A SUPPLEMENT TO

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS

From Babies to Boomers: Understanding Nuances for Stratum Corneum Care

ISSN: 1545 9616

January 2019 • Volume 18 • Issue 1 (Supplement)

JO0119

From Babies to Boomers: Understanding Nuances for Stratum Corneum Care

ORIGINAL ARTICLES

Disclosure of Commercial Support
This supplement to the *Journal of Drugs in Dermatology* is supported by Unilever.

 ORIGINAL ARTICLE Journal of Drugs in Dermatology

Skin Barrier Insights: From Bricks and Mortar to Molecules and Microbes

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ABSTRACT

Recent advances in genomics, spectroscopy, and immunology have increased our understanding of the skin barrier. A new model of barrier lipid organization has emerged owing to the application of advanced modeling and microscopy techniques. The contribution of filaggrin gene mutations to atopic dermatitis has increased our appreciation of the role barrier perturbations play in inflammatory dermatoses. Next generation sequencing techniques have led to a greater understanding of the diversity of resident skin microorganisms and the close association between microbes and the host immune system. This paper reviews the basics of stratum corneum structure and function, with an emphasis on recent advances in our understanding of barrier perturbations and their effect on skin health.

J Drugs Dermatol. 2019;18(1 Suppl):s63-67

INTRODUCTION

The skin has evolved a unique structure that is essential for survival; the stratum corneum (SC). The SC prevents excess water loss and forms a formidable barrier to the ingress of microorganisms and exogenous materials. Morphologically, the SC is comprised of corneocytes interspersed in lipid bilayers, the so called "brick and mortar model".[1] However, the analogy suggests that the SC is an inert, unchanging structure and fails to convey the extent to which metabolism and remodeling continue as the corneocytes transit from the base of the SC to the surface. The explosion in microbiome research has demonstrated that the SC harbors a rich diversity of microbes[2] that form an additional barrier to the colonization of pathogens. Moreover, the microflora communicates with and *directs* the host immune system and can be considered an integral part of the skin's immunity. The intimate association of microbes and skin is such that, perhaps, the bricks and mortar analogy should be updated to include skin's microbiota as a third component, wherein the microbes form the shingles on the roof of a bricks and mortar house.

Stratum Corneum Formation

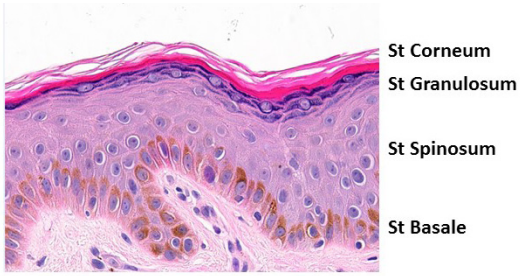
The epidermis has several distinct layers. At the dermal-epidermal junction sits the basal layer of proliferating keratinocytes. Within this layer reside both epidermal stem cells and transit amplifying cells that are destined to detach from the basement membrane and begin the process of terminal differentiation. As keratinocytes differentiate, they enlarge and progressively flatten. This progression is accompanied by a bewilderingly complex set of changes in the expression of specialized proteins and lipids. Terminal differentiation culminates in the transition of the granular layer cells to corneocytes, anucleate, and proteinaceous sacs, surrounded by a lipid envelope, and interspersed in lipid lamellae. This amazing conversion from viable keratinocyte to corneocyte occurs in a highly ordered fashion within the space of *one cell layer*, cued by mechanisms that are still not clearly understood (Figure 1). It is truly a remarkable transformation.

Cornified Envelope

Keratins are cytoskeletal proteins that form intermediate filaments and serve as the scaffolding for cornified envelope (CE) formation. Commitment to differentiation is evidenced by a switch to a predominance of K1 & K10 in the spinous layer where the synthesis of proteins, such as involucrin, also begins. In the granular layer, these proteins are crosslinked into the CE by the action of transglutaminases. Specialized lipids are secreted into the extracellular space and will form the lipid coat that surrounds each corneocyte, the cornified lipid envelope (CLE). The stratum granulosum (SG) is so-named because of the presence of keratohyalin granules (KHG) containing loricrin and small proline-rich proteins (SPR), which further reinforce the CE. KHGs also contain filaggrin. This protein aggregates keratin filaments and promotes the collapse of the keratinocyte. The lamellar granules (LG) are also extruded from granular cells releasing their precious cargo of lipids and proteins.

As the keratinocyte transitions to a corneocyte, nuclei, intracellular organelles, and plasma membrane components are degraded. Desmosomes, the molecular rivets between adjacent keratinocytes, are converted to corneodesmosomes (CD) by the addition of corneodesmosin[3] strengthening cell:cell adhesion. Maturation continues as the corneocyte transits through the SC. Crosslinking of proteins such as loricrin, trichohyalin, and SPRs into the CE continues and this facilitates the switch from a "fragile" to a "rigid" phenotype.[4] In dry or photoexposed skin, the ratio of rigid:fragile in the outer SC is decreased indicat-

FIGURE 1. H&E stained section of epidermis.



ing the presence of immature corneocytes.[5] Desquamation is the loss of corneocytes from the surface at a rate that balances (ideally) the rate of proliferation, and CD degradation is crucial for proper desquamation. In the lower SC, CDs may be found on all sides of the corneocyte, however, in the upper half, many CDs have been degraded and only peripheral CDs persist. CD degradation requires the activity of proteases and the kallikreins, a family of serine proteases, are the key enzymes in CD degradation.[6,7]

The activity of these degradative enzymes needs to be tightly controlled to prevent premature or over-activation and that is accomplished, in part, by enzyme inhibitors that are synthesized in and secreted by LG. Dysregulation of enzyme:inhibitor balance has been reported in phenotypes as distinct as dandruff and peeling skin disorders.[8,9] The protease inhibitor, lymphocyte-epithelial Kazal-type related inhibitor (LEKT1) maintains a block on the activity of several KLKs, dissociating as the SC acidifies.[10] Netherton syndrome, a rare autosomal recessive mutation in the gene encoding LEKT1, is characterized by overactivation of KLKs, excessive desquamation, and barrier defects. Tight junction (TJ) proteins were identified in close association with CDs[11] and it was hypothesized that TJ may limit access of proteases to CDs thus controlling the site-specific degradation of CD.[12]

Filaggrin proteolysis also takes place in SC[13] and generates hydrophilic amino acids that are key components of the skin's natural moisturizing factor (NMF).[14] Water is an absolute requirement for the activity of enzymes thus the water-holding capacity of SC is critical in supporting the activity of SC enzymes. Xerosis and scaling disorders such as icthyosis vulgaris (IV) and atopic dermatitis (AD) are characterized by defects in NMF production leading to reduced hydration and desquamation and impaired barrier function. Mutations in the filaggrin gene are a strong risk factor for development of IV and AD.[15-17] Because of the compromised barrier, these individuals are more susceptible to entry of allergens that may contribute to prolonged inflammation. However, some individuals who are homozygous for loss-of function mutations exhibit no symp-

FIGURE 2. Ceramides consist of a sphingoid base bonded to a fatty acid via an amide linkage. Ceramides are denoted by "Cer-fatty acid-sphingoid base". The sphingoid base can be either sphingosine (S), 6-hydroxy sphingosine (H), dihydroxy sphinganine (T), dihydrosphingosine (dS), or phytosphingosine (P). The fatty acid chain is denoted as non-hydroxy (N), α-hydroxy (A), ω-hydroxy (O). ω-Hydroxy ceramides contain an additional fatty acid, usually linoleic acid, esterified to the fatty acid denoted by "E".

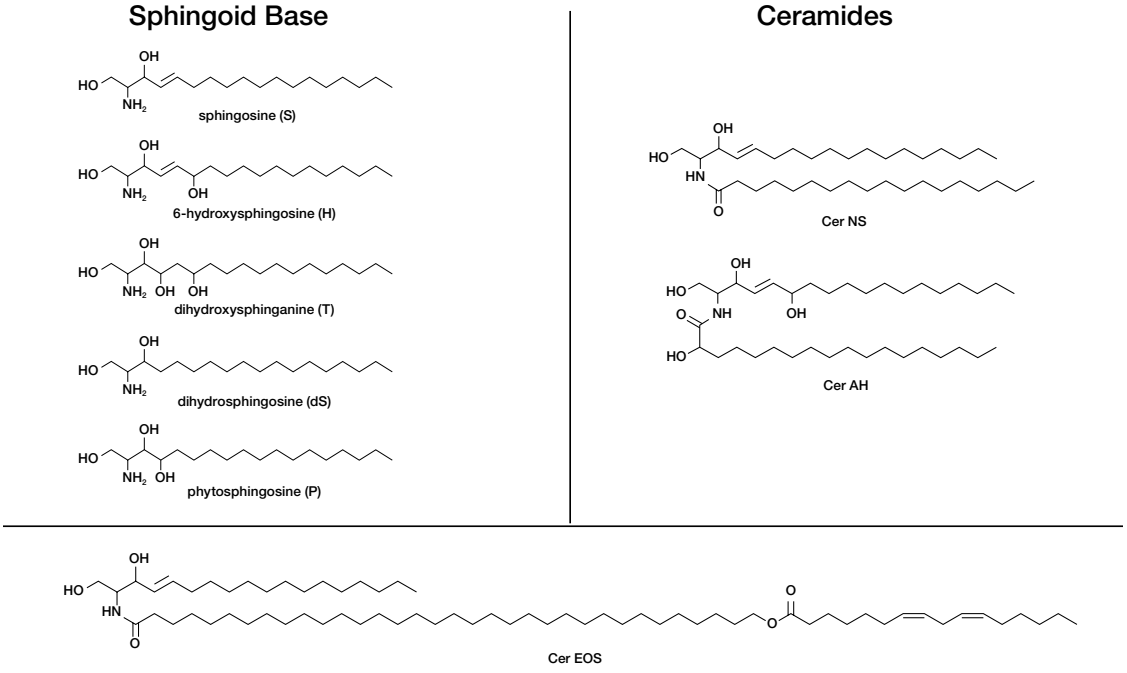
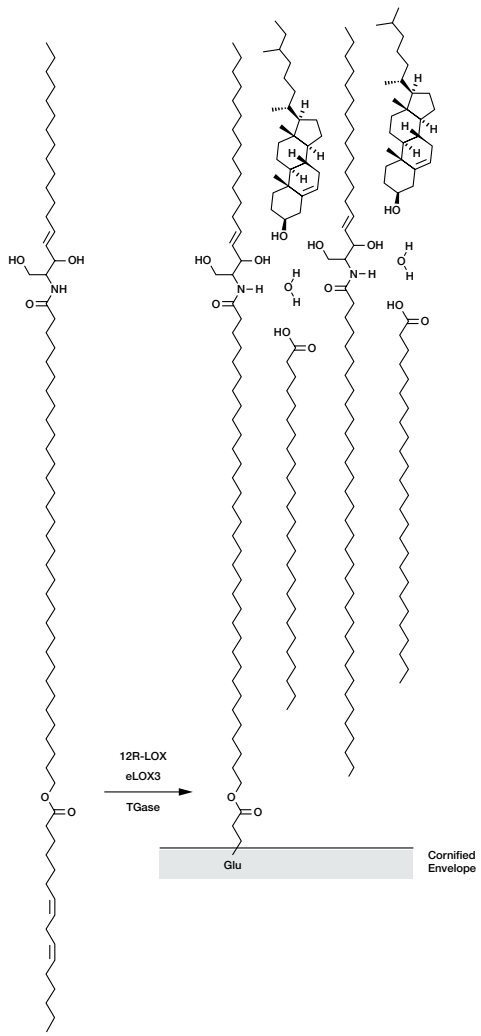


FIGURE 3. Schematic of lamellar lipids demonstrating the organization of ceramides (Cer), cholesterol (Chol), and free fatty acids (FFA).[43] Ceramides are represented in the splayed conformation. Very long chain ω-hydroxy ceramides are enzymatically processed prior to incorporation into the cornified envelope.



toms suggesting that other factors are also important in disease progression.[18] Furthermore, filaggrin expression is downregulated in *all* AD patients, even those with no demonstrable filaggrin gene mutations,[19] and this may be secondary to the enhanced Th2 cytokine milieu that suppresses the expression of differentiation-associated proteins.[20,21] Moisturizers can help restore enzyme activity by supplying humectants, to augment skin's natural moisturizing systems, and occlusives, to retard water loss thus promoting desquamation and reduced scaling.

