Exploiting Emollient Selection for Tunable Design of Skin-Care Formulations Affecting Cutaneous Barrier and Biomechanical Function

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Abstract

Background: Since consumer perception of formulation efficacy is strongly affected by skin hydration, a key metric to optimize performance is the biomechanical stress developed in the SC during dehydration. Formulations that include ingredients with strong, beneficial synergies should significantly reduce drying stress in the SC and yield positive perceptions of skin comfort and softness. Determining a rational basis for understanding, predicting, and leveraging ingredient interactions is a critical step to elevate the customized design of advanced formulations that benefit skin health. Our objective was to provide insights with a holistic study involving fourteen skin-care formulations containing ten cosmetic emollients with widely varying properties and molecular structures whose individual effects were previously characterized.

Methods: Biomechanical stress development due to SC drying was measured *in vitro* using a substrate curvature technique. Special attention was given to formulation mediated changes in the maximum stress values that affect consumer perception. The maximum penetration volumes of formulations in the SC were characterized to compare with known mechanisms underlying individual ingredient effects.

Results: Remarkably, the linear correlation between penetration volume and stress reduction known for individual emollients was found to extend to formulations. Penetration volumes of ingredients increased dramatically when included in formulation, up to volumes of 37%. The polyacrylate thickener formed a tensing film on the SC surface, increasing stress by approx. 0.7MPa for all formulations. However, the synergistic effects underlying enhanced ingredient penetration overcame this increase such that most formulations exhibited improved biomechanical stress reduction over individual ingredients. The stress and penetration volume results were understood through a multi-parameter model considering the molecular weight, diffusivity, polarity, and viscosity of the emollient along with the known penetration enhancing effects of water.

Conclusion: We establish how multiple ingredients may behave synergistically to control the development of biomechanical stress affecting SC barrier function and consumer perception. Namely, this study reveals how combined ingredients amplify total penetration into the SC to strongly reduce stress and support the use of surface tensing films that may otherwise cause uncomfortable tightness. This predictive understanding is vital to ensure that when designing new cosmetic formulations, emollients and other ingredients are selected whose interactions maximize a positive impact to SC biomechanics and benefit skin health.

Keywords: Skin barrier; Cosmetic emollient penetration; Formulation skin care; Stratum corneum; Skin biomechanical properties

Introduction.

Cosmetic formulation ingredients, such as emollients and humectants, are widely used in skin-care formulations due to their efficacy in promoting skin health and pliant skin feel through moisturization and maintenance of the skin barrier function. A key aspect of the barrier function is the biomechanical properties of human stratum corneum (SC) that are critical to consumer sensorial perception. Although recent work has elucidated individual ingredient effects on SC biomechanical barrier properties, understanding is lacking about how ingredients affect optimum product performance when applied as part of a full skin-care formulation. In this case, ingredients including cosmetic emollients, humectants, emulsifiers, polymer additives, water, and/or other molecules may act together to amplify, reduce, or compensate for individual component effects.

Typically, formulation ingredients are included for purposes unrelated to SC biomechanics, though each has significant effects on the SC biomechanical barrier function. Cosmetic emollients (long-chain organic molecules with polar functional groups) are often incorporated due to their ability to "smoothen" and "soften" the skin while forming an oily, partially occlusive film that fills the space between superficial corneocytes [1]–[3]. Thus, emollients enable formulation spreadability and contribute to a positive skin-feel during formulation application [4]–[6].

Individual emollient effects on SC biomechanics have been closely linked to the degree an emollient penetrates the SC [7]. Specific molecular features, for example, molecular weight, diffusivity, topological polar surface area (TPSA), and viscosity can be used together to effectively predict the ability of an emollient (or other ingredient) to penetrate the SC, reduce the development of skin stress, and promote skin health and positive perceptions. The fundamental connection between emollient penetration and reduced SC stress has previously been established by a combined molecular diffusion and mechanics model, which also predicts the biomechanical effects of water or other ingredient diffusion through the skin [8], [9].

