneocyte compartment which is interspaced by the hydrophobic lipid bilayers (15). Although strongly lipophilic substances may readily permeate through the SC (intercellular route), they partition poorly into the hydrophilic viable epidermis beneath, which represents another barrier to delivery. This means that active drugs must exhibit balanced physiochemical properties (e.g. solubility in lipids and water for instance) to partition into and permeate across the physiochemically different skin compartments to reach their target site. Small, predominantly lipophilic molecules with some hydrophilic properties can pass through the skin by simple diffusion (16). For other types of molecules, achieving sufficient bioavailability at the target site within the skin requires assistance. A third, indirect, route of drug absorption involves the pilosebaceous unit (12). In this case, the hair follicle acts as a reservoir from which drug is slowly released over time. The most common route of drug absorption is the intercellular path through the SC, followed by the follicular path. Through careful design, vehicles can be designed to disrupt the barriers presented along these paths to facilitate the absorption of the drug (12). The amount of active drug that ultimately passes through the skin and enters systemic circulation is generally very low. In the case of TCSs the amount that is systemically absorbed is typically less than 5% of the applied drug (17).

The anatomical site of drug application is an important consideration. Anatomical variations in the density of hair follicles, sebum production, sweat, moisture levels and SC thickness all affect absorption (18). The number of corneocyte layers making up the SC varies from 6 on the genitals to 86 on the heel in healthy adults, significantly affecting the permeation barrier and consequently drug bioavailability (19). This is reflected in the range of SC thickness from 66 microns on the eyelid to 660 microns on the sole of the foot (20). As a result the greatest absorption of TCS is on the eyelid, genitals, the rest of the face, and the flexures, and these are therefore at greater risk of local

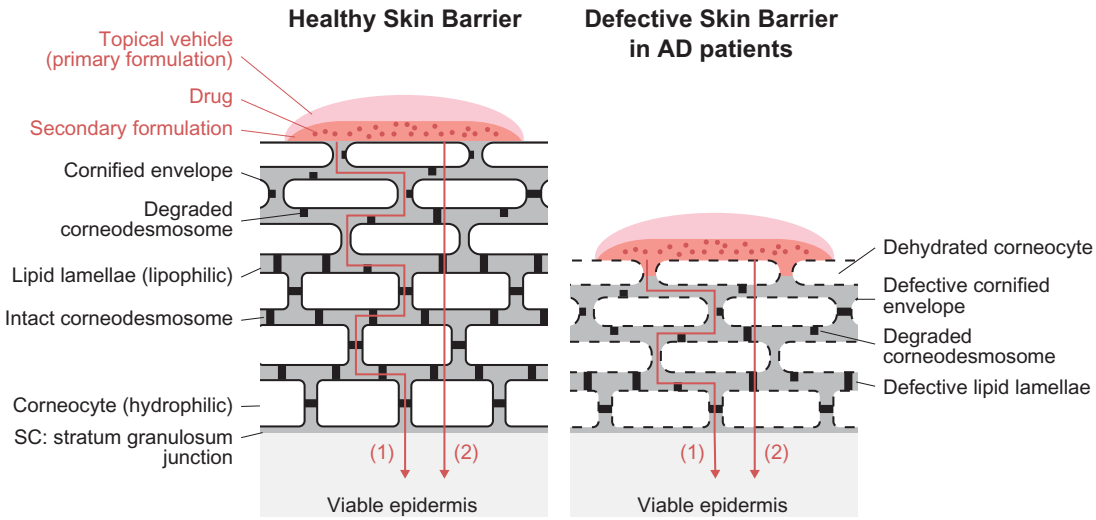

Figure 1. The structure of the skin barrier in healthy and AD skin. The vehicle and the paths of drug delivery are illustrated in red. The first path (1) is the intercellular route around the corneocytes. The second path (2) is the transcellular path, which passes through the hydrophilic corneocytes and the lipophilic lipid lamellae. The path of drug delivery is shorter and less challenging in the skin of AD patients.

adverse side effects (21,22). In patients with AD the drug permeability barrier is diminished due to pathological degradation of the skin barrier, meaning that patients with AD are, in general, at greater risk of systemic drug absorption depending on the severity of the condition (23).

Vehicle formulation

It is difficult to appreciate the skill involved in formulating and creating topical vehicles when reviewing a list of excipients. As an example of this unseen complexity, Stoughton revealed that generic formulations of triamcinolone acetonide and betamethasone valerate preparations were significantly less potent than the original trade name preparations (24). In this case, triamcinolone acetonide cream from the original manufacturer at three different strengths, 0.025%, 0.1% and 0.5%, exhibited similar potency, with vasoconstriction scores of 54, 56, and 54, respectively (a higher score indicates higher vasoconstrictor activity and therefore greater potency). All potencies, including 0.025%, displayed greater potency than 5 generic 0.1% triamcinolone acetonide formulations from other manufacturers, which displayed vasoconstriction scores ranging from 21 to 41.

No single approach is suited to all drugs and uses, and so a bespoke approach is required based upon the physiochemical properties of the drug (12,13). Some of the common ingredients of vehicles and their functions are provided in Table 1 for reference (25). Broadly, to enhance drug delivery, vehicles can be designed to alter the solubility of the drug, include chemical or physical carriers or carrier systems and/or occlude the skin (ointments or films). Physical occlusion increases the hydration of the skin and markedly increases skin penetration of applied substances. This phenomenon underpins the usefulness of patch testing to readily assess skin responses to irritants and allergens. Hydrocarbon ointments provide reasonable skin occlusion and so aid drug delivery (26).

The solubility of the drug is manipulated to improve partitioning from the vehicle into the SC. Malzfeldt et al. demonstrated that the solution capacity of the vehicle can greatly affect the clinical efficacy of betamethasone-17-benzoate preparations despite the drug concentrations being the same (27). In this case, betamethasone-17-benzoate (0.0056%) delivered in a vehicle as a suspension (i.e. having low solubility in or affinity for the vehicle) yielded 80% clearance of dermatoses compared with only 40% clearance in a solution type vehicle (wherein the drug was 50× more soluble).