Lamellar Lipids

Lamellar lipids are stored as precursors in LG and secreted at the interface of the SG and SC.[22] Enzymes that process these lipids to mature forms are also packaged in and secreted by LG.[23] Comprised primarily of ceramides, cholesterol, and fatty acids, (in an approximate molar ratio of 1:1:1) with small amounts of cholesterol sulfate and cholesterol esters, the extracellular lipids form a highly ordered structure that resists the flux of water. The effectiveness of this lipid matrix is highly dependent on the relative proportions of the major lipid classes[24] and is altered in xerosis,[25,26] aging,[26,27] and AD.[28,29] The structure of the individual lipid species also affects barrier quality. Ceramides and free fatty acids with longer acyl chains tend to form highly ordered, orthorhombic phases while shorter acyl chain variants form less ordered hexagonal phases.[30] The acyl chain length of SC ceramides in AD is shorter and correlates with decreased lipid order and barrier function.[31] Lipid order as measured by FTIR is also significantly decreased in dry skin subjects.[32]

Perhaps as many as 1000 species of free ceramides and corneocyte-bound ceramides have been identified in SC[33-35] (Figure 2). While most ceramide-derived fatty acids are saturated with acyl chain lengths of between 16 and 32 carbons, there exist some very long carbon chain lengths (30 to 34) that are particularly important in SC function[36]; these are the ω-hydroxy ceramides that contain the unsaturated essential fatty acid (EFA), linoleic acid, esterified to the fatty acid. It is the ω-hydroxy ceramides that become covalently bound to the CE forming the CLE and act as scaffolding for the free ceramides that comprise the intercellular lipid bilayers. Two lipoxygenases process the ω-hydroxy ceramides prior to incorporation into the CLE.[37] Lipoxygenases are usually associated with arachidonic acid metabolism and inflammation. However, 12RLOX and 3eLOX3 sequentially oxidize the linoleic acid moiety and this processing is required for ester formation between ceramide and CE proteins (Figure 3). Ultimately degradation of ceramides may also be required for reduced cohesivity and desquamation and this is accomplished by the action of acid and alkaline ceramidases in the SC.[38]

A novel model of SC lipid organization was proposed by Norlen and colleagues in which the ceramides are fully extended or "splayed'[39] (Figure 3) and this conformation was confirmed by infrared spectroscopy.[40] The proposed structure contrasts with the previously described sandwich model in which ceramides were represented in a folded position.[41]

The question of how fatty acids contained in moisturizers and cleansers interact with SC and affect lipid organization is pertinent. Bouwstra and colleagues demonstrated that topically applied C16 fatty acids are elongated to C24 and 26. Furthermore, these fatty acids integrated into the lamellar structure and increased lipid order.[42] This suggests that topical application of the appropriate fatty acid can be used to improve the permeability barrier in compromised skin.

Acid Mantle

The pH of healthy SC is acidic and several potential acidifying mechanisms have been identified.[43] Acidification is important

for antimicrobial defense, enzyme activity, and cytokine activation. Elevated SC pH is associated with perturbations in barrier function as many enzymes involved in lipid metabolism and CD degradation require an acidic environment.[44] Elevated pH is also associated with shifts in the microbial composition toward potentially pathogenic organisms.[45] These findings provide support for use of acid-neutral pH cleansers and moisturizers in the prevention and treatment of barrier deficiencies.[46]

Microbiome

The skin harbors a diverse population of microbes whose composition is largely determined by site-specific factors such as moisture and sebum content.[47] The skin's invaginations and appendages harbor a large number of microorganisms but microbial DNA has also been found deep within the dermis.[48] This surprising finding challenges many existing concepts of skin, its microflora, and the mechanisms by which the host immune system is educated by the microbiome.

The SC provides a formidable barrier to microbial colonization due to the physical barrier, low water and nutrient content, acidic pH, and antimicrobial lipids (AML) and peptides (AMP). Sphingosine and free fatty acids are potent AMLs and are found in ample concentrations in SC.[49] AMPs are a diverse, yet highly conversed set of proteins belonging to the host innate immune system that kill microbes primarily through disruption of the cell membrane. The predominant AMPs of skin belong to the cathecidin and defensin classes and are delivered to the SC via LGs or glandular secretions.[50] However, microbes can also produce AMP-like proteins. *S. epidermidis* produces AMPs that inhibit colonization of *S. aureus,*[51] however strain variation is significant, and the commensals in some AD patients lack the ability to produce AMPs selective for *S. aureus*.[52] Microbial AMPs also synergize with host AMPs, thus the secretome of commensals could be viewed as an integral part of most innate defense system.[53]

There exists a complex interplay between the microbiome and the host immune system. The innate and adaptive arms of the immune system modulate the composition of the microbiome and in turn, the microflora communicates with and directs the host immune response.[54] *Propionibacteria acne*s induces expression of AMPs and inflammatory cytokines in keratinocytes in a toll-like receptor-dependent (TLR) fashion.[55] Staphylococcal lipoteichoic acid blunts inflammation via interaction with TLR3 and stimulates wound healing.[56] These are but a few examples that illustrate how the microflora directly modulates both the innate and adaptive arms of the host immune response. The complexity of this interaction suggests a coevolution of host and microbes and this balance may be disrupted by our rapidly changing environment; diet, hygiene, and antibiotics could affect the microbiome at a faster rate than the microbiota can adapt. This has led some researchers to speculate that these changes are responsible for the dramatic increase in the incidence of inflammatory diseases such as AD.

Barrier perturbations can drive changes in the skin's microbiota, ie, dysbiosis. There is now a strong recognition that barrier dysfunction is a driving element in many inflammatory skin disorders and not merely a bothersome sequela. Most notably patients with AD tend to be at increased risk of infection and colonization by *S. aureus*.[57] In contrast to the many microbiome studies on AD patients, definitive studies on microbial changes that might accompany cosmetic dry skin are yet to be published.[58] On the other hand, mild cleansers have been shown to help restore normal flora.[59] The use of mild cleansers that protect the skin's barrier lipids[60,61] would be expected to help maintain a "healthy" microbiome.

CONCLUSIONS

Barrier impairment, whether the result of genetic or environmental influences, increases the flux of water out of and exogenous materials in to the skin. The consequences of this increased permeation will depend, in large part, on the host response to that stimulus. In some instances, the host response can further degrade barrier function leading to a vicious cycle of stimulus and response. Optimizing a skin care regime to support the skin's own barrier repair mechanisms is an integral part of any successful therapy. Continued research efforts are necessary to provide the scientific foundation for identifying new therapies and optimal skin care regimes.

DISCLOSURES

Carol Bosko is an employee of Unilever.

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 ORIGINAL ARTICLE Journal of Drugs in Dermatology

The Spectrum of Sensitive Skin: Considerations for Skin Care in Vulnerable Populations

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ABSTRACT

Sensitive skin is a multifactorial condition, where the underlying pathology is not fully understood, and the clinical signs may not always be present or obvious. Despite this challenge, there has been recent progress to understand the different subtypes of sensitive skin, as well as new methods to measure the sensorial response that may not be obvious from visual examination. Similarly, there has been progress in understanding in the management of symptoms through skin care regimens designed for sensitive skin. The implications of this new research indicate the potential of better clinical outcomes for sensitive skin sufferers, as well as regimens more personalized to different triggers in the full spectrum of sensitive skin.

J Drugs Dermatol. 2019;18(1 Suppl):s68-74

INTRODUCTION

Sensitive skin, or increased irritation or sensorial response to skin care products, environmental factors, and/or stressors compared to population norms, has been increasingly studied over the past 30 years. The face has been shown to be more sensitive than other parts of the body[1,2]; however, skin sensitivity can also vary significantly between individuals due to a number of factors such as ethnicity, gender, age, product irritancy, etc.[3-7]

Rising prevalence of sensitive skin and research on previously unknown factors that increase the symptoms of sensitive skin has further fueled the need to better understand the condition, as well as research into different skin care technologies to address the symptoms and minimize the onset of future sensitive skin events. The intensity of the symptoms varies widely and can also change throughout an individual's lifetime. Although erythema and dryness are typically involved, sensations such as stinging, burning, tingling, tightness, itching, pain, etc. can persist with no clinical signs of dryness or erythema. Sensitive skin sufferers have lower Quality of Life (QoL) scores compared to normal-skin individuals, and impaired barrier function is the main biophysical finding across the different subtypes of sensitive skin individuals.[8-11]

Research in this area has resulted in more comprehensive subtyping of sensitive skin, to better understand the underlying causes and, consequently, potential skin care regimens to alleviate symptoms for a particular sub-type.

Kligman et al[12] described the characteristics of sensitive skin by different symptoms:

- *Subjective irritation:* irritant response (eg, sting, burn, itch) without visible clinical signs
- *Neurosensory irritation:* neurally mediated responses such as itching, stinging, burning, tightness
- *Chemosensory:* relates to sensory responses induced by chemicals in contrast to physical, mechanical, and environmental factors
- *Psychophysical irritation:* implies a psychological component.

Pons-Giraud[14] proposed three clinical forms or subtypes of sensitive skin individuals:

- *Very sensitive skin:* a subtype of individuals with especially strong reactions to external factors such as cosmetic product usage and environmental;
- *Environmentally sensitive skin:* reactive to rapid temperature and environmental changes, with frequent bouts of flushing; and
- *Cosmetically sensitive skin:* a lower intolerance compared to the very sensitive skin group, and often limited to specific identifiable cosmetic products.

The methods for positively identifying sensitive skin individuals or subtypes have evolved over time. One of the first methods used was the lactic sting assay,[15] to identify sting potential individuals for facial skin. One limitation to this method is that an individual's response to sting can vary over time and in addition this can be a very small subset of the population, whereas the prevalence for individuals with sensitive skin is much higher. In addition, a negative response in the lactic acid sting test is not a predictor for a sensitive skin response to other ingredients. Retinoid intolerance, for example, is fairly common in sensitive-skin individuals and will not necessarily be identified in this test. The time course for the dryness, irritation, and other symptoms in retinoid-intolerant populations follow-

ing topical application also varies widely across individuals. Consequently, subjective surveys and QoL questionnaires have been validated to confirm the sensitive skin subtypes and/or better understand the impact of products designed specifically for sensitive skin.