Humectants, such as glycerol, enhance skin hydration by absorbing into the SC then attracting and retaining moisture [1], [10]. Similarly, humectants also reduce biomechanical stress by penetrating the SC to replace lost water volume [11]. Amphiphilic emulsifiers help

disperse other components to enable uniform distribution throughout the formulation. As surfactants, emulsifiers such as sodium stearoyl glutamate (SSG) also strongly affect stress and enhance formulation penetration by altering SC lipids which make up the diffusion barrier of the skin [12]–[14]. Some evidence has also suggested the common antimicrobial preservative phenoxyethanol (PHE) may also enhance SC permeability through effects on intercellular lipids [15]–[17]. Ethylhexylglycerin (EHG), often included to boost the effects of PHE, also has surfactant properties owing to its amphiphilic structure [18], [19]. Water, a ubiquitous solvent in skin-care, should also be noted for its somewhat limited though significant ability to enhance ingredient penetration by altering or fluidizing the lipid diffusion barrier, hydrating the SC, and swelling the tissue [14], [20], [21].

Polymer additives thicken and stabilize the formulation emulsion to sustain component functionality. Evidence also indicates some polymer additives form a tensing film on the SC surface that reduces the appearance of wrinkles and provides other skin health benefits [22]–[24]. Consequently, both synthetic and naturally occurring polymers are investigated and optimized as additives. However, polymer surface films are also expected to increase biomechanical stress in the SC. Unacceptably large stress increases are known to weaken the SC barrier function, exacerbate painful skin conditions, and negatively impact skin perception with feelings such as “tightness” or “discomfort” [8]. The thin SC is critical to tactile perception because its stiffness is much greater than that of underlying skin layers, allowing the SC to control *local* skin deformation that activates mechanoreceptors [25], [26].

In the present study, we assess the ability of the ingredients described above to synergistically interact and affect SC biomechanical stress beyond the ability of an individual ingredient. Fourteen skin-care formulations are studied containing ten widely varying cosmetic emollients, a common film-forming polymer additive, and in some cases a well-known humectant. The individual effects of all ingredients on SC properties were previously characterized for comparison. Formulations that include ingredients with strong synergistic interactions should have the highest potential to significantly reduce drying stress in the SC and yield positive perceptions of skin comfort and softness, even if a tensing film polymer is utilized for anti-wrinkling or other purposes. Determining a rational basis for understanding, predicting, and leveraging these ingredient interactions is a critical step to guide the design

and customization of new, advanced cosmetic formulations that maintain or improve skin health.

Materials and Methods.

Stratum Corneum Preparation

Full-thickness samples of *ex vivo* human skin were obtained from Caucasian female donors through the National Disease Research Interchange (NDRI). The SC was isolated from these full-thickness abdominal samples through a trypsin-digest process described previously [27]. The SC was stored in a low humidity chamber [approx. 10–20% relative humidity (RH)] at an ambient temperature of approx. 18–23°C. The SC does not experience rapid apoptosis and structural damage after harvesting like most soft tissues in the body, since the SC is non-vascularized tissue composed of cornified anucleate cells. While floated on the surface of the trypsin digest solution, only the uncornified cells of the living epidermis are targeted for digestion thus leaving the cornified SC layer unaltered with the same structure it had *in vivo* [28], [29]. The experiments described in the present work were performed on this isolated SC at room temperature (approx. 25°C).

Emollient and Formulation Details

A list of the emollients used in this study and their physical properties can be found in Table 1. Their chemical structures are included in Fig.1. Two varieties of the coco-caprylate / coco-caprate (COC) emollient were used with differing average molecular weights. The larger molecular weight variety is abbreviated as COC_{large}, and the smaller as COC_{small}. Previous data depicting the effects of pure emollients are included in this work for comparison [7], though in current experiments cosmetic emollients were applied to the SC as part of a complete formulation.

Two different chassis formulations were used that either did or did not contain glycerol. The two types of formulation compositions are shown in Table 2. Fourteen unique formulations were studied and are referred to by the abbreviation of the included emollient name. If the formulation also contains glycerol, "+G" is added to the abbreviated name. A simple formulation of 1% sodium polyacrylate and 99% water was also tested to study the independent effects of polyacrylate film formation on SC biomechanical stress.