The metamorphosis of the vehicle following application can have a profound effect of drug solubility and partitioning (18). Upon application, volatile solvents, such as water, alcohol, and propellants (used in foams and sprays) begin to evaporate and change the solubility of the drug. The excipients remaining on the skin surface following the evaporation of these volatiles is often referred to as the secondary formulation. In sophisticated formulations, this is used to force partitioning of the drug into the SC. In this way, aqueous-ethanolic quick-break foam formulations of betamethasone valerate can yield greater bioavailability than cream formulations due to the rapid evaporation of ethanol upon application (28). Note that the bioavailability of the foam formulation was comparable to the ointment formulation; the semi-occlusive property of ointments appears to enhance drug delivery compared to creams. In another example, however, calcipotriene and betamethasone dipropionate in an aerosol foam delivered greater bioavailability compared to an ointment vehicle (29). This nicely demonstrates that both the "form" (foam vs. cream vs. ointment) and "composition" (discussed below) contribute to bioavailability.

To facilitate drug delivery, chemicals that disrupt the structure of the SC, referred to as penetration enhancers, are used. Many penetration enhancers, like propylene glycol, are also solvents and so can be used, alone or in combination, to help facilitate both the partitioning into and the passage through the SC. However, care must be taken in selecting and using chemical penetration enhancers. Overzealous use can lead to unwarranted systemic absorption of the drug and skin irritation. Propylene glycol is a commonly used solvent and penetration

Table 1. Examples of common vehicle ingredients and their properties,.

Ingredient type	Role[a]	Examples	Effects on the skin[b]
Lipids and hydrocarbons (oils and waxes)	Main structure forming materials for semi-solid dosage forms	White soft paraffin/petrolatum, liquid paraffin, lanolin, beeswax, carnauba wax, cetyl alcohol, isohexadecane	Occlusive and skin conditioning (skin soothing and softening agents)
Thickening/gelling agents	Main structure-forming materials for gels and viscosity-enhancing agents for creams and lotions	Carbomer, methyl cellulose, guar gum, gelatin, sodium alginate	–
Silicones	Lubricant and film-forming agent	Dimethicone	Occlusive and skin protecting
Humectants (polyols)	Promotes water retention in the vehicle system and skin	Glycerol, sorbitol	Moisturizing, skin protecting, skin barrier stabilizing
Emulsifiers	Surfactants use to make emulsions of water and lipids	Glycerol monostearate, cetostearyl alcohol, cetyl palmitate, polysorbate 60, sorbitan monostearate	Skin conditioning. Harsh surfactants can have deleterious effects by dissolving lipids and irritating the skin
Solvents	Used to dissolve or disperse the drug	Water, propylene glycol, hexylene glycol, oleyl alcohol, mineral oil/ liquid paraffin	Various, as described for other types
Penetration enhancers		Propylene glycol, oleic acid, isopropyl myristate, ethanol	Disrupt the skin barrier to enhance drug delivery. Can be irritating in high concentrations
pH regulators	Maintain optimum pH for drug/ delivery system	Citric acid, lactic acid, phosphoric acid, sodium hydroxide	Products with high buffering capacity can alter skin surface pH positively and negatively
Antioxidants	Help stabilize the active drug	Butylated hydroxyanisole, butylated hydroxytoluene	Oxidative stress within the SC is associated with barrier disruption and inflammation
Preservatives	Prevents microbial contamination of the product	Parabens, benzyl alcohol, chlorocresol, ethylene diamine tetraacetate	These are added to protect the product rather than exert an antiseptic effect on the skin

[a]Many ingredients display multiple properties and effects on the skin.

enhancer, which is thought to integrate into the hydrophilic regions of the packed SC lipids and increase the solubility of this domain for the permeant (15), yet at high concentrations (above 10%) can irritate the skin (12,30). In contrast, long chain fatty acids like oleic acid insert between the hydrophobic lipid tails to increase the fluidity of the lamellar bilayers. Surfactants and detergents also act as penetration enhancers by solubilizing the SC lipids (31). With respect to the treatment of patients with AD, however, there is a more fundamental issue concerning the integrity of the skin barrier. Abrogation of this defensive barrier, which leaves the skin exposed to irritants and allergens, is an important factor in the development and exacerbation of AD (3). Penetration enhancers by nature damage this barrier, and so a careful tradeoff must be made between delivering a therapeutic drug dose and protecting the integrity of this barrier. The cutaneous inflammation experienced by patients with AD promotes hypersensitivity and also suppresses skin barrier function (8). The effective delivery of anti-inflammatory drugs, including corticosteroids and calcineurin inhibitors, using penetration enhancers can therefore bring about a net improvement in skin barrier function when used in the right way to inhibit inflammation (32,33). In an added complication, the prolonged use of TCSs after resolution of inflammation prevents full recovery of the skin barrier owing to suppressive effects of the drug on skin barrier genes, which are linked to the widely established atrophic effects of this therapy (34,35).

Beyond chemical penetration enhancers, other formulation technologies can help deliver drugs to the target site within the skin and in a controlled way. Some examples include nanoparticles, liposomes, noisomes, transferosomes, ethosomes, and microemulsions. Nanoparticles appear to concentrate drug delivery to the epidermis and limit onward transit (36). Liposomes are purported to slowly release the drug to achieve sustained delivery over longer periods of time, while also minimizing systemic absorption (37). In addition to augmenting the delivery of active drugs microemulsions display skin barrier protective and moisturizing properties (38).