Despite the prevalence of sensitive skin, and possibly because the symptoms are not always visible, many individuals will not seek help of a physician to alleviate the symptoms.[13,15]

Characteristics of Sensitive Skin

Subject Self-Assessment Surveys and Quality of Life Measures

Querleux et al showed a strong prevalence in individuals with self-perceived sensitive skin prone to the following symptoms or triggers: irritation, redness, reactivity to products, temperature (eg, hot and cold environment or rapid change in environment), wind, sun, and pollution.[17] These questions, particularly when an individual responds to several factors, are a valuable way to confirm if there is general facial skin sensitivity. In this study, functional MRI (fMRI) was used to evaluate subjects' responses to a lactic acid sting test in both sensitive skin and normal subjects. Application of lactic acid increased activity in the primary sensorimotor cortex contralateral to the application site with greater intensity in sensitive skin individuals compared to the control group.

The Bauman Skin Type Indicator (BSTI) describes 16 different skin facial sub-types using the axes of dry or oily; sensitive or resistant; pigmented or nonpigmented; and wrinkled or unwrinkled (tight).[18] Within the sensitive skin category, there are four discrete subtypes described: acne, rosacea, stinging, and allergic.

The links between sensitive skin and oily and dry facial skin types has been investigated in a prevalence study in a population of 1000 subjects, representative of US demographics.[19] Approximately half of the population was sensitive-skinned. The authors compared the prevalence in sensitive to non-sensitive skin individuals with dry, normal, oily, or combination facial skin, and saw that for dry and combination skin there was greater prevalence of sensitive skin individuals compared to normal skin individuals, and approximately equal prevalence for oily skin.

Sensitive skin can alter an individual's QoL, as has been assessed by the Dermatology Quality of Life Index.[9] Health-related quality of life (HRQOL), an individual's perception of their physical, mental, and social health, is very often impaired in patients with chronic sensitive skin[14, 19-21] Misery et al.[22] assessed QoL using the short form (SF-12) questionnaire and depressive symptoms using the Hospital Anxiety and Depression (HAD) rating scale. Subjects with sensitive skin had lower QoL scores, and this worsened with increasing skin sensitivity.

Skin Barrier and Tolerance in Sensitive Skin

Compromised skin barrier is a commonality across different sensitive skin subtypes and therefore has led to study of potential morphological and biophysical differences between groups with relatively higher skin sensitivity.[9,10]

Overall, sensitive skin is characterized by decreased natural moisturizing factors (NMFs), ceramides, and fatty acids, as well as an increased transepidermal water loss (TEWL) and increased permeability to exogenous environmental factors.[10,23,24] More recent studies have shown promise with other biophysical measurement evaluations of sensitive skin responses, such as fMRI[17] and sensorial thresholds.[25]

Sensitive Skin Populations

Ethnic Skin Differences

Some of the population surveys have not shown an association with sensitive skin and ethnicity.[22,26] This was further studied in a series of sting tests followed by immunostaining and biophysical measures, comparing Caucasian subjects to Japanese subjects in age-matched cohorts. The goal of these studies was to see if the skin reactivity to products differed between the two populations and if there were underlying physiologic differences. Healthy female subjects provided informed consent to participate in these double-blind, Institutional Review Board-approved studies.

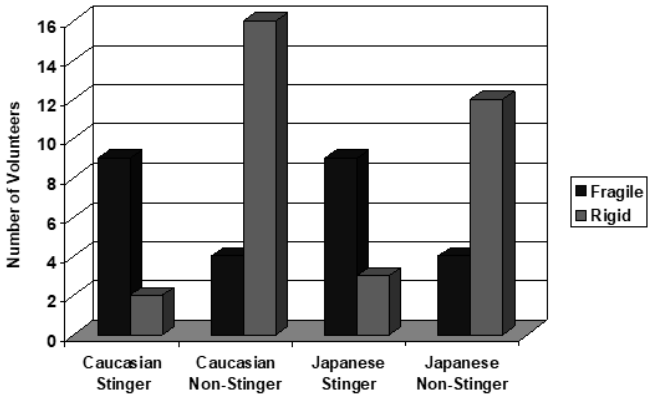
Japanese vs Caucasian Stinger Study [27]

Thirty-four Caucasian subjects were from New York, NY and the surrounding area, and thirty-one Japanese subjects were from Tokyo, Japan. Following application of glycolic acid lotion, subjects reported self-perceived unpleasant sensations (sting, itch, burn, and others). Subjects were categorized as stingers or non-stingers based on a cumulative score. Sellotapes® were collected from the sub-orbital cheek region for corneocyte structure analysis, and a board-certified dermatologist collected a punch biopsy (2 mm) from a pre-selected site on the hairline for H&E staining and immunolocalization.

A greater number of Japanese women were characterized as strong stingers (48%) compared to Caucasian women (32%). Japanese women characterized as stingers were more likely to have greater numbers of fragile corneocytes (9 of 12; Figure 1). Japanese women characterized as non-stingers were more likely to have greater numbers of rigid corneocytes (12 of 16). A similar trend was observed for Caucasian women, with stingers having greater numbers of fragile corneocytes (9 of 11) and non-stingers having more rigid corneocytes (16 of 20; Figure 1).

No difference in staining patterns between non-stingers and stingers was observed, or between Japanese and Caucasian. This suggested that there was no change in underlying markers of epidermal proliferation and differentiation that may contrib-

FIGURE 1. Corneocyte structure analysis: Fragile: Number of volunteers who had greater than 60 % of corneocytes as fragile. Rigid: Number of volunteers who had greater than 60% of corneocytes as rigid.



ute to increased sensitivity to sting. There were significantly fewer cells per unit area of epidermis in stingers compared to non-stingers (15%, *P*=0.02; Figure 2).

The results of this study confirmed previous reports that Japanese women are more sensitive to irritants than their Caucasian counterparts.[7,28] The observation of greater numbers of fragile corneocytes in Japanese compared to Caucasians provided evidence that the stratum corneum of Japanese women may not be as structurally resilient as Caucasian women. Further, the increased amount of fragile corneocytes found in 'stingers' of both populations provided evidence that the stratum corneum of sensitive individuals may have a structural weakness. This offers a potential explanation for these individuals' increased sensitivity as topically applied irritants may be able to penetrate a weakened skin barrier.

Differences in Sensory Nerve Distribution on the Cheek Between Japanese and Caucasian Stingers[29]

Study populations (twelve Caucasian and twenty-three Japanese) were segmented into stingers (S) and non-stingers (NS) based on their response to glycolic acid-induced sting. Biopsies

FIGURE 3. PGP9.5 immunofluorescent staining in epidermis. Example of images used in image analysis quantification. Left panel shows negative control (primary antibody omitted). Scale bar = 50µm.

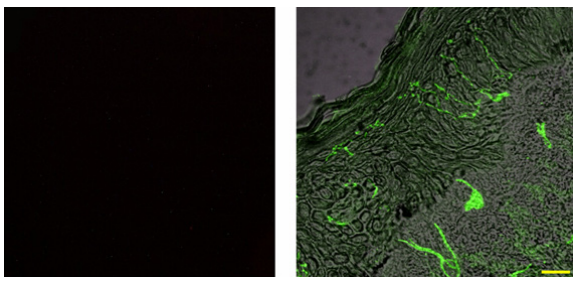
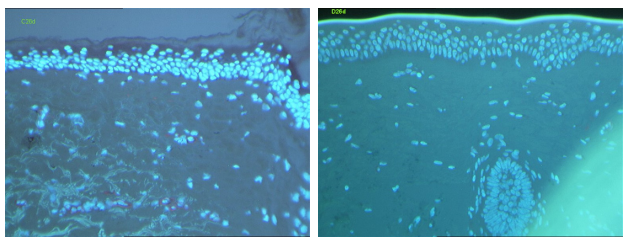


FIGURE 2. Comparison of epidermal cellularity (H&E staining) between representative non-stinger **(2A)** compared to a stinger **(2B)**.

(2A) Non-Stinger **(2B)** Stinger



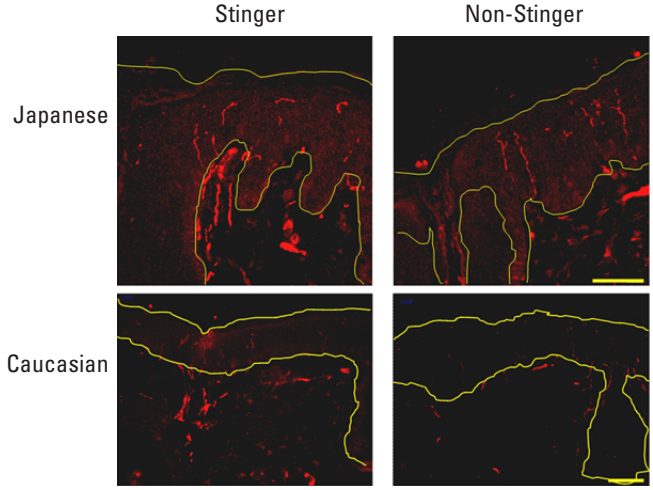
were obtained with punch biopsies (2mm) from the face (cheek site), followed by immunostaining to evaluate epidermal nerve amount and density.

Hot pain (HP), cold pain (CP), warm sensation (WS), and cool sensation (CS) detection thresholds were measured by a thermal probe applied to skin using the Quantitative Sensory Testing (QST) device. Tactile thresholds were determined by touching the skin gently with Von Frey hairs.

Fibers in the epidermis were clearly seen as well as nerve bundles in the dermis. The nerve terminals terminated at different levels in the epidermis, with the highest at the stratum corneum/granulosum interface (see Figures 3 and 4). Epidermal nerve fiber quantity (PGP9.5 staining) in Japanese subjects was not significantly different from Caucasian subjects.

Japanese stingers had less overall nerve fiber quantity than the non-stingers ($P<0.05$), whereas there was no statistically significant difference in the Caucasian subjects. Innervation density (fiber quantity/distribution area) was five-fold less in Japanese

FIGURE 4. PGP9.5 immunofluorescent staining in stinger and non-stinger Japanese and Caucasian cheek biopsy samples. Images orientated with epidermis at the top. Scale bar = 50µm



compared to Caucasian women (*P*=0.0005). Innervation density was 3.5-fold higher in Japanese non-stingers than stingers (*P*=0.022), but this was not observed in Caucasians.

The Japanese cheek site was more sensitive to hot pain (*P*=0.001) than Caucasians. Japanese stingers were more sensitive to von Frey hairs (*P*<0.05) and cold pain (*P*<0.05) than non-stingers. No sensory differences were observed in Caucasian sub-populations.