Table 1 Names and relevant physical properties of emollients

Emollient Abbreviation	INCI Name	Average Molar Mass ($g \cdot mol^{-1}$)	Average Molar Volume ($cm^3 \cdot mol^{-1}$)	Topological Polar Surface Area ($Å^2$)	Viscosity at 20°C (mPa•s)	Diffusivity in SC ($cm^2\ s^{-1} \cdot 10^{-10}$)
DPC	Dipropylheptyl Carbonate	342	484	35.54	12	1.09
DBA	Dibutyl Adipate	260	358	52.61	5	3.28
HDC	Hexyldecanol	242	369	20.23	37	0.81
COC_{large}	Coco-Caprylate / Coco-Caprate	335	403	26.3	10	-
COC_{small}	Coco-Caprylate / Coco-Caprate	280	326	26.3	5	-
CTG	Caprylic/Capric Triglyceride	500	706	78.92	30	1.50
DCC	Dicaprylyl Carbonate	286	415	35.54	7	1.33
DCE	Dicaprylyl Ether	242	382	9.23	4	0.68
PHC	Propylheptyl Caprylate	284	441	26.3	5	2.06
OLE	Oleyl Erucate	590	860	26.3	45	1.01

Table 2 Formulation ingredients and concentrations

Ingredient Name	Concentration in Formulation (wt%)	
	Formulations Without Glycerol	Formulations With Glycerol (+G)
Emollient	15	15
Water	83	80
Glycerol	0	3
Sodium Polyacrylate	1	1
Phenoxyethanol / Ethylhexylglycerin	1	1
Sodium Stearoyl Glutamate	0.05	0.05

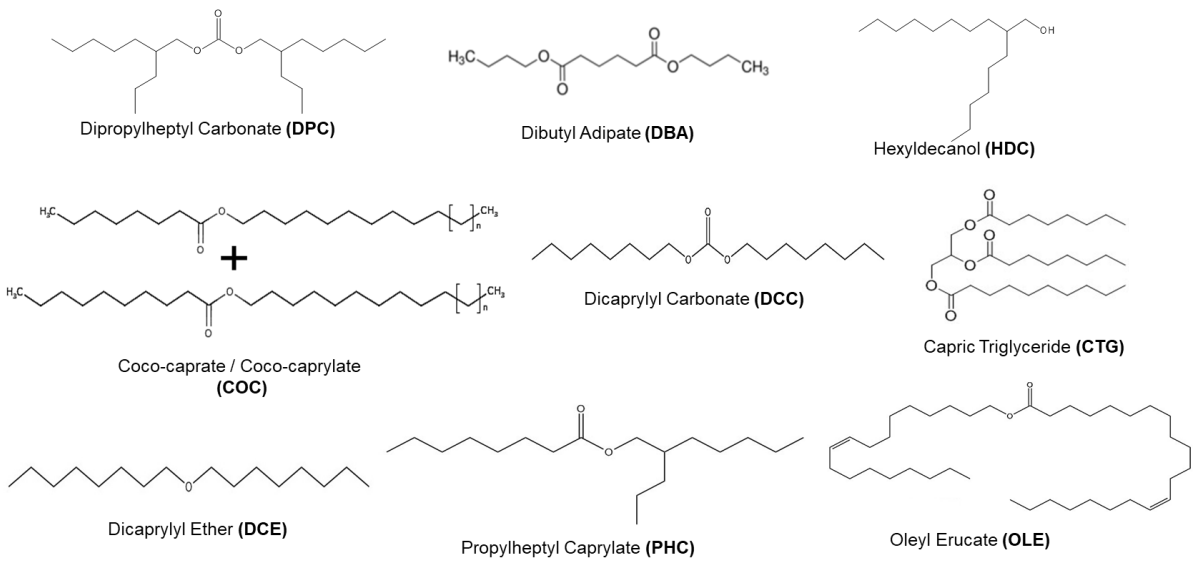

Fig.1 Molecular structures of the emollients used in this study. Abbreviations of names used to identify emollients and formulations in this work are shown in parentheses.

Drying Stress Substrate Curvature

The substrate curvature experiments have been described elsewhere in detail [8], [11], [30], [31]. Isolated SC was fully hydrated and adhered to 22 x 22 mm borosilicate glass cover slips of approx. 170 μm thickness with Cr/Au (3.5 nm / 46.5 nm) films on one side to improve reflectivity. Slippage of the SC does not occur, due to interactions between SC protein components and the borosilicate glass [8]. A scanning laser substrate curvature instrument (FLX-2320, Tencor Instruments, Mountain View, CA, USA) was used to determine the average curvature of the substrate. A curvature measurement was taken every 15 min until stresses plateaued and a peak stress was reached.