The application of these strategies to improve drug delivery has led to the development of TCSs with wide-ranging clinical effects, even where the active corticosteroid and concentration in the vehicle are the same. Betamethasone dipropionate, for example, is represented in 4 potency classes from mid-strength to super-potent, at the same drug concentration of 0.05% (Table 2) (12). This is achieved in part by augmenting the vehicle formulation using solvents and penetration enhancers, principally including propylene glycol (39,40). Although ointments generally appear to perform better than creams and lotions, the higher potency of augmented betamethasone dipropionate 0.05% cream over betamethasone dipropionate 0.05% ointment is a good example of how this assumption can be misleading (18). Moreover, the form of vehicle chosen should be based upon more than drug delivery.

The properties of vehicles

Topical vehicles take a number of different forms, which are summarized in Table 3 (42). Beyond the physiochemical requirements of the active drug, clinical need and cosmetic acceptability play important roles. For the treatment of AD, vehicle forms with a high content of lipids and skin conditioning agents (also known as emollient ingredients) are optimal owing to their ability to soften, soothe, and protect the skin (41). Adherence to topical therapies is notoriously low (43), and so the choice of product should be guided first and foremost by the preferences of the patient, with regard to cosmetic acceptability, to ensure it is used in necessary quantities (44). Poor adherence to topical therapies prevent patients from achieving control of their skin dysfunction/disease (45).

Creating different dosage forms requires a wide range of different ingredients referred to as excipients in pharmaceutical formulation. Excipients typically make up more than 90% of a finished pharmaceutical product, and are often considered 'inactive' in terms of their effects on the skin (13). As alluded to above, however, the ingredients of vehicles are shared with another important class of topical preparation: emollients. Emollients are skin moisturizers that are based upon ingredients with 'skin conditioning' and 'occlusive' properties (46,47). Where these ingredients are seen as excipients in vehicles, they are considered active compounds in emollients due to the diverse benefits they impart on the skin (Table 1). Therefore, it is important to recognize that rather than being inert carrier systems for drugs, emollient vehicles possess therapeutic potential in their own right. Indeed, many vehicles are marketed as emollients, so it should be clear there is no distinction between the two.

The therapeutic mechanism of action of emollients (used alone or as vehicles)

Topical emollients (henceforth meaning emollients used alone and emollients used as vehicles), exhibit therapeutic effects in AD patients beyond that expected of simple moisturizers (48). Although a new generation of skin barrier repair emollients aim to directly correct skin barrier dysfunction by enhancing the expression of key skin barrier genes (49) or by replacing the essential skin lipids required for optimal function (50), the focus here is on the traditional mechanisms currently common to topical emollients.

Artificial restoration of the skin barrier

Emollients are typically based around long chain hydrocarbon mixtures such as petrolatum (soft paraffin) and mineral oil (liquid paraffin). When applied to the skin these hydrocarbons form an occlusive layer over the surface of the skin (26). Rather than simply sitting on the top, they appear to enter the defective SC matrices and replace the intercellular lipid bilayers. In doing so, permeability barrier function is transiently restored (Figure 2). Pure ointments have been shown to transiently reduce transepidermal water loss by as much as 50%. By trapping water underneath this artificial barrier, the SC is rehydrated and softened. The effect is transient, lasting at most 8 h, necessitating frequent application (51,52). The semipermeable barrier formed by petrolatum creates an optimum environment for rapid skin barrier repair following damage (53). Complete occlusion of the skin with an impermeable barrier inhibits the repair response, whereas dry skin is prone to excessive inflammation leading to tissue hyperplasia. Rather than being a purely physical effect, recent evidence suggests that skin occlusion and skin treatment with a simple paraffin-based cream independently trigger molecular changes that drive the repair response (54). These changes include increased expression of genes encoding skin barrier structural components (filaggrin [*FLG*] and loricrin [*LOR*]) and

Table 2. Topical corticosteroid potencies.

Class	Generic name (brand name)	Dosage form	Strength (%)
Class I (super potent)	Betamethasone dipropionate (Diprolene)	Ointment	0.05
	Clobetasol propionate (Temovate, Dermoxin)	Ointment, cream	0.05
	Diflorasone diacetate (Fluorone, Psorcon)	Ointment	0.05
	Halobetasol propionate (Ultravate)	Ointment, cream	0.05
Class II (very potent)	Amcinonide (Cyclocort)	Ointment	0.1
	Betamethasone dipropionate (Diprolene, Diprosone)	Ointment, cream, foam, solution	0.05
	Desoximetasone (Topicort)	Ointment, cream	0.25
	Desoximetasone (Ibaril)	Gel	0.05
	Diflorasone diacetate (Florone, Maxiflor)	Ointment	0.05
	Fluocinonide (Lidex)	Ointment, cream, gel	0.05
	Halcinonide (Halog)	Ointment, cream	0.1
	Mometasone furoate (Elocon, Ecural)	Ointment	0.1
	Triamcinolone acetonide (Kenalog)	Ointment, cream	0.5
Class III (potent)	Amcinonide (Cyclocort)	Cream, lotion	0.1
	Betamethasone valerate, (Valisone)	Ointment	0.01
	Diflorasone diacetate (Florone, Maxiflor)	Cream	0.05
	Fluticasone propionate (Cutivate)	Ointment	0.005
	Fluocortolone (Ultralan)	Cream	0.25
	Fluocinonide (Lidex E cream, Topsyn)	Cream	0.05
	Halcinonide (Halog)	Ointment	0.1
	Triamcinolone acetonide (Aristocort A)	Ointment	0.1
	Triamcinolone acetonide (Aristocort-HP)	Cream	0.5
Class IV (moderately potent)	Betamethasone valerate (Valisone, Luxiq)	Lotion	0.01
	Desoximetasone (Topicort-LP)	Cream, gel	0.05
	Fluocinolone acetonide (Synalar-HP)	Cream	0.2
	Fluocinolone acetonide (Synalar)	Ointment	0.025
	Flurandrenolide (Cordran)	Ointment	0.05
	Halcinonide (Halog)	Cream	0.025
	Hydrocortisone valerate (Westcort)	Ointment	0.2
	Mometasone furoate (Elocon, Ecural)	Cream	0.1
	Triamcinolone acetonide (Kenalog)	Ointment	0.1
Class V (moderate)	Betamethasone dipropionate (Diprosone)	Lotion	0.05
	Betamethasone valerate (Valisone)	Cream	0.01
	Fluocinolone acetonide (Synalar)	Cream	0.025
	Fluocinolone acetonide (Dermasmoothe/FS)	Oil	0.01
	Flurandrenolide (Cordran)	Cream	0.05
	Fluticasone propionate (Cutivate)	Cream	0.05
	Hydrocortisone butyrate (Locoid)	Cream	0.1
	Hydrocortisone valerate (Westcort)	Cream	0.2
	Triamcinolone acetonide (Kenalog)	Lotion	0.1
Class VI (mild)	Alclometasone dipropionate (Aclovate)	Ointment, cream	0.05
	Betamethasone valerate (Valisone)	Lotion	0.05
	Desonide (Desowen, Tridesilon)	Cream	0.05
	Fluocinolone acetonide (Synalar)	Cream, solution	0.01
	Prednicarbate (Dermatop)	Cream	0.1
	Triamcinolone acetonide (Aristocort)	Cream	0.1
Class VII (very mild)	Dexamethasone (Decadron phosphate)	Cream	0.1
	Hydrocortisone (Hytone, others)	Various	0.5, 1, 2.5