No correlations between PGP9. 5 staining density and QST data were found in Caucasians or their sub-populations. Japanese subjects as a whole showed that an increasing amount of nerve fibers had a lower cold sensation threshold (felt cold at a lower temperature) (r=-0.56; *P*=0.006). Japanese stingers with an increasing amount of nerve fibers had a lower cold sensation threshold (felt cold at a lower temperature), which was not seen in non-stingers (r=-0.60; *P*=0.01). Japanese non-stingers with an increasing amount of nerve fibers had a higher hot pain threshold, which was not seen in stingers (r=0.86, *P*=0.03).

This study demonstrated that nerve fiber type, distribution and expression of receptors may play an important role in determining sensory response. A separate study on Japanese subjects showed that the cheek site showed greater nerve innervation compared to a hairline site.[25]

Baby Skin

The infant skin barrier formation begins in utero. Recent research has shown that infants with elevated transepidermal water loss two days after birth are more likely to develop atopic dermatitis.[30-32] Further, during early skin maturation and barrier development, infant skin is more vulnerable to chemical damage, microbial infection, and skin diseases, which can develop into longer-term health issues of greater consequence.[33]

There are several structural and functional differences between infant skin compared to adult skin. Stamatas et al. showed structural differences in infants compared to adults included smaller corneocytes, a thinner stratum corneum and epidermis, and denser microrelief lines, which could all be factors in faster transport of an external irritant through the skin and faster loss of hydration to maintain a healthy skin barrier.[34]

There are also compositional and functional differences in the infant skin barrier compared to adult skin such as decreased NMFs, sebum, and lipid to protein ratio, as well as high transepidermal water loss and rate of water absorption.[32,34-36]

Very young infants also show lower diversity in the skin microbiome compared to adult skin.[37] The clinical consequence of this could leave young infants less able to resist environmental alterations and chemical or physical irritants.

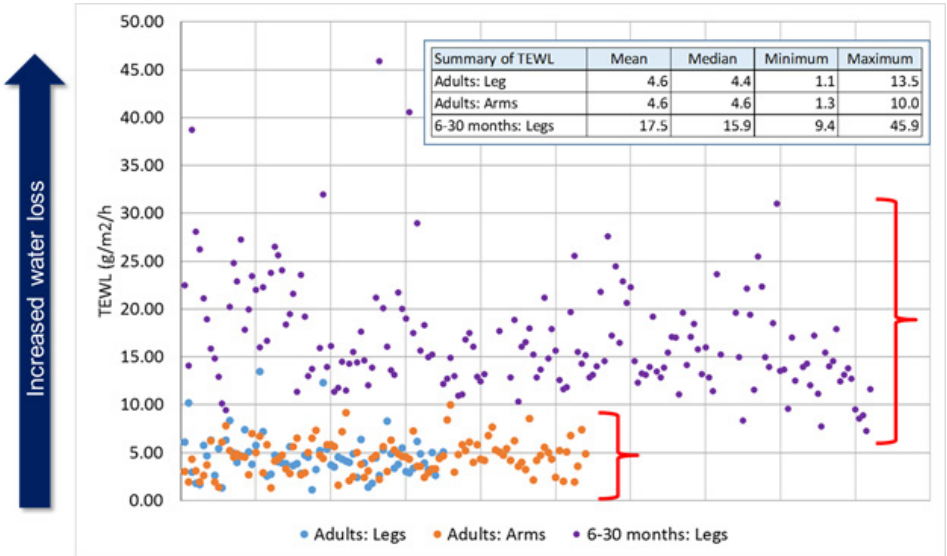
When matching the same body sites on arms and legs for adults compared to infants, transepidermal water loss is much higher in infants compared to adults (Figure 5).

Although the severity may vary between infants and sensitive skin adults, there is a similar vulnerability between the two groups in terms of decreased NMFs, elevated TEWL, and increased permeability to exogenous factors, compared to healthy adult skin.

'Prone' Skin (Eczema, Acne, Rosacea, etc.)

Although no agreed definitions exist for 'prone' skin (eczema-,

FIGURE 5. Transepidermal water loss in infants compared to adult body sites on arms and legs.



acne-, and/or rosacea-prone), common standards reference either a previous diagnosis of the condition by a physician and/or a familial/genetic predisposition for the disease. A common symptom across all three conditions is inflammation and erythema, although the nature of this varies across subtypes, and dryness and itch with eczema- and rosacea-prone skin.[18]

Acne-prone skin is common in adolescents and young adults, and to a lesser degree as late-onset or adult-onset in women in their 30s and 40s. Adjuvant products for acne-prone skin include products for the reduction of sebum production, pore cleansing/unclogging, bacteria removal, and reduction of inflammation and redness.[18] Mild cleansing and moisturization has been previously shown to improve skin barrier and overall skin condition.[38-40]

Rosacea is a chronic condition that primarily affects the central face, and most commonly occurs in adults from 30s onward. Although the cause is as yet unknown, common facial signs linked to rosacea include flushing/blushing and persistent inflammation, erythema, telangiectasia, coarseness of skin, and an inflammatory papulopustular eruption resembling acne.[41] People with rosacea-prone skin typically see increased symptoms or flare-ups with common triggers such as changing environmental conditions, drinking hot or caffeinated beverages, exercise, consuming spicy foods or alcohol, stress, topical products that irritate the skin, etc.[41] Recent research includes identifying genomic regions potentially associated with rosacea symptom severity,[42] and genetic loci associated with rosacea.[43] Typical topical products for rosacea-prone skin include mild cleansers intended for sensitive skin use and skin barrier repair facial lotions.

Eczema-prone individuals typically experience symptoms such as moderately to severely dry, red, itchy and inflamed skin. Eczema is more common in infants and young children but can also occur in adults with no prior history of childhood eczema. Most eczema-prone individuals have experienced moderate to severe symptoms of itch, which can lead to excessive scratching and further disruption of the skin barrier. Typical topical products for eczema-prone individuals include mild cleansers and barrier repair moisturizers. In addition, moisturizers that provide longer-lasting hydration throughout the day are more effective for alleviating symptoms and preventing triggers with changing environmental conditions throughout the day than those intended for instant moisturization benefits only.

The symptoms of erythema, inflammation, and dry skin itch can have a dramatic effect on QoL, for example discomfort with associated symptoms, functional capabilities, and social interactions,[44,45] as well as mental well-being,[46] perceived stress,[47] and self-esteem.[48]

There are important learnings from the compatibility of cosmetic products for daily use with diseased skin – for example, to minimize dryness and redness either in frequency or severity of symptoms. In recent studies, a mild non-foaming face cleanser with a low level of non-ionic surfactant and fatty acids was compatible for daily use in patients with rosacea using topical metronidazole.[49] When the only change to daily regimens was the replacement of the patients' normal cleansers with the mild non-foaming face cleanser, 96% of patients showed improvement or remained unchanged in dermatologist-assessed erythema and dryness, and subjective evaluation of tightness, irritation, and tingling was significantly reduced (P<0.05). Subjects also noticed significant improvement to skin smoothness following the switch to the non-foaming face cleanser.

Similarly, a mild syndet bar intended for sensitive skin has been shown to be compatible for daily use in patients with acne and rosacea.[36] In the acne group, 75% of subjects indicated they would prefer to use the mild syndet bar in place of their usual cleanser and the bar was well tolerated in both patient populations.

These studies in diseased skin state highlight the importance of cleanser selection, to ensure the skin barrier is not further compromised.

Aging/Xerotic Skin

Dry, itchy, senile xerotic skin is associated with decreases in stratum corneum (SC) lipid levels with aging, especially ceramide levels, reduced desquamation, and epidermal turnover.[50,51] In addition, with aging/xerotic skin there is a decline in SC natural moisturizing factor (NMF) levels, which impacts SC water holding capacity.

In the dermis, dermal proteins (predominantly elastin and collagen), proteoglycans [PGs] and glycose aminoglycans [GAGs]) decrease with age, impacting the water-holding properties of the dermis. As a results of a more fragile skin barrier with aging, xerotic skin, TEWL is also elevated.

Clinical signs can vary widely, including intense itching and pruritis, erythema, scaling, flaking due to abnormal desquamation, and cracking. Xerosis can progress to asteatotic eczema, where fissures and excoriation allow environmental irritants to penetrate the skin and cause inflammation, compromising the stratum corneum.[50]

Similar to other sensitive skin subtypes, changes in the environment (eg, loss of humidity), harsh cleansers, chemical irritants, etc. can further exacerbate the condition. With the rise in the aging population, and the high prevalence of skin disorders in the elderly population, a good skin care regimen to maintain the fragile skin barrier is particularly important for this group.[50]

Implications for Skin Cleansing and Care

While sensitive skin is multifactorial, and hence the underlying external or physiological triggers vary, there is a commonality in skin care to return the condition of the sensitive skin individual to a 'balanced', healthy skin barrier similar to a non-sensitive individual. Another commonality across subtypes is susceptibility of the skin barrier to irritation resulting in increased dryness, redness, and/or sting.

Previous research has shown mild cleansing with sun protection and moisturizers that improve condition of the skin barrier is beneficial to subjects with self-perceived sensitive skin and a history of reactions to cosmetic products, a history of rosacea with an atopic background, or previous history of retinoid sensitivity.[52]

With the advent of more personalization in skin care, it is expected that there will be continued improvement in clinical outcomes for sensitive skin sufferers, both from relief from symptoms as well as improvement to the skin barrier, which in turn will minimize the frequency and severity of symptoms.

DISCLOSURES

The authors are employees of Unilever.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

The Importance of Understanding Consumer Preferences for Dermatologist Recommended Skin Cleansing and Care Products

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ABSTRACT

Dermatologist recommendations of skin care products are critical to the management of compromised and healthy skin and appreciated by patients. Professionals must carefully weigh not only the safety and efficacy but also the aesthetics of products if they are to achieve the desired outcome of satisfied patients. This article elucidates the relevance of product sensory characteristics and consumer preferences, with specific focus on what appeals to men vs. women, those with self-perceived sensitive skin, and acne sufferers. Different product formats with novel aesthetics are also discussed. Dermatologists' recommendations are clearly essential to ensure that patients use the most appropriate products; however, sensorial aspects of products should be taken into consideration when making those recommendations, to help motivate continued adherence.

J Drugs Dermatol. 2019;18(1 Suppl):s75-79

INTRODUCTION

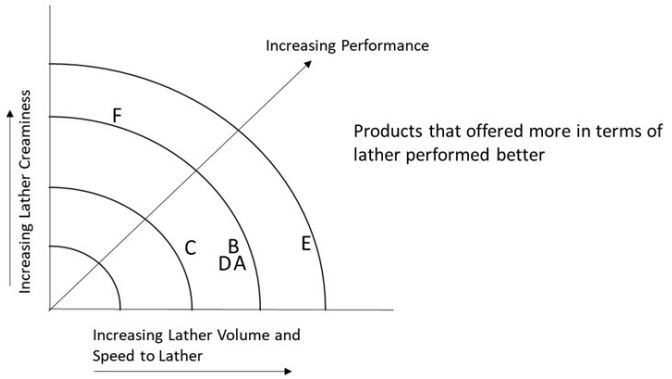
Adherence to treatment is a critical factor for the successful management of dermatologic conditions. It is especially important for conditions where the skin barrier is compromised, such as psoriasis, rosacea, and atopic dermatitis. Published studies have explored the rates and variables relating to adherence to topical medications for such diseases, and evidence has shown that the vehicle or aesthetics of a treatment can be a contributing factor to lack of compliance.[1,2,3] With many product delivery choices available, dermatologists must carefully weigh both therapeutic efficacy and aesthetics as they make treatment recommendations to patients.