The relationship between the SC biaxial drying stress, σ_{SC}, and elastic curvature, K, may be expressed by Stoney's equation shown as Eqn. 1:

$$\sigma_{\mathrm{SC}} = \frac{E_{\mathrm{sub}}}{(1-\nu_{\mathrm{sub}})}\frac{h_{\mathrm{sub}}^2}{6h_{sc}}K \qquad (1)$$

where E_{sub}, ν_{sub} and h_{sub} are the Young's modulus, Poisson's ratio, and thickness of the substrate, respectively [8]. Initial and final h_{SC} values were measured with a digital micrometer (Micrometer 293-348-30; Mitutoyo U.S.A., Aurora, IL, USA) and intermediate values were assumed to vary directly with curvature measurements.

After preparation, hydrated specimens were first exposed to a dry air (< 5% RH) environment to characterize the drying stress of the tissue without an emollient treatment applied. The specimens were then placed in a 100% RH air chamber for 2 h to fully rehydrate and return drying stress to zero. The SC was then treated with a formulation containing an emollient from Table 1 using a cotton-tipped dowel and a gloved finger to coat the tissue gently and evenly. The amount applied was approx. 2 mg cm^{-2}. This amount was chosen to reflect skin-care industry standards. Immediately after treatment, the specimen was returned to the wafer curvature instrument to undergo a second drying cycle, now with curvature measurements taken every 5 min. Data is presented as normalized to the peak stress reached during control drying to facilitate comparison between measurements and different tissue samples.

Penetration Volume Measurements

To measure emollient penetration volumes, the mass of a square SC piece (size 2 cm by 2 cm) was measured using a mass balance, before being placed in a petri dish and coated top and bottom with a cosmetic emollient formulation. After 1 h, excess formulation was removed by blotting the SC surface with filter paper and the new mass of the SC was recorded. Any increase in mass was taken to indicate the presence of formulation components residing within the SC. By using the measured density of each emollient, the increase in mass was converted into an estimate of formulation volume in the SC. Pure emollient penetration volumes were cited from previous experiments [7], though due to material constraints the COC_{small} pure emollient was not previously studied.

Results.

A schematic illustrating the transport of molecular species through the SC and applied formulation during drying is shown in Fig.2a. Mechanical stress develops in the SC during the drying process and due to water volume loss. Polymers forming a tensing film on the SC surface during drying can further increase stresses, as observed in drying tests with the 1% polyacrylate / 99% water formulation where total measured drying stress increased by approx. 0.7MPa. Stress development can be mitigated in part through emollient or formulation ingredient diffusion into the SC (Fig.2b). The total measured stress is therefore the sum of SC drying stress from water loss, stress reduction from ingredient or emollient uptake, and the tensing stress generated by the polymer.