Adapted from Hengge UR, Ruzicka T, Schwartz RA, et al. Adverse effects of topical glucocorticosteroids, J Am Acad Dermatol, 2006;54(1):1–15, with permission from Elsevier (21).

innate immune system mediators (IL-1b, IL-6, and IL-8). IL-1b, IL-6 and IL-8 are important pro-inflammatory cytokines released in response to skin barrier disruption that help orchestrate the repair response. IL-17 and IL-22 are inducers of antimicrobial peptide expression. The increased expression of IL-17 and IL-22 was accompanied by increased expression of the antimicrobial peptides S100A7, S100A8, S100A9, S100A12, lipocalin 2, LL37, PI3, and chemokine ligand 20. An earlier study by Buraczewska et al. support these findings by demonstrating that the long-term treatment of skin with two different moisturizers differentially affected the expression of genes involved in keratinocyte differentiation and desquamation (55). The hydrocarbon-rich cream (20% isohexadecane and 20% paraffin) increased gene expression of involucrin, transglutaminase 1, kallikrein 5, and kallikrein 7, whereas the comparator cream (with low levels of hydrocarbons) inhibited expression of cyclin-dependent kinase inhibitor 1A.

Patients with AD exhibit weakened physical and antimicrobial defenses supporting the therapeutic benefits of this novel mechanism of action of paraffin-based emollients (3,9). Suppression of these skin barrier functions is driven by the Th2-skewed inflammatory state of AD skin, characterized by a cytokine milieu comprising IL-4, IL-5, and IL-13. A clear inhibitory effect of petrolatum on Th2 inflammatory responses was not observed by Czarnowicki et al.; however, a reduction in inflammatory cell infiltrates was observed in petrolatum treated skin (54). Petrolatum has also been found to inhibit the synthesis of prostaglandins in the skin (56). Prostaglandins are important mediators of tissue inflammation in patients with AD. Further back, in 1975, Tree and Marks first uncovered the antimitotic effects of petrolatum on the skin and raised the therapeutic implications this could have for topical placebos (7).

How exactly simple paraffin-based creams elicit these molecular changes independent of occlusion/hydration is

Table 3. Common vehicle forms.

Form	Description[a]	Clinical use and acceptability	Comments
Ointment	A suspension or emulsion semisolid dosage form that contains <20% water and volatiles and >50% of hydrocarbons, waxes, or polyols	Suited to palmoplantar skin and infiltrated, lichenified lesions	Often comprising >80% petrolatum, they display superior occlusive and emollient properties compared to other forms. However, the greasy nature of ointments makes them less acceptable to patients
Cream	An emulsion semisolid dosage form that contains >20% water and volatiles and/or <50% of hydrocarbons, waxes, or polyethylene glycols. Emulsifiers are used to create and stabilize the emulsion between the phases (18)	Acute and subacute lesions	The active drug is dispersed between the water and oil phases depending on its partition coefficient. Being easy to apply, these provide a good compromise between emollient efficacy and patient compliance
Gel	A semisolid dosage form that contains a gelling agent to provide stiffness to a solution or colloidal dispersion	Suitable for all lesions	An easy to apply alternative to creams; however, aqueous (monophasic) gels lack emollient properties. To improve the suitability of gel vehicles for AD treatments, emulsified gels (emugels) have been developed (dual phase systems of lipid dispersed in water)
Lotion	An emulsion liquid dosage form with >50% water and volatiles	Acute and subacute lesions. Not generally suitable for use on very dry skin	Easily applied over large areas of skin, but do not display the benefits of lipid-rich cream and ointment vehicles (41)
Foam	Multiphase suspension containing a propellant stored under pressure and forming a foam upon release that quickly breaks down on the skin	Suited to inflamed or sensitive areas because of the reduced need to rub them into the skin	Particularly suited to hairy areas of skin. Typically have limited occlusive properties

[a]Descriptions taken from Buhse et al., 2005 (42).