This same principle applies to skin care recommendations. Adjuvant topical skin care as part of an overall regimen can be beneficial to patient outcomes and overall skin health. For example, the use of mild and moisturizing cleansers and lotions or creams can help alleviate symptoms of sensitivity and dryness in those with a compromised or dysfunctional skin barrier.[4] However, adherence to a daily routine is essential to achieve positive results.

Dermatologists' recommendations for skin care products play an important role. Patients are not only receptive to, but also proactively seek, the opinion of trusted professionals because of the abundance of therapeutic products available on the market today. Typically, recommendations are centered on a goal of doing no harm, ie, reducing the likelihood of irritation, as well as helping to improve symptoms. Therefore, both safety and efficacy are paramount. Yet, patients do not always abide by a recommendation. A 2015 consumer survey demonstrates how significant the sensory aspects of products can be to adherence. In this survey, 229 consumers who received a recommendation for a skin cleanser from a dermatologist and had started using that product, were queried. When asked if they still use that recommended product, 31% had stopped using it and the top two reasons cited were that they did not like the product or preferred another product/brand.

Given its value, understanding consumer preferences can be advantageous to those who are making skin care recommendations, as well as to those who are formulating the products that are being recommended. Unilever scientists have spent decades decoding the ways in which consumers evaluate products, with particular focus on sensory aspects. For example, in a recent body wash launch, nearly a dozen consumer studies were completed with more than 2,000 consumers having experienced the product during its development. Through this testing, the sensory characteristics of body wash that please a large segment of consumers were uncovered and, just as noteworthy, those sensory characteristics that they disliked, and this learning was applied to the final product development. Abundant effort has also been devoted to understanding what appeals to specific populations, such as men vs. women, sensitive skin consumers, those with conditions like acne, and more. It is known that often there is more than one segment of consumer preference within these groups, but the learnings generalized here represent the sensories most preferred in the population, while other sensories may still be acceptable. This article will further elucidate the aesthetics and sensory aspects of skin care products that appeal to specific types of consumers.

FIGURE 1. Home use test results compared to product characteristics.



Men vs Women: The Ever-Challenging Contrast in Preferences

It is well known that men and women have different skin biology and skin care behaviors. In terms of biology, men's skin tends to be thicker, oilier, and hairier than women's skin. They also have a lower skin pH.[5] Because of these differences, men likely have a desire to use stronger cleansing agents that end up being more disruptive to the skin barrier. In terms of behavior, generally men do not consider skin care a priority; they generally think about their skin when an issue arises. Additionally, most men do not moisturize their skin and therefore dryness is a foremost complaint. In addition to choosing stronger cleansers, men also tend to be over-aggressive during cleansing as they believe it is the physical cue that a product is working when they scrub. Cleanser selection is especially important in men's care because of an aggressive cleansing habit and also because it may be the one and only step in a daily regimen to provide hydration benefits to the skin's barrier.

Additionally, consumer research has shown that men and women have different preferences in terms of aesthetics of body cleansing products. Women tend to look for opaque, creamy-looking products that produce a thick, creamy lather and leave skin feeling comfortable and moisturized. See Figure 1 where product's lather characteristics are compared to overall liking performance in a home use test (HUT). This test was performed on 1200 women, ages 18-59, where each bodywash was used by 200 of the women. The products that offer more in terms of lather perform better than the other products during use.

A male preference mapping study was done to further understand the US male body wash consumer. This was a home use test where 850 men, ages 16-65, tested 10 products at home in their shower. The analysis uncovered different segments of the male consumer. Figure 2 shows a simplified version of this map dividing the male preference and sensory space into two groups. The largest group, segment 1, are characterized by their desire for clean, quick rinsing, and no residue on skin. They also dislike thick, creamy lather. For this group of men, abundant, open lather and transparent appearance are a must. On the opposite side of the sensory map is segment 2, characterized by their preference for opaque, thick product with creamy lather, and their acceptance of residue on skin that imparts softness and smoothness to the skin post use.

FIGURE 2. Sensory preferences of US male consumers.

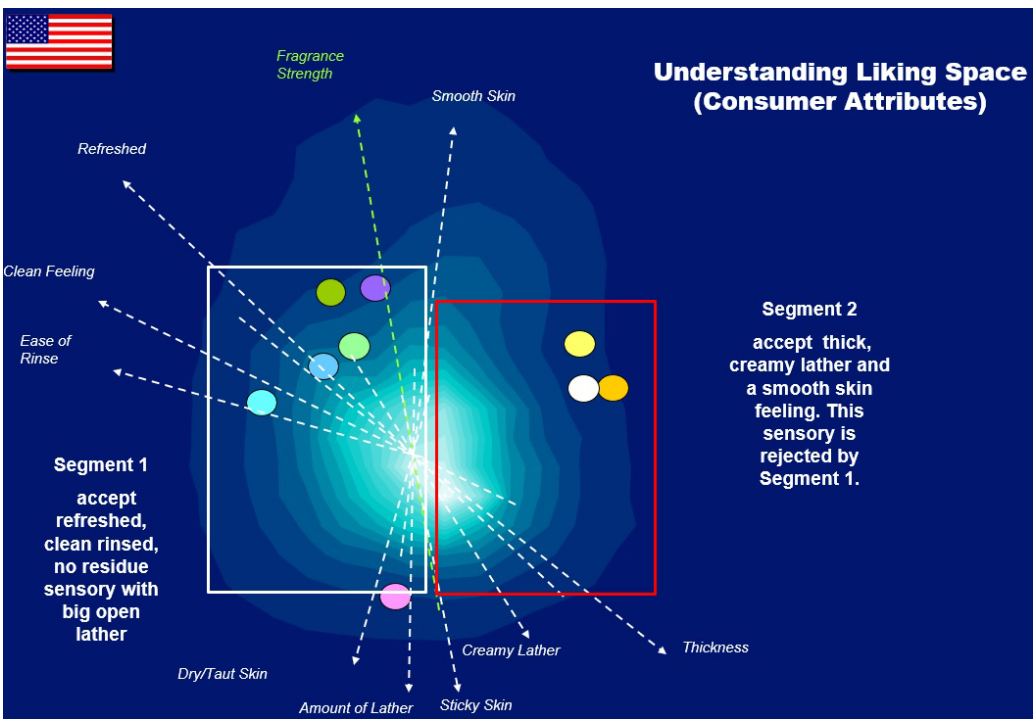
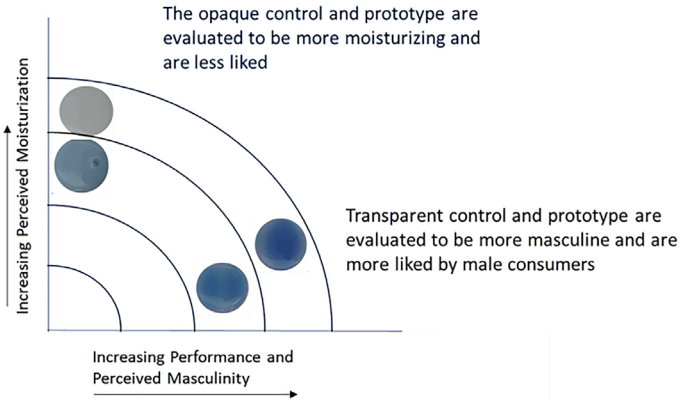


FIGURE 3. The result of opacity on overall opinion and perception of masculinity and moisturization.



As seen in the preference mapping work, a large segment of men prefer a clear formulation, light airy abundant lather, and a clean rinse without a residue. Additionally, a nation-wide consumer test was done in the US on over 1700 men who were potential consumers of men's bodywash products. Figure 3 shows that as opacity increases so does moisturized skin feel, but overall opinion and perceived masculinity is low. The transparent products are evaluated to be more masculine and are more liked by male consumers. Thus, many body cleansing formulas that are marketed toward men are structured as translucent, gel-like washes that provide abundant lather and a clean rinse. However, some cleansers in the market, in order to provide desired sensories, rely on relatively harsher formulations. Therefore, it is valuable for dermatologists and other recommenders to understand the relative differences among types of cleansers.

The skin care market has recently seen an explosion of products specifically targeting men, including face wash and shave gel. A sensory targeting exercise was conducted in several countries with between 35 to 50 men ages 18-40 that were regular users of face cleansers and/or face care products. They were asked to evaluate a range of products representing a wide array of sensories, each compared to a control product. Results of this research in the US have shown that, for facial cleansing, the products that performed well with men delivered on the perception of "refreshes and revives tired skin." These perceptions can be delivered through a blue transparent color, a smooth skin feel after wash, and a crackling sound. The novelty of a cooling/crackling soap drove the perception of refreshment. As with body wash previously described, men do not want thick, opaque formulations, but prefer clear products with suspended bubbles in the formula. In this same sensory targeting exercise, we have seen similar results for men's lotions as well. For a product to be well-liked, it must deliver on the perceptions of refreshment, revive tired skin, and appear attractive. The visual appearance that cues these attributes are blue and light green colors, translucency, gel texture, and glossiness. Oils and extremely thick creams do not deliver on these attributes. Overall, the US male consumer is concerned about feeling refreshed and avoiding skin problems such as dryness. In a shaving HUT, completed with 123 men, aerosols (both foams and gels) performed well and creams did not, showing that format plays a role in perceived performance.

Overall, men and women have very different preferences with respect to lotions and cleansers. A large majority of women prefer thicker, creamier, more opaque products and, in general, men prefer more translucent products with a lighter skin feel. Keeping these preferences top of mind could be useful as recommendations are considered, to help encourage continued consumer use.

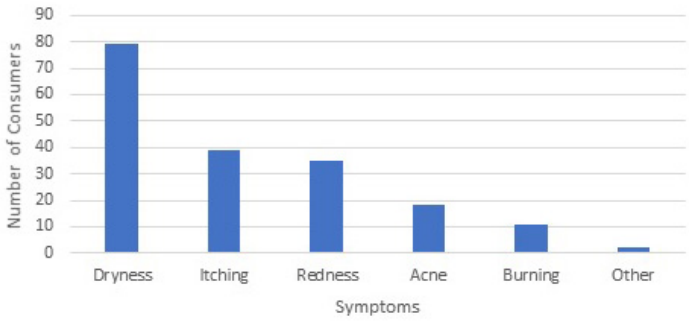
Self-Perceived Sensitive Skin

Almost 50% of the US population has self-perceived sensitive skin.[6] Research has shown that the symptoms and causes of sensitive skin vary along with the product sensory preferences and benefits sought by consumers. While ultimately the dermatologist is the most appropriate expert to identify which products are best for each patient to help reduce sensitivity symptoms, an important goal is patient adherence to the regimen, which could potentially be better achieved by taking patient preferences and priority product attributes into account.