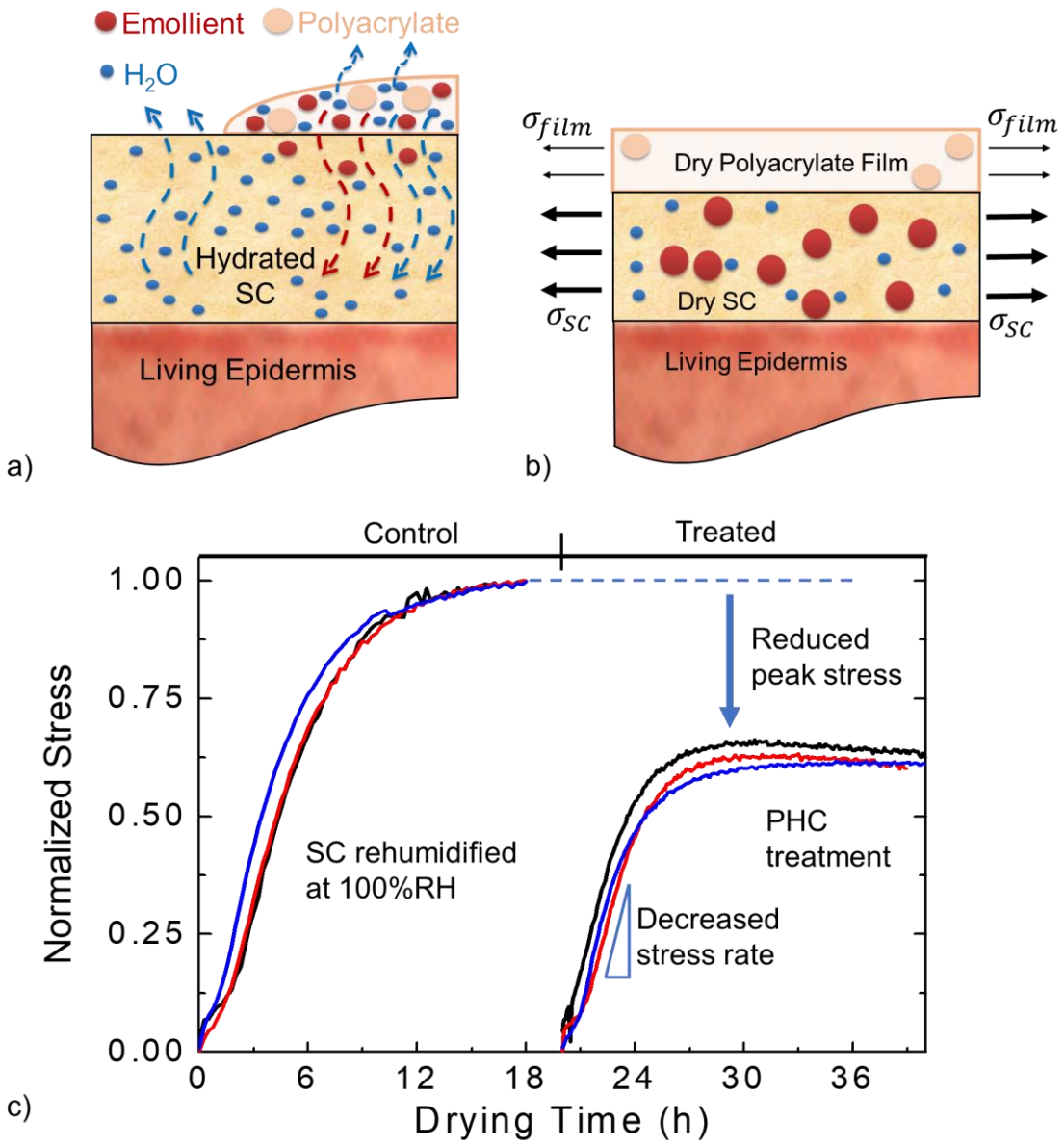

Fig.2 a) Schematic of the diffusion processes occurring *in vivo* within SC during drying with an applied skin-care formulation. Dotted lines show water diffusion out of both the tissue and formulation, as well as emollient and water diffusion into the SC. **b)** Schematic illustrating the biomechanical stress developed in the SC and tensing polyacrylate film due to drying water loss. *In vivo*, drying stress occurs because SC drying contraction is constrained by the thick epidermal and dermal layers. **c)** SC biaxial stress measurements collected during drying. First, an untreated control is dried and measured, then the sample is rehydrated, treated with formulation, and dried again. Stress data is normalized to the control peak stress. Curves in black, red, and blue indicate three separate repeat experiments where the PHC formulation was applied.

Measurements of SC drying stress before and after treatment with the propylheptyl caprylate (PHC) formulation are shown in Fig.2c. These curves and repeatability of measurements are representative of all stress experiments performed using the formulations described in this work. Results show how during drying the control SC stress increases steadily until reaching a peak stress value when water loss has completed. SC stress returns to zero after a 2 h rehydration, and the PHC formulation is applied. Drying the treated SC reveals the PHC formulation caused an average reduction in peak stress of 36% and a reduction in the maximum rate of stress development of 7%.

A plot of formulation mediated peak stress reduction versus penetration volume is shown in Fig.3, with previously reported pure emollient data included in black for comparison. All formulations reduced peak stress, with the smallest reduction of 12.5% from the smaller molecular weight coco-capryalte / coco-caprate (COC_{small}) and the largest of 36% from the PHC formulation. All formulations also showed increased penetration volumes compared to pure emollients, with the smallest increase of 7% with the dicaprylyl ether (DCE) and the largest increase of 25% with the capric triglyceride (CTG) formulation. The addition of glycerol (+G) into four formulations also further enhanced penetration volumes and increased stress reduction. Glycerol most benefited the oleyl erucate (OLE) formulation, enhancing penetration volume by an additional 6.5% and stress reduction by 9%.