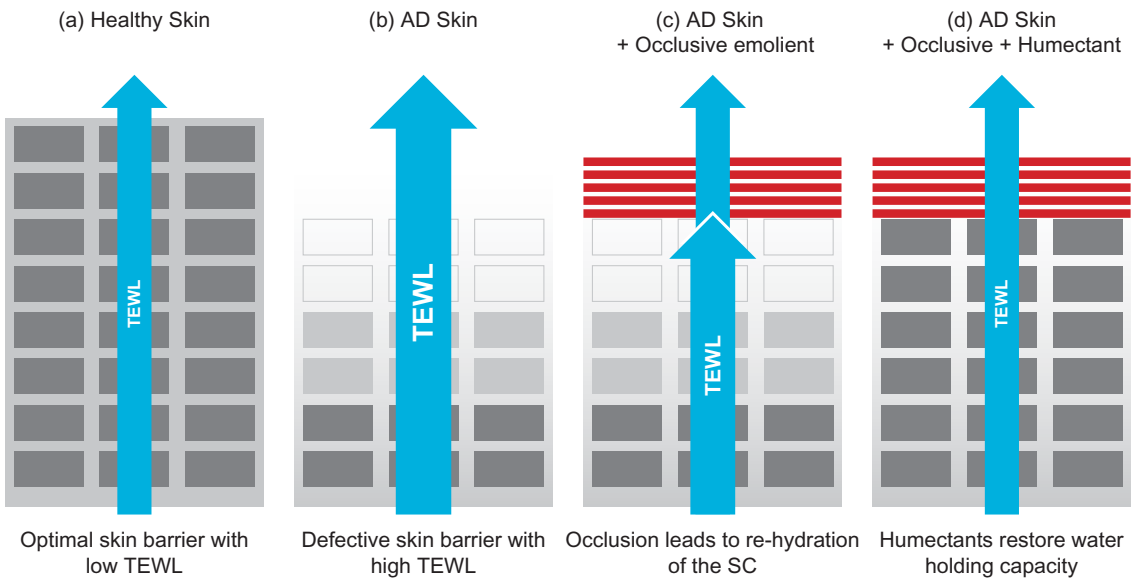

Figure 2. Mechanism of action of emollients. A healthy skin barrier (a) comprises two main structural compartments; including the corneocytes (boxes) and the extracellular lipid lamellae (shading around the boxes). The corneocytes contain natural moisturizing factors (NMF) that bind to water and keep the stratum corneum hydrated. The lipid lamellae are a highly ordered matrix of lipids that prevents the movement of water between the corneocytes. Together these compartments form an effective permeability barrier to water and external irritants and allergens. In AD skin (b) there is a deficiency in NMF and a lipid abnormality that disrupts the permeability barrier, leading to elevated transepidermal water loss (TEWL) and increased susceptibility to irritants and allergens. Occlusive emollients (c) coat the skin to form a transient semi-occlusive barrier. This nonphysiologic barrier artificially restores barrier function and traps water in the SC to rehydrate the skin. Humectants (d) are added to emollients to replace the lost NMFs and increase the water-holding capacity of the skin.

unclear. One possible explanation is the persistence of trace amounts of aromatic hydrocarbons from the purification of paraffin (54). Aromatic hydrocarbons trigger IL-17 and IL-22 mediated responses via the aryl hydrocarbon receptor (AHR), and it is now thought these underpin the therapeutic effects of coal tar in the treatment of psoriasis (57,58).

Replenishment of skin moisturizers

Although pure ointments display good occlusion, emollient creams and gels exhibit limited occlusive effects due to the reduction in waxes and oils (52). In these cases, humectants are often added to improve their moisturizing effects. When applied to the skin they help replenish the low levels of NMF associated

with AD (Figure 2) (59). Polyols are particularly effective humectants, with glycerin (synonyms glycerol and glycerin) commonly found in emollient creams and lotions (46). Other humectants that can be found in emollients include pyrrolidine carboxylic acid, lactic acid, and urea, which are constituents of NMF in the skin. In very dry environments, humectants exhibit reduced efficacy. Under such circumstances, glycerol and urea have been found to soften the skin by inhibiting the transition of the intercellular lamellar lipids from liquid to solid crystal phase. This skin conditioning property is also associated with increased permeability, meaning humectants like glycerol and urea can be utilized in vehicles as penetration enhancers (60,61).

Beyond skin moisturization, humectants appear to help accelerate skin barrier repair. Although some of this effect can be attributed to their humectant activity, they also display distinct molecular effects. Glycerol, for instance, significantly accelerates skin barrier recovery when applied to the skin following disruption (62,63). Urea, but not glycerol, appears to strengthen the skin barrier and protect against surfactant induced irritation (64,65). This effect has been attributed to the ability of urea to stimulate the expression of keratinocyte differentiation-dependent genes such as the one encoding the structural protein filaggrin (49,66). Filaggrin gene defects in particular are a strong predisposing factor for AD (67). Lactic acid promotes the expression of genes involved in ceramide synthesis (68). As mentioned above, the skin of patients with AD is characterized by abnormal differentiation, which predominantly includes reduced expression of filaggrin, and altered lipid metabolism leading to reduced ceramide levels (5,51).

Altering skin surface properties

An often-overlooked aspect of topical products is how they affect the physiochemical properties of the skin surface. The pH of the skin surface is a particularly important property with relevance in the pathophysiology of AD (69). Healthy skin exhibits an acidic surface of pH 4.5 to 5.0 that restricts corneocyte shedding (desquamation), promotes lipid processing, and prevents the growth of pathogenic bacteria. In AD, skin surface pH increases, reaching as high as pH 7.0 at acute skin lesions. As a result, the SC becomes thinner as desquamation outstrips the formation of new corneocytes, lipid processing is inhibited, and the skin microbiome changes markedly. In particular, the skin environment becomes more conducive to *S. aureus* colonization. More than 90% of AD lesions are colonized by this bacterium, the extent of which closely associates with severity of the condition (11). In animal models, the maintenance of an acidic SC can prevent the emergence of AD, highlighting the potential benefit of manipulating skin pH in humans (70). Topical leave-on products can be used to manipulate the pH of the skin surface. Preparations that lower the pH of the skin appear to enhance skin barrier structure and alter the skin microbiome (71). Unfortunately, however, the majority of emollients appear to exhibit a relatively high pH that could contribute to the abnormal skin barrier homeostasis seen in patients with AD (72).