According to Unilever consumer research that surveyed 151 consumers that use sensitive skin body wash, the most common sensitive skin complaints include redness, acne, dryness, and burning (see Figure 4). Sensitive skin consumers are looking for products that do not exacerbate these symptoms and further aggravate their skin. This means that mildness is a critical attribute for sensitive skin cleansers, however, consumers typically cannot perceive it and may be judging efficacy by other product attributes and claims. In one US consumer study, 208 self-perceived sensitive skin female consumers were asked what they were looking for in a sensitive skin body wash. At least 90% agreed that it should be non-irritating and gentle, it should leave skin feeling clean, moisturized, nourished, soothed, soft, and smooth, and be easy to rinse without leaving a residue. When asked open ended questions, answers show that these benefits were cued by a thick, creamy, dense product texture, moisturized feeling without greasiness, mild clean, fresh smell, minimal dyes, and no beads or other abrasives.

When it comes to skin care products developed for those with sensitive skin, it is important for the product to provide a pleasurable experience. Masking unpleasant product odors, natural non-irritating colors, and a comfortable after-use skin feel contribute to creating an enjoyable cleansing experience. Unilever understands the value sensitive skin consumers attribute to the usage experience, and recently launched a therapeutic range

FIGURE 4. Complaints reported by those with sensitive skin.



designed for extremely dry, sensitive skin using sensory profiling to inform the formulation direction. The range included a body lotion that was designed to not only provide robust moisturization efficacy but also feel less greasy than other typical therapeutic lotions. It was also formulated to be thick and creamy and provide a soft, smooth post-use skin feel to help meet those specific consumer needs.

Overall, sensitive skin consumers seek a variety of benefits from skin care products. Some wish to avoid specific ingredients, while others are looking for products that do no harm or provide extra moisturization. Often the color, scent, and skin feel are all important to deliver an overall "skin calming" effect. Patients may be arriving at the office with preconceived notions about the cause of their sensitive skin and what kind of product they need as a result, which may affect the conversation around recommendations.

Acne

Acne is a common dermatologic disorder. As a result of both its prevalence and often highly visible presentation on the face, consumers wish to find immediate relief and often choose the internet or other sources for counsel. This creates a challenge for dermatologists, who understand the complexities of this condition and the critical need for adherence to a therapeutic regimen to resolve it. This may include recommendation of a facial cleansing product to be used concurrently with a prescription medication. Research has been conducted to better understand the product preferences sought by acne sufferers and the sensory cues that would signal efficacy.

An online qualitative study was conducted in eight different countries, including India, UK, Philippines, China, Thailand, Indonesia, Mexico, and South Africa. Results show that consumers rely heavily on in-use sensory of products as proof of efficacy. Globally, among the acne consumers studied, the feeling of dryness is desired. Tightening of facial skin is a positive cue that pimples were on their way to disappearing. Cooling, tingling, or the roughness of a scrub gave consumers a sense

FIGURE 5. Sensory targets for consumers in each group.

Sensory Targets for a Majority of Consumers in Each Group				
	Women	Men	Sensitive Skin	Acne
Visual Appearance	Opaque, creamy	Translucent, gel like	Minimal dyes, no beads	No preference as long as it is non-offensive and effective
Lather Characteristics	Thick, rich	Light, airy	Thick, creamy, easy to rinse	
Skin Feel	Comfortable, moisturized	Refreshed, revived, cooling	Non-irritated, clean, moisturized	Tightened facial skin, cooling, no oil/greasiness

that something beneficial was happening during use. Face washes were viewed as effective if they felt refreshing and left the skin looking different after use (no oil, lighter/brighter). Unfortunately, many of these sensory cues do not align with the types of products that dermatologists recommend for acne. That said, based on these findings, if a mild, non-irritating facial wash could help to control oil and leave skin feeling refreshed as well, it may be more positively accepted by these consumers.

Formats

With the proliferation of skin care products in the marketplace today, it would appear as though there is a product to meet every need. See Figure 5 for a summary of sensory needs by consumer segment. Their needs can be met through traditional cleansing products or with newer formats. Consumers have become accustomed to continual expansion and rapidly-appearing innovation, so they crave new formats with novel sensory experiences. Some examples of new formats in body cleansing include mild self-foamers, aerosol foams, and scrubs. These can now be designed to provide specific skin benefits and sensory experiences that appeal to consumers, while also maintaining a mildness profile that dermatologists desire. While foams have been traditionally viewed as harsh due to the types of surfactants required to generate lather, new sulfate-free, self-foaming technologies have been created with glutamate and glycinate to provide mild cleansing along with an easy rinse, for those consumers looking for a lighter feel than traditional body wash. Directly Esterified Fatty Isethionate-based body scrubs are now being made without sulfated surfactants and a softer level of abrasion combined with a creamy, cushiony, experience consumers view as gentle, unique, and effective. As always, it can be advantageous for dermatologists to become familiar with these new skin care product formats as they arise, so that they can make suitable recommendations for patients who seek novel experiences.

CONCLUSIONS

Overall, it is well-recognized that a dermatologist's recommendation can be vital to encourage patients to try a product that is suitable for their skin type, yet the role that aesthetics play in their continued use is sometimes overlooked. Efficacy, safety, and sensory aspects of products should all be weighed

as recommendations are determined. It is important to note that consumers often devise their own perceptions of how well products work based on in-use experiences and sensory cues. How these products look, smell, and feel can all contribute to the user experience and the assessment of skin benefits. Preferences also stem from factors such as gender differences and skin types or conditions. Balancing all of these considerations could have a potential impact on adherence.

DISCLOSURES

The authors are employees of Unilever.

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 ORIGINAL ARTICLE Journal of Drugs in Dermatology

Recent Advances in Mild and Moisturizing Cleansers

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ABSTRACT

Mild and moisturizing cleanser technologies, and the science underpinning them, have progressed significantly over the past decade. This includes introduction of amino-acid based milder surfactants into the cleansing arena, a deeper understanding of the roles of stratum corneum lipids and proteins in their interaction with cleanser surfactants, the role of pH in skin cleansing, and the development of improved methodologies for predicting skin irritation and drying potential of cleansers. In this paper, the recent advances in these areas as well as newer technologies are reviewed, and the future directions are outlined.

J Drugs Dermatol. 2019;18(1 Suppl):s80-88

INTRODUCTION

Cleansers are designed to remove dirt, sweat, sebum, and other unwanted materials from skin. Normal exfoliation of superficial dead cells is also aided by the cleansing process. Thus, cleansing is the first step in daily skincare.

The cleanser actives, surfactants, are designed to remove oily materials and drive the cleansing process. The challenge is in limiting the interaction of surfactants to just removal of undesirable materials and preventing them from altering the properties of the stratum corneum barrier, leading to skin dryness, irritation, itch, and other undesirable events. It is well-known that cleansers based on alkaline soaps are more irritating to skin than those based on synthetic surfactant actives, commonly referred to as syndets, which function under neutral pH conditions.[1] It has also been established that the harshness of alkaline soaps stems from their harsh cleanser active, the soap molecules, and their high pH.[2,3] Early work on interaction of surfactants with stratum corneum has been reviewed extensively in the literature[4-11] and the importance of milder surfactants underscored.

The emergence of liquid cleansers in the 1990's opened up opportunities for a wider range of surfactants to be explored in the cleansing arena. Synergistic combination of surfactants can lead to improved mildness.[4,7] However, the challenge has been in designing ultra-mild products without compromising on consumer-desired sensory properties such as lather. In fact, dermatologists would acknowledge that compliance even among those with compromised skin is poor for products that have inferior sensory. Recent advances in cleansing surfactant systems have resulted in ultra-mild systems without any compromise on the sensory.[4,12,13]

The liquid format also made it possible to develop technologies that deposit moisturizing and sensory enhancing actives during the wash process. Benefit actives from wash-off systems include humectants such as glycerol, oily materials such as triglyceride oils and petrolatum, sensory enhancers such as silicones, and skin-natural lipids such as fatty acids and sterols.[4,9]

Along with the progress in cleanser technologies, the ability to predict the skin irritation and drying potential of cleansers and assess the skin barrier quality also has advanced significantly.[14]

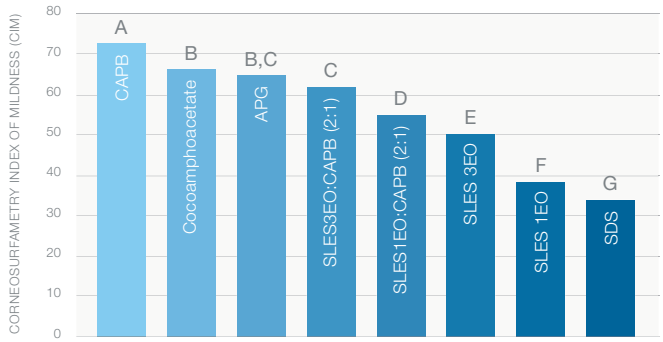
Interaction of Cleanser Surfactants With Stratum Corneum

The human stratum corneum consists of flattened corneocyte cells embedded in a lipid matrix.[15,16] While the corneocytes with their cross-linked keratins and natural moisturizing factors (NMFs) contribute to the mechanical and water holding properties of the stratum corneum (SC), the lipid matrix acts as the main barrier to water loss from the body.[17,18] Recent advances in our understanding of the stratum corneum have shown that it is not only a physical barrier, but also an immunological and a microbial barrier.[19, 20] Thus, any damage to the stratum corneum from use of harsh cleansing products can impact its multiple barrier functions.

Interactions of Surfactants With SC Proteins and Relevance to Skin Irritation

The early work on interaction of common cleanser surfactants with skin showed that in vivo irritation potential of surfactants correlated with the ability of surfactants to denature proteins such as BSA or Zein, and/or swell cross linked proteins such as collagen.[4,7] Over the years, there have been attempts to use stratum corneum itself as a substrate for in vitro irritation studies.[5,6,14, 21] Skin irritation potential of some of the common

FIGURE 1. Corneosurfametry index of mildness (CIM) values for individual surfactants. Bars having the same letter are not significantly different from each other. Results showed CAPB was the mildest and SDS was the harshest and also showed SLES 1 EO to be milder than SLES 3EO and SLES 1 EO and 3EO blends with Betaine were milder than the corresponding SLESs. SDS: sodium dodecyl sulfate, SLES xEO: sodium lauryl ether sulfate with x number of ethylene oxide groups, CAPB: cocoamidopropyl betaine, APG: Alkyl polyglucoside



cleanser surfactants assessed in a modified ex vivo corneosurfametry assay is given in Figure 1.