A linear fit of the formulation data is highly correlated with an R^2 value of 0.92, indicating a direct dependence of peak stress reduction on penetration volume. A linear dependence between penetration volume and peak stress reduction was also reported previously of the pure emollient data [7]. Interestingly, the order of emollients ranked by penetration volume is different depending on whether the emollients were applied in a pure form or as part of a full formulation. However, a key result is that regardless of changes in the relative ability of different emollients to penetrate the SC in formulation compared to in pure form, the amount of peak stress reduction is always linearly dependent on the amount of ingredient penetration volume.

Similar slopes are observed for both linear fits, allowing the determination of an approximate y-axis offset of 15% or 0.7 MPa. This offset would seem to suggest formulations with penetration volumes similar to that of a pure emollient are reducing stress less effectively.

However, the 0.7 MPa offset is the same magnitude as the stress increase caused by the polyacrylate tensing film, thus illustrating how multiple ingredients interact to produce the total stress change in the SC.

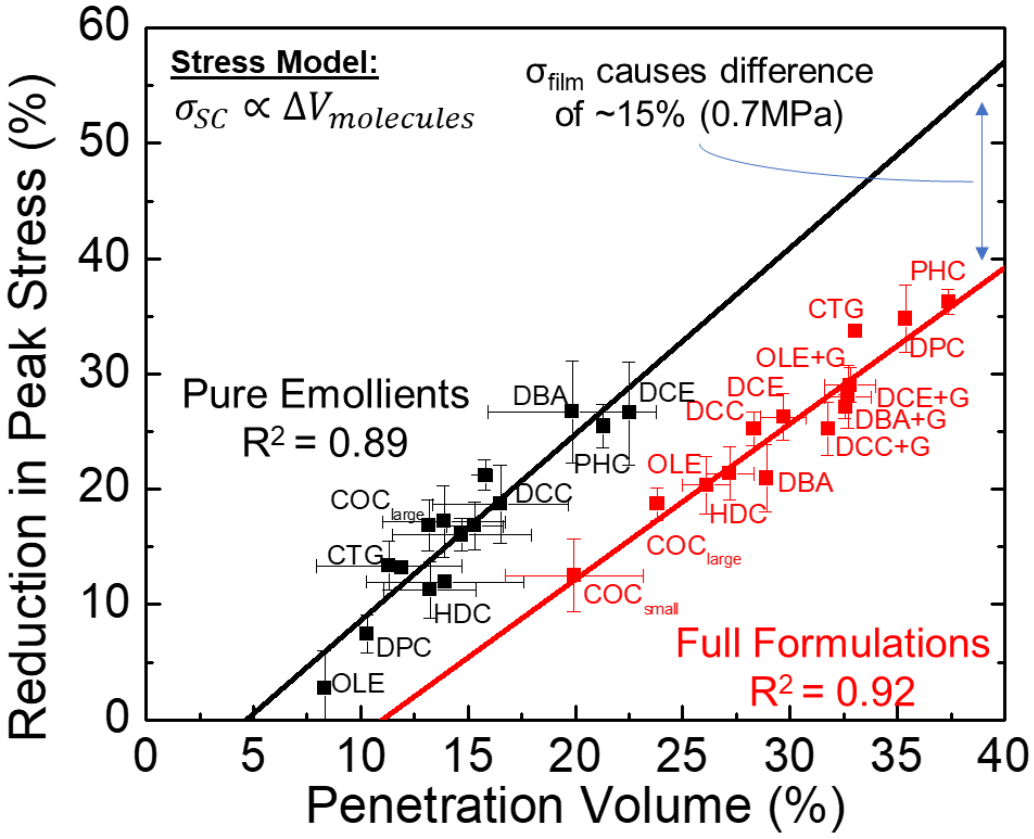

Fig.3 Observed peak drying stress reduction plotted against the measured penetration volume of emollients or formulation components in the SC (as a percentage of initial SC volume). Previously reported data concerning application of pure emollients is shown in black, and only those emollients now tested in formulation are labeled [7]. Linear fits are shown for pure emollient and formulation data with R^2 values of 0.89 and 0.92, respectively. The apparent offset of the formulation data from pure emollient trend is explicable as a result of the polyacrylate film included in formulation increasing stress by approx. 0.7 MPa.