Clinical efficacy of emollients (used alone or as vehicles)

The evidence presented above suggests that far from being simple moisturizers, emollients help correct two key pathophysiological processes underpinning AD by promoting skin barrier restoration and innate immune responses at a molecular level. Clinically there is robust evidence that the regular use of emollients reduces the severity of AD; however, the level of reduction is small and of questionable clinical significance (48,73). Patients agree that using emollients is more effective at reducing the severity of AD overall, and specifically at reducing itch, compared with no treatment. When used as a maintenance therapy following flare resolution, emollients significantly prolong the period before the next flare, reducing the risk of a new flare by 3.74× compared with no treatment (74,75). The use of an emollient was also associated with a reduced need (by half) for TCSs as a rescue therapy. When emollients are used in combination with TCSs, clinical efficacy was significantly improved and the risk of new flares reduced by 2.38× compared with TCS treatment alone.

The benefits of using emollients are highly dependent on the frequency of application (51), in agreement with the transient effects of occlusive ingredients. Although there is very limited evidence comparing emollients with other emollients, it is clear that not all emollients are equal. Some emollients, like Aqueous Cream BP, containing harsh surfactants, damage the skin barrier and consequently increase the risk of cutaneous adverse reactions (76). Glycerol-based emollients in general exhibit significantly greater efficacy at treating skin dryness compared to emollients without glycerol, and concordantly demonstrate greater overall efficacy in treating AD (48). Caution is required in generalizing the benefits of emollients based on a single perceived active ingredient, however, as the interaction between active moisturizing agents and other excipients is known to substantially affect overall efficacy, much like vehicle design appreciably affects drug delivery and response (77,78). Unfortunately, few studies directly compare the efficacy of emollients at reducing the severity of AD or improving the control of the condition, especially considering the wide array of emollient formulations available. In a recent example, Akerstrom et al. directly compared a urea-containing emollient to a bland emollient without humectants in a randomized, controlled flare prevention trial (79). A greater than two-fold difference in the propensity to new flares of AD was found between the treatment groups. Together these findings on emollients support a wider role for emollients as important adjuvants to topical active therapies such as TCSs, rather than stand-alone therapies.

Vehicles display heterogenous efficacy in AD clinical trials

It is common practice to compare new topical pharmaceutical treatments to their vehicles or a similar topical control in randomized controlled trials (RCTs). Often the term placebo is used, however, this is incorrect and misleading given that vehicles/topical controls are often essentially emollients with inherent therapeutic effects (80). Very rarely would no treatment be used as a control due to the ethical implications of withholding treatment. Recent systematic reviews have compiled and compared the clinical responses to drug treatments for AD, including corticosteroids and calcineurin inhibitors (73,81,82). What is striking about these studies is the often marked response to the control treatment. Table 4 summarizes some of these studies, providing the relative responses to the pharmaceutical drug treatment and the vehicle control. Following the strategy of Fishbein et al., responders were defined as patients displaying either a 'good response' as defined by the study protocol, a 50% reduction in AD severity, or AD rated as cleared

Table 4. Vehicle effects in randomized controlled trials of AD therapies.

Study	Treatment[a]	Control	Number of patients (treatment, control)	Population	Frequency of application	Duration of treatment (days)	Response to treatment[b]	Response to control[b]	Ratio of response
Topical corticosteroid ointments[c]									
Udompataikul and Limpa-o-vart, 2012 (83)	Hydrocortisone 1% ointment (VII)	Dexapanthenol 5% ointment	26, 26	Mild-moderate	BID	28	87	87	1.00
Topical corticosteroid creams[c]									
Sudilovsky et al., 1981 (84)	Halcinonide 0.10% cream (II)	Vehicle, cream	58, 58	Not reported	BID	21	57	17	3.35
Sugarman and Parish, 2009 (85)	Fluticasone propionate 0.05% cream (III)	Emollient cream containing a ceramide dominant mixture of physiologic lipids	59, 53	Moderate-severe	BID	28	44	36	1.22
Abramovitis and Oquendo, 2010 (86)	Hydrocortisoine butyrate 0.1% lipocream (V)	Vehicle, emollient cream	131, 133	Mild-moderate	BID	21–29	63	28	2.25
Stalder et al., 1994 (87)	Desonide 0.1% cream (III)	Placebo, cream	18, 21	Not reported	QD	7	57	14	4.07
Rauschkolb et al., 1981 (88)	Halcinonide 0.025% cream (IV)	Placebo, unspecified cream	79, 79	Not reported	TID	14	81	51	1.59
Luger et al., 2001 (89)	Betamethasone valerate 1% cream (III)	Vehicle, cream	42, 43	Moderate-severe	BID	21	88	16	5.50
Subtotals							65	27	2.99
Topical corticosteroid lotions[c]									
Matheson et al. 2008 (90)	Hydrocortisone butyrate 0.1% lotion (V)	Vehicle, lotion	139, 145	Mild-moderate	BID	28	49	24	2.04
Eichenfield and Miller, 2006 study 1 (91)	Fluticasone propionate 0.05% lotion (V)	Vehicle, lotion	110, 110	Moderate-severe	QD	28	75	32	2.34
Eichenfield and Miller, 2006 study 2 (91)	Fluticasone propionate 0.05% lotion (V)	Vehicle, lotion	111, 107	Moderate-severe	QD	28	66	27	2.44
Subtotals							63	28	2.27
Topical corticosteroid gels[c]									
Hebert et al., 2007 (92)	Desonide 0.05% gel (VI)	Vehicle, hydrogel	425, 157	Mild-moderate	BID	28	39	11	3.54
Topical calcineurin inhibitor creams[d]									
Luger et al., 2001 (89)	Pimecrolimus 1% cream	Vehicle, cream	45, 43	Moderate-severe	BID	21	53	16	3.31
Eichenfield et al., 2002 (93)	Pimecrolimus 1% cream	Vehicle, cream	267, 136	Mild-moderate	BID	28	31	11	3.65
Kapp et al. 2002 (94)	Pimecrolimus 1% cream	Vehicle, cream	204, 47	Mild-severe	BID	21	55	39	1.41
Ho et al., 2003 (95)	Pimecrolimus 1% cream	Vehicle, cream	123, 63	Mild-moderate	BID	21	44	17	2.47
Subtotals							46	21	2.71
Topical calcineurin inhibitor ointments[d]									
Boguniewicz et al. 1998 (96)	Tacrolimus 0.03% ointment	Vehicle, ointment	43, 44	Moderate-severe	BID	21	58	27	2.15
Boguniewicz et al. 1998 (96)	Tacrolimus 0.1% ointment	Vehicle, ointment	49, 44	Moderate-severe	BID	21	43	27	1.59
Subtotals							51	27	1.87
PDE4 inhibitors									
Paller et al. 2016 study 1 (97)	Crisaborole 2% ointment	Vehicle, ointment	503, 256	Mild-moderate	BID	28	52	41	1.27
Paller et al. 2016 study 2 (97)	Crisaborole 2% ointment	Vehicle, ointment	513, 250	Mild-moderate	BID	28	49	30	1.63
Subtotals							51	36	1.45