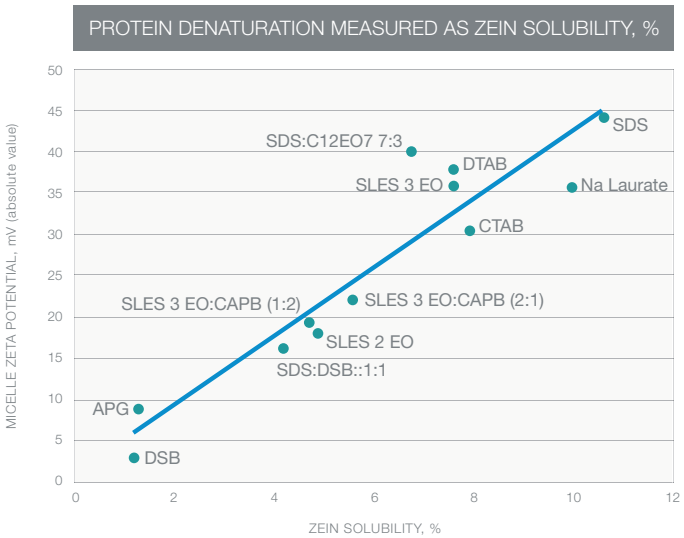
The results in Figure 1 show that anionic surfactants are harsher than amphoteric and nonionic surfactants and addition of amphoteric surfactants to anionics make them milder. This assay has been previously validated for its correlation with in vivo evaluation of formulation mildness and irritancy potential.[14]

It is evident from the past work that the charge of the surfactant plays a role in their irritation potential. Further research along these lines has led to the development of a quantitative relationship between the charge density of surfactant micelles (self-assembled surfactant aggregates in solution) in the cleanser system and their skin irritation potential (see Figure 2).[22] Such quantitative structure–function relationships will help formulators assess the relative irritation potential of technologies prior to expensive clinical studies.

The reason SC swelling by surfactants correlates with skin irritation is because, upon swelling, the permeability of the structure increases, significantly leading to penetration of foreign materials into deeper layers causing a biochemical reaction that manifests as irritation, inflammation, and itch.

The inherent irritation potential of surfactants and other chemicals to skin can be determined from keratinocyte cell culture studies or living skin equivalent (LSE) models studies in which irritation can be related to the release of inflammatory biomarkers such as IL1 alpha (interleukin 1α (IL1-α) and IL1-Ra).[23,24] Since these systems do not have a fully developed corneum barrier, they may not predict the irritation potential under normal use conditions. However, such testing may be appropriate for testing products intended for compromised skin situations such as those in sensitive, atopic, and infant skin.

FIGURE 2. Correlation between protein denaturation measured as zein solubility in 5% surfactant solutions and the charge density of micelles estimated from micelle zeta potential measured at 1% surfactant level. Protein denaturation potential scales linearly with the micellar charge/potential. Correlation appears to hold good for a wide range of surfactants including anionic, zwitterionic, nonionic, and even cationic surfactants and surfactant mixtures. This provides a quantitative ruler for mildness assessment of surfactants and surfactant mixtures toward proteins. SDS: sodium dodecyl sulfate, SLES xEO: sodium lauryl ether sulfate with x number of ethylene oxide groups, APG: alkyl polyglucoside, DSB: dodecyl sulfobetaine



Surfactant Interactions With Skin Lipids

Surfactants are designed to interact with fatty materials such as sebum and skin lipids. While removal of sebum is important during cleansing, interaction with SC bilayer lipids is not desirable as the latter constitutes the main barrier to water transport through skin. Cleanser surfactants can intercalate into the bilayer and increase its permeability by altering the bilayer structure.[4,25] It can also extract the "more extractable" lipids such as medium chain fatty acids (eg, palmitic or stearic acid) and cholesterol and affect the skin permeability.[4,25-28] A quantitative determination of the amount of SC bilayer lipids during cleansing has been a challenge because of their complexity in terms of chain length and the absolute amounts involved.[28] Superficial effects of surfactants on skin lipids may not immediately lead to skin irritation, but may manifest as skin dryness.[4, 27] With continued damage, such a situation can progressively result in scaling, flaking, and disruption of barrier.

Several in vitro methods exist to estimate the tendency of surfactants to damage SC lipids.[4, 25-29] This includes simple assays

to determine the solubility of SC lipids such as fatty acids, cholesterol and ceramides in surfactant solutions, destruction of model bilayer membranes in the form of vesicles, removal of lipids from isolated SC, or changes in bilayer structure of isolated SC by vibrational spectroscopy. Such studies have also shown that the tendency of surfactants to damage lipids may not be the same as that for damaging SC proteins.[4] For example, certain nonionic surfactants such as alkyl polyglucosides and amphoteric surfactants such as cocoamidopropyl betaine (CAPB) have minimal tendency to interact with proteins, but show higher tendency to interact with lipids. Mild cleansing requires mildness towards both proteins and lipids and therefore choosing surfactants that are mild towards both is important. A combination of anionic surfactant with amphoteric and/or nonionic surfactants can lead to such optimal conditions.

The past work also showed that an amino acid surfactant, cocoyl glycinate, is as mild as the well-known syndet surfactant, cocoyl isethionate, commonly used in neutral pH syndet cleansing bars. These findings created the pathway for the introduction of an amino acid surfactant-based body wash by a major brand several years ago[13] and the potential for other amino-acid surfactants in the future.

Role of pH in Skin and Skin Cleansing

It is well established that alkaline soaps are harsher than neutral pH syndet surfactant based cleansing bars.[1-4] It is also well-known that the natural pH of SC is around 4.5 to 5.0.[30] Korting et al have shown that use of alkaline soaps lead to a transient increase in pH of the order of almost 2 units and it returns to normal skin pH values with time.[30] However, continued use of alkaline soaps can lead to a change in the steady state pH of skin and accompanying changes in the skin microflora.

An elevation in the steady state pH has been observed also for abnormal different skin conditions. For example, it has been shown that extremely dry and atopic skin generally have higher than normal pH values, eg, around 5.5 to 6.0 or even higher.[31] In such cases, it is not clear if skin pH change is the cause or the effect of skin conditions.

Elias and team have shown that hyper acidification of SC can lead to improved SC cohesion, increased lipid synthesis, and enhanced antibacterial activity.[32, 33] Subsequent work by several researchers has shown that intentionally lowering the pH of skincare lotions to values below the SC pH can lead to improved rates of recovery of tape stripped skin or even elderly dry skin.[34, 35] Thus, there may be a case for lowering the pH of lotions and creams for improved skin benefits. More work is needed to validate the generality of these findings.

In the cleansing arena, there have been attempts to make implied skin benefit claims by formulating skin cleansers under skin pH or even lower than skin pH conditions.[10,36] In such cases, the claims have been based on just the pH of the product alone, rather than any experimental evidence of skin benefits for low pH cleansers.

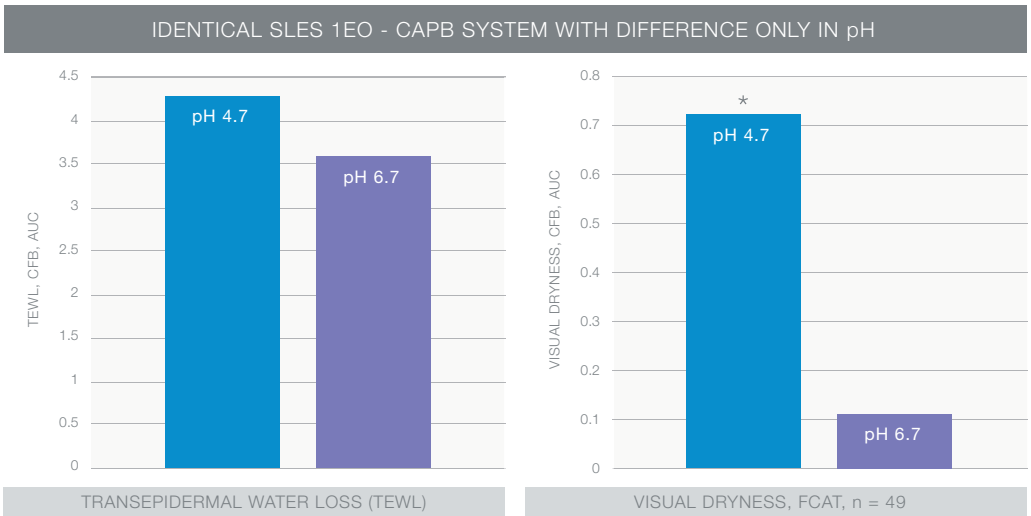
In order to test the effect of pH on skin cleansing systems, two identical syndet bar formulations, one under neutral pH conditions and the other under low pH conditions, were tested for their relative mildness in a typical forearm controlled application test (FCAT), which is commonly used to rank relative disruption to the skin's barrier following exaggerated use conditions.[10,37] The results showed that the neutral pH cleansing syndet bar was milder by lower transepidermal water loss (TEWL) and clinical visual dryness.[10] Results of similar studies carried out with a typical SLES (sodium lauryl ether sulfate, 1 EO) and CAPB systems are shown in Figure 3.[38] These results also show that the lower pH cleanser is harsher than the neutral pH cleanser in TEWL and visual dryness.

The above study results suggest that neutral pH is better for mild cleansing. These are contradictory to the leave-on results mentioned earlier and can be explained as follows. The isoelectric point of keratin is around pH 5.[39] The results for the zeta potential of human stratum corneum given in Figure 4 also shows that the IEP is around 5. Therefore, skin proteins have a net negative charge under neutral pH conditions. As the pH is lowered from neutral to acidic values, skin will have more positively charged sites than under neutral pH conditions and this in turn should promote increased binding of anionic surfactants to skin.[10,11] Significant reduction in the zeta potential of SC in the presence of an anionic surfactant, SLES, is evident from the results given in Figure 5 and this is brought about by the binding of surfactants to the SC. Thus, in systems with predominantly anionic surfactants, there can be more residual surfactants left on skin under low pH conditions than under neutral pH conditions leading to more damage.

The other question that arises when comparing neutral pH cleansing vs acidic pH cleansing is whether long-term use of a neutral pH cleanser elevates the pH of SC from its normal value. Previous reports show that transient pH change immediately after cleansing with a neutral vs a mild low pH cleanser is about the same and the skin pH values return to normal in less than an hour in both cases. Furthermore, even water wash is known to lead to a transient increase in pH that returns to normal values in less than one hour.[38] Thus, unlike alkaline pH cleansing, neutral pH cleansing itself does not pose any harm to the SC.

Note that the above arguments do not imply that it is not possible to create a low pH cleanser that is very mild. The current observation simply implies that conventional anionic surfactant rich-cleansers can be more irritating under low pH conditions.

FIGURE 3. FCAT (Forearm controlled application test) study results for SLES 1 EO-CAPB based regular body wash formulations differing only in pH. Results show that the lower pH formulation at pH 4.7 is more drying to skin than the one at pH 6.7. Bars represent change from base line (CFB) of area under the curve for TEWL (trans-epidermal water loss) and dryness over the test period. SLES 1EO: sodium lauryl ether sulfate with 1 ethylene oxide group, CAPB: Cocoamidopropyl betaine



Role of Fatty Acids in Skin Mildness

An approach to minimizing the tendency of surfactants to cause delipidization and the consequent skin dryness has been the incorporation of fatty acids in the formulation.[12,28,40] This stems from the hypothesis that fatty acids and cholesterol are the surfactant-extractable lipids in the SC and, between the two, fatty acids are more extractable. Incorporation of fatty acids can prevent extraction of medium chain fatty acids from skin as well as replenish fatty acids that are likely to be removed during the cleansing process.[28,40] Figure 5 reproduced from reference 12 shows how addition of stearic and palmitic acids improves the relative reduction of TEWL and visual dryness in an FCAT clinical study even in a relatively mild isethionate surfactant system.[12] In addition to modulating the harshness of cleanser surfactants, fatty acids may also provide other skin benefits and this aspect will be examined in a later section.