The increase of formulation penetration volume over pure emollient penetration volume is plotted against a combination of pure emollient diffusivity, TPSA, molecular weight, and viscosity to probe why some emollients benefitted more than others from inclusion into full formulation (Fig.4a). A rough trend is apparent in which including an emollient into formulation has less effect on enhancing penetration volume when that emollient has a larger diffusivity, lower molecular weight, lower TPSA, and lower viscosity. Emollient size is explored individually by plotting the increase of formulation penetration volume against the

pure emollient molar volume (Fig.4b). Interestingly, the three largest emollients (OLE, CTG, DPC) were also the same emollients whose penetration volume was most strongly enhanced by inclusion into a full formulation. A peak in the molar volume effect appears around the volume of DPC, suggesting very large emollients or ingredients may not have penetration enhanced in formulation. Note the molecular weights of DPC (342 g mol^{-1}) and CTG (500 g mol^{-1}) also indicate the beneficial enhancement from formulation inclusion begins dissipating as emollient size approaches 500 g mol^{-1} and beyond, a typical benchmark connected to reduced penetration.

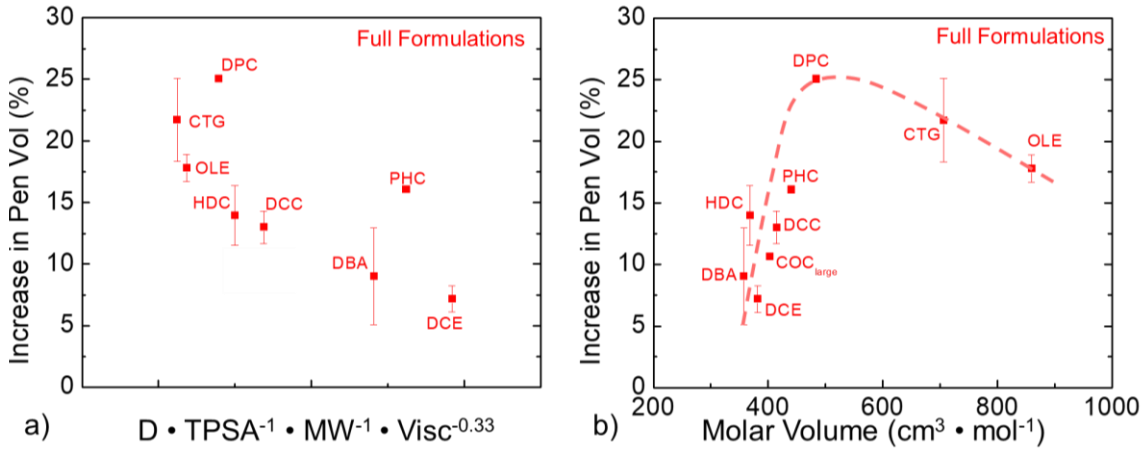

Fig.4 a) Increase in formulation penetration volume over pure emollient penetration volume plotted against a multi-parameter with diffusivity, TPSA, molecular weight, and viscosity dependence. This multi-parameter was previously used to understand pure emollient penetration volume [7]. **b)** Increase in formulation penetration volume plotted against pure emollient molar volume.

Discussion.

Continued evidence of a linear correlation between the reduction of the peak SC drying stress under dehydrating conditions and the treatment penetration volume into the SC was found even when full formulations are applied instead of pure ingredients. This is consistent with a recently reported combined diffusion and SC stress model for pure emollient ingredient molecules that provides a mathematical framework connecting the ingredient penetration, SC volume gain and drying stress reduction [9]. These combined findings provide remarkable insights into not only individual ingredient selection but the task of the full formulation to reduce SC stress during dehydration, protecting the SC biomechanical barrier by replacing lost water volume. These reductions of SC stress also have important implications for

consumer perception of skin tightness, with larger reductions strongly correlated with sensorial perception of skin comfort and reduced tightness.

To rationalize the synergistic ingredient effects causing enhanced formulation penetration volumes, first the polyacrylate film will be considered followed by the effects of other formulation ingredients including the SSG emulsifier, the EHG and PHE preservatives, water, and glycerol.

It is important to note the stress measured after formulation application is a composite of the stress caused by the polyacrylate polymer film that forms after formulation application and internal SC stresses due to water or ingredient diffusion. Key insights are provided by the observed offset between the linear trend exhibited by the pure emollients and that of the formulations. First, the offset exactly matches the 0.7 MPa magnitude stress increase caused by the applied polyacrylate film in isolation, in other words, the film stress adds to the SC stress to cause a shift of the trend observed (Fig. 3). This uniform shift for all formulations further suggests that the film does not affect the internal SC stress by penetrating the tissue or altering the total amount of water volume lost as the trend with the measured penetration volume is unchanged.