[a]Topical corticosteroid potency class in brackets.
[b]Percentage of patients achieving clear or almost clear.
[c]See systematic review by Fishbein et al., 2019 (81).
[d]See systematic review by El-Bataway et al., 2009 (82).
BID: twice daily; OD: once daily.

or controlled in order to overcome the reporting differences (81). This is an important limitation, and extreme caution should be taken in interpreting the responses quoted due to the methodological differences between the studies. On average, 65% of patients responded to treatment with various corticosteroid preparations administered for between 1 and 4 weeks compared with 32% for the control group. The response to the vehicle was heterogenous, ranging from 11% to 87%. This heterogeneity of response could not be explained by the age of participants or the duration of treatment. One contributing factor could be the severity of the AD. A smaller difference between the efficacy of a vehicle and TCS would be expected in mild AD relative to severe AD.

A crude observation is the overall response associated with each form of vehicle. Lotion vehicles were associated with a response rate of 28%, compared with 27% for creams, and 87% for the only ointment preparation tested. The lowest response of 11% was reported for a hydrogel vehicle, containing the humectant glycerin and no emollient ingredients (92). Notably, this study reported one of the largest separations in the effect of the pharmaceutical active preparation (desonide, 0.05%, potency class IV) and vehicle despite a moderate response to the former. It is tempting to postulate that the absence of a strong vehicle effect revealed a more pronounced effect of the active drug. In a subsequent RCT, desonide 0.05% gel was compared with desonide 0.05% ointment (98). The ointment preparation was associated with a greater reduction in the severity of AD compared with the gel. It is not clear whether this difference stems from an enhanced therapeutic effect of the vehicle, enhanced drug delivery. or a combination of both. A similar situation was reported by Stalder et al., where a large separation in the effects of desonide 0.1% cream (potency class III) was observed compared with a vehicle lacking in occlusive and emollient ingredients (87). Just 14% of patients responded to the control, whereas 57% responded to the pharmaceutical desonide preparation.

At the other end of the spectrum, Sugarman and Parish demonstrated equivalent efficacy between a complex emollient containing a ceramide dominant mixture of physiologic lipids and fluticasone propionate 0.05% cream (potency class III) (85). Similarly, Udompataikul and Limpa-O-Vart found a comparable therapeutic response to hydrocortisone 1% ointment (potency class VII) and a vehicle ointment containing the cosmetic skin conditioning ingredient dexpanthenol (83). Parneix-Spake et al. investigated the effects of clobetasol butyrate 0.05% cream compared with its vehicle and hydrocortisone 1% cream on nickel-induced contact dermatitis (patches containing nickel were applied to induce dermatitis prior to the 7-day treatment period) (99). Although clobetasol butyrate displayed the greatest therapeutic effect, the vehicle alone displayed greater efficacy at reducing dermatitis and correcting skin barrier dysfunction than either no treatment or treatment with hydrocortisone 1% cream. The positive effects of the vehicle have been attributed to its high concentration of the humectant glycerol. This is also a good example of where the vehicle for a pharmaceutical product is also marketed in its own right as an emollient treatment for dry skin.

Looking to other anti-inflammatory treatment for AD, RCTs of calcineurin inhibitors tacrolimus and pimecrolimus appear to show a stronger vehicle effect for the ointment base of the former compared to the cream base of the latter (82). The strength of this response appears to reduce the perceived efficacy of the more potent tacrolimus compared with pimecrolimus. A particularly strong vehicle effect was also reported in the RCTs for the newly developed phosphodiesterase 4 inhibitor crisaborole in patients with mild to moderate AD, which appears to conceal the otherwise strong response to the drug treatment (97). These observations beg the question of whether drug effects always augment vehicle effects (the assumption that underpins the vehicle control design) or whether they in fact mask them by reducing the therapeutic window.

Vehicles and flare prevention

The proactive use of topical pharmaceutical treatments at reduced application frequencies over long periods of time has been shown to reduce the risk of flares and improve the long-term control of AD (100). As mentioned above, emollients display significant potential as flare reduction therapies in their own right (48). This suggests that the vehicle effect may be stronger in flare prevention studies conducted over longer periods of time. In a study by Siegfried et al., significantly more participants receiving proactive treatment with pimecrolimus cream were flare free at 6 months (52%) compared with those receiving vehicle (34%) (101). Similar findings have been reported in other studies (94,102,103), suggesting a 1.5× lower risk of flares in the interventional group compared with the vehicle group overall. Although there is a clear distinction between the vehicle plus active drug and the vehicle alone in each case, the difference in effects is notably smaller than reported in trials of short-term reactive treatment. In the study by Kapp et al., the response to treatment was monitored at 3 weeks, 6 months, and 12 months (94). Although pimecrolimus 1% cream displayed significantly greater efficacy compared with the vehicle at 3 weeks in this study, the difference in effects was lost after 12 months due to an enhanced response to the vehicle with time. Studies by Wiren et al. (75) and Weber et al. (74) demonstrate that emollient treatment alone can significantly reduce the risk of flares, highlighting the potential for strong vehicle effects in this type of study.