Secondly, and related to the above, the nearly identical slopes of the linear fits indicate that stress reduction is always related to the SC penetration volume despite the significant differences between the fits regarding the order of emollients ranked by penetration volume. This in turn suggests that the polyacrylate film does not affect the extent of diffusion of components of the formulation into, or out of, the SC. The kinetics may be affected, in the present study we find the water dehydration kinetics are faster and related to an increased transient drying stress rate but not to the final penetration volume. Further work should probe this possibility to confirm the main biomechanical effect of the polyacrylate film is to remain on the SC surface and increase stress.

It is clear, however, that our measurements of significantly increased formulation enhanced penetration volume compared to the pure emollients (which comprise the largest fraction of the formulations at ~15 wt.%) indicate that some combination of lipid fluidization, SC hydration, and tissue swelling provide an easier pathway for ingredient penetration. In this regard, we note the presence of other ingredients including the preservatives PHE and EHG,

the emulsifier SSG, and water which interact with the intercellular SC lipids and may influence permeation of substances. The mass concentrations of SSG (0.05%) and PHE/EHG (1%) are, however, relatively small compared to the emollients (Table 2). When applied in excessive concentrations, PHE and EHG have been linked to skin sensitization or irritation due to high skin permeability [18], [32]. Glycerol also likely enhances penetration by further hydrating the tissue.

Previously, pure emollient penetration volume was found to be highly correlated with increasing diffusivity and decreasing molecular weight, TPSA, and viscosity of emollients [7]. Strikingly, with regards to the measured increases in penetration volume, the opposite trend is observed such that poorly penetrating pure emollients with low diffusivity and high molecular weight, TPSA, and viscosity benefited the most from inclusion into full formulations. Furthermore, the penetration enhancement of poorly permeating pure emollients appeared to correlate most with emollient molar volume. Large emollients with high molecular weights are expected to have more difficulty permeating the SC due to the dense, highly-organized packing structure of intercellular lipids [33], [34]. Those emollients with molecular weights greater than 500 g mol^{-1} are especially likely to have low penetration into the SC, given the so-called "500 Dalton Rule" reported previously [35].

Thus, these results reveal how those emollients that penetrated least effectively in a pure form, due to their large size, are typically the most enhanced by other ingredients when included into full formulation. Additionally, emollients with properties similar to those of PHC emerge as key options to optimize the biomechanical effects of formulations. Although the fourth largest emollient tested, PHC still penetrated well in its pure form due to a high SC diffusivity. Additionally, PHC was not so large that its penetration ability became limited by the 500 Dalton Rule, as appears likely in the case of CTG and OLE. Consequently, the moderately large PHC benefited from a significant degree of penetration enhancement in formulation, an increase which compounded with the inherent permeability of the emollient and led to the best performing stress reduction observed in the present study, easily compensating for the presence of the polyacrylate tensing film.

Conclusion.

The study offers new insights on how ingredient choice affects cosmetic formulation performance and reduces drying stresses while also demonstrating a robust ability to predict these effects based on ingredient characteristics. The critical relationship known between water volume loss, pure emollient SC penetration, and SC stress development was found to describe formulation penetration and extend to higher penetration volumes. We establish how multiple ingredients behaving synergistically in formulations amplify penetration of substances into the SC and strongly reduce the development of the biomechanical stress that affects SC barrier function and consumer perception. Larger emollients that poorly penetrated in pure forms were observed to benefit most from inclusion in full formulation. Depending on emollient choice, the observed stress reduction easily compensated for increased stress caused by a polyacrylate tensing film, enabling film benefits without negative stress effects. Understanding the combined effects of ingredients on the SC biomechanical barrier function is vital to ensure that when designing new cosmetic formulations, emollients and other formulation components are selected based on positive interactions to deliver optimum performance, positively impact SC biomechanics, help to maintain skin health, and meet customer needs.

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Conflict of Interest Statement. AM, AS, MD, HR, JK, YG, JC, and TA are employees of BASF Personal Care and Nutrition GmbH, Duesseldorf, Germany.

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