It is interesting that despite the therapeutic contribution of some emollients in minimizing the occurrence of flares, an often-overlooked factor in pharmaceutical product flare prevention trials is the concomitant use of emollients (101). The impact of this baseline therapy is unclear, and rarely characterized in RCTs. It begs the question 'does the concomitant use of emollients simply improve the overall therapeutic effect or does it mask the effects of the pharmaceutical treatments delivered in a vehicle?'

The interaction between vehicles and other topical products

It has become common practice to combine the use of topical anti-inflammatories in emollient vehicles with separate emollient products in the treatment of AD. The use of emollient therapy in addition to TCS is superior to the use of TCS alone (47,104). Moreover, Lucky et al. first reported that once-daily TCS application regimens combined with emollient therapy can be as efficacious as twice-daily TCS application regimens without emollient therapy (105). This finding has since been replicated in a number of studies that support a significant steroid-sparing effect of concomitant emollient therapy by as much as 50% (106,107). There are two explanations for this effect. The first is

the therapeutic efficacy of emollients reviewed above. The second is the interaction between the two treatments leading to altered drug uptake.

A critical factor here is the persistence of drug in the SC following application. In the case of TCSs, the drug reservoir in the SC lasts for up to 14 days following application depending on the vehicle formulation—the length of time it takes to renew the SC (108). Occlusion of the skin at any point during this time results in a second dose as the corticosteroid stranded in the SC is driven into the deeper skin layers (28). Similarly, the application of emollients can liberate corticosteroids from this reservoir and facilitate permeation (96,109,110). The type of emollient applied, specifically the solvent and penetration-enhancing properties of the constituent ingredients, is important. Emollients displaying steroid-sparing effects contain penetration enhancers such as propylene glycol and butylene glycol (106). They are commonly added to emollients to improve moisturizer efficacy, but will indiscriminately increase SC permeability. Unfortunately, even as there has been interest in investigating the steroid-sparing effects of new emollients, there has been very limited attention placed on understanding the interaction of different emollients on SC drug reservoirs.

Although the interaction between emollients and TCS can enhance the overall therapeutic effect of a treatment regimen, there are also concerns that it may reduce corticosteroid responses by diluting the dose or inhibiting uptake (111). Barrier preparations are designed to help protect the skin from potential irritants and allergens, and so could conceivably impede drug uptake if applied first. A small-scale RCT appears to have found just this, with the application of emollient 15 min before TCS diminishing the response to the treatment compared with application of the emollient 15 min after the TCS (112,113). Current guidance for patients and healthcare professionals on the concomitant use of emollients and topical anti-inflammatory treatments is varied. Despite a lack of evidence there is a belief that emollients should be applied with TCS, separated by 'several' to 60 min, either before or afterwards depending on the guidance followed (112). The lack of clarity is unhelpful for patients, and so there is a need to understand the necessity for combined application, the order of application and the interactions between different TCS formulations and different emollients. Suboptimal combinations have the potential to reduce treatment responses, or at the other end of the spectrum, increase the risk of systemic adverse effects due to excessive drug delivery. It would seem therefore, that both the vehicle and concomitant emollient use are important determinants of drug efficacy.

Conclusion

The design of vehicles has a clear and profound effect of the bioavailability, and consequently the clinical efficacy, of pharmaceutical drugs. From this comes the impetus to develop the most sophisticated vehicles to achieve the maximum therapeutic response possible in randomized vehicle-controlled trials. But what if that pursuit actually reduced the chances of finding a significant therapeutic response because of the effects of the vehicle itself?

The same technology that improves drug delivery and response is used to enhance the moisturizer efficacy of emollients. Due to the inherently defective skin barrier in AD patients, emollient vehicles with moisturizing effects are therapeutically advantageous on multiple levels. They both facilitate drug delivery and bring about changes in the skin at the molecular level, which promotes skin barrier repair, enhances innate defense systems and suppresses inflammation. These intrinsically multi-functional vehicles therefore exhibit independent therapeutic effects. The question is 'do these effects add to the potential effects of drug treatments or mask them?'

In the absence of robust evidence, it is not possible to determine whether vehicles do in fact compete with pharmaceutical drugs to reduce the distinction in the effects between finished pharmaceutical product and vehicle. Yet vehicles do often display strong treatment responses compared with drug treatments. It suggests a need to reevaluate the design of RCTs to quantify the therapeutic effects of sophisticated emollient vehicles. We must avoid a situation where vehicles are designed without consideration for the benefits of emollients as this will ultimately reduce the convenience of use and ultimately patient adherence to treatment regimens.

Looking beyond the vehicle, emollients used in conjunction with pharmaceutical drugs display (secondary) vehicle effects and can modify treatment responses. The interactions between the drug, its vehicle and the other products applied to the skin are not fully understood, and yet evidence demonstrates that such interactions can significantly affect clinical performance. We must understand these interactions to streamline treatment regimens and maximize therapeutic responses. Understanding how to best use TCS and emollients was recently highlighted as an important issue for patients and healthcare professionals. Failing to understand this issue could jeopardize treatment responses in practice and hinder the development of new therapies.

Given the complexities of the interaction involved, perhaps the best solution is to take a holistic approach to topical treatment, where emollient and anti-inflammatory drug combinations are co-developed and tested together against the current standard of topical therapy in clinical practice.

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