Moisturization from Cleansers

Moisturizing cleansers are designed to provide positive skin benefits beyond simple mild cleansing. Typically, these are measured as increased hydration levels and reduced visible skin dryness and transepidermal water loss in comparison to starting conditions. These are typically achieved by depositing "oily" materials such as petrolatum or triglyceride oils often in combination with humectants such as glycerol[4,9,41] and such deposition provides an immediate visual dryness reduction benefit.

There are products in the marketplace that emphasize both mildness and moisturization and others that emphasize more on just moisturization. The rationale behind the use of a strong moisturization system with less regard for the mildness of the cleanser base is that the former can overcome the negatives of the harsh base while maintaining its overall sensory properties. Our hypothesis, based on previously published research on cleanser mildness, is that both of these elements are critical for superior skincare from cleansing systems.[42] It has also been shown that it is possible to create ultra-mild systems without any compromise on sensory properties.[12,13]

FIGURE 4. Stratum corneum zeta potential as a function of pH. Sonicated pieces of corneum dispersed in water and treated with 0.01% SLES. Isoelectric point of SC appears to be around 4.5. In the presence of SLES, the SC corneum charge becomes significantly more negative because of anionic surfactant binding. As the pH is lowered from neutral to lower values, more surfactant binding can be expected.

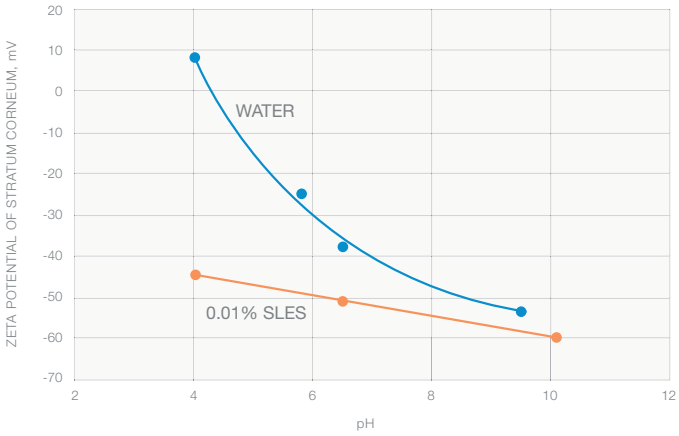
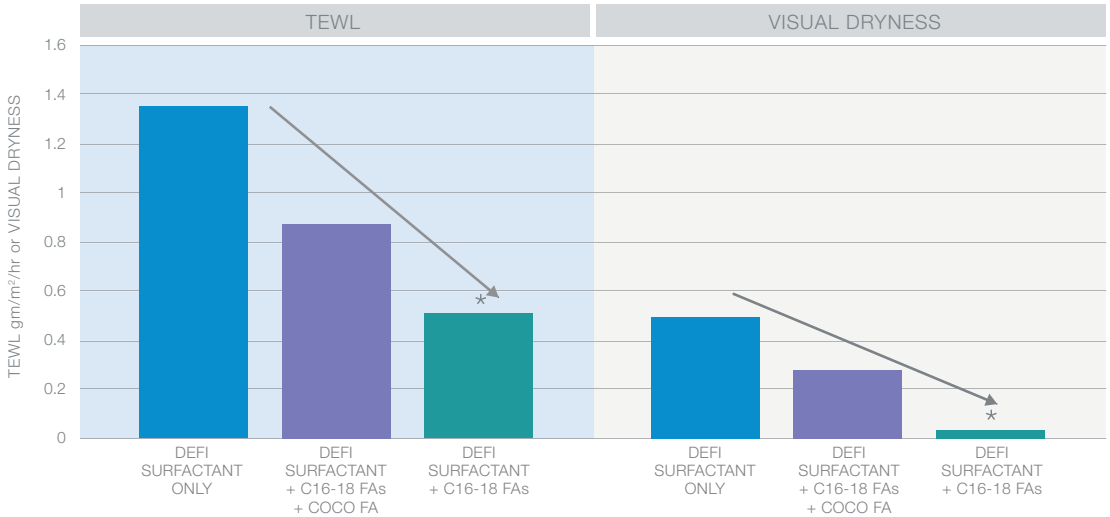


FIGURE 5. The effect of fatty acid addition to a prototype body wash formulation with DEFI surfactant (directly esterified isethionate) on in vivo TEWL and visual dryness in a standard FCAT study. No emollients present in the BW. DEFI is directly esterified fatty isethionate surfactant. In systems with fatty acids, total fatty acid level is 7.3%, in system with both coco and longer chain fatty acids, coco fatty acid level is 2.8%. *Indicates statistically significant from the surfactant only system. Visual dryness scale 0 to 6.



Rebuilding the Skin Barrier With Advanced Skincare Benefit Technologies

Beyond the immediate visual dryness reduction and improved skin hydration benefits, moisturization technologies are progressing towards improving damaged skin barrier from wash-off and leave-on formats. As discussed earlier, ensuring minimal changes to skin pH is the first step towards skin barrier repair.

Another approach to barrier repair is the use of complex lipid mixtures consisting of ceramides, fatty acids, and cholesterol that can form SC bilayer-like film on the skin surface.[43,44] Such films can be expected to reduce the water loss and help repair the barrier. This can be considered as an "outside-in" approach as the barrier reinforcement is essentially coming from the outside. This is similar to the use of an occlusive such as petrolatum. However, because of the differences in the composition of the film, their performance can be different from that of petrolatum.

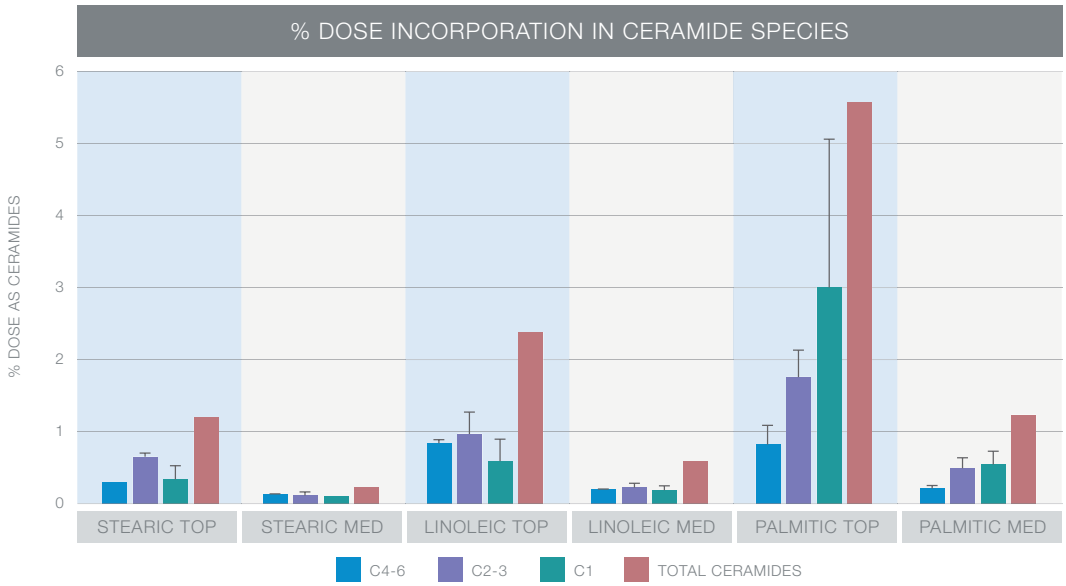
Pro-lipid technologies aim to supply ingredients that the skin can utilize to rebuild the barrier from within. The early work by Rawlings et al involving the use of triglyceride oils as a source of essential fatty acids that skin can utilize to increase the synthesis of ceramides is noteworthy.[45] Subsequent work by Harding et al in living skin equivalent (LSE) models showed that fatty acids, especially palmitic acid, can be utilized by skin to increase synthesis of ceramides in skin.[46] In these studies, radiolabeled palmitic acid and stearic acid were applied to LSE topically as well as in the culture medium. Analysis of SC lipids after 24 hours of incubation showed the presence of radiolabeled ceramides in them indicating the incorporation of the fatty acids into the building of ceramides (see Figure 6). In this regard, recent work by Bouwstra and team is also noteworthy.[47] The latter group showed that addition of deuterated palmitic acid to their cultured skin model resulted in elongation of the fatty acid to longer chain fatty acids such as C22 and C24 fatty acids. This shows another route by which palmitic acids can be taken up by skin to build SC bilayer lipids. Note that in vivo leave-on and wash-off study results with products containing fatty acids such as palmitic and stearic acids have clearly shown that they do penetrate into deeper layers of skin.[9,28] In vivo demonstration of conversion of fatty acids, ideally using deuterated fatty acids, may be a logical next step in this research.

Similar to the case of fatty acids, externally applied ceramides from leave-on formats in LSE-type models have also been suggested to be taken up by skin in the creation of ceramides.[48] Noting that the skin barrier in the case of LSE models is relatively weak compared to a healthy corneum, penetration of ceramides into deeper layers for incorporation is yet to be validated. In fact, some of the recent studies using Raman imaging and microscopy suggests that externally applied ceramides tend to get trapped in skin's furrows and valleys rather than penetrating deeper into skin.[49] Given the two-tailed structure of ceramides, its high molecular weight and its low solubility in typical cleansing and leave-on systems, its lack of penetration into skin is not surprising.

Cleansing Technologies

Based on the above discussion, a strategy for developing cleanser technologies to meet the various market needs is outlined in Figure 7. Current market trends for various cleansing applications is shown in Figure 8. For a specific type of cleanser

FIGURE 6. Fatty acids applied either topically or into the medium in a radiolabeled form to a living skin equivalent model skin shows conversion of fatty acids into different forms of ceramides after 24 hours of incubation. Palmitic acid shows more conversion than other forms. *Reproduced from Harding C and Alexis J*[54]



system, one approach to increasing the overall mildness is by reducing the level of the surfactant in the formulation. This is commonly practiced in the liquids area and the recent launch of micellar water is an example of this approach. In the bars area, there have been attempts to make the bars milder by reducing the total fatty matter (TFM), ie, the surfactant active in the bar. Addition of polyols and other mildness enhancers can further improve their mildness.

Cleansing Technologies for Vulnerable Skin Conditions

Cleansing technologies for sensitive skin and other vulnerable skin conditions such as infant skin and atopic skin generally differ from the typical adult cleansing systems. Even in adult cleansing, "gentler" technologies are thought to be ideal for facial cleansing.

Infant Skin Cleansing

Infant skin at the time of birth is not as fully developed as the adult skin and it takes as much as a couple of years before it is fully matured.[50] Recognizing that the infant skin barrier is relatively weak, extra care should be exercised in the development of baby cleansers. In addition, some of the recent findings suggests that early skincare, particularly during the first year of birth, can help prevent such conditions as atopic dermatitis and other allergies in the future.[51] Noting that skincare starts with skin cleansing, the importance of mild cleansing for infants cannot be overemphasized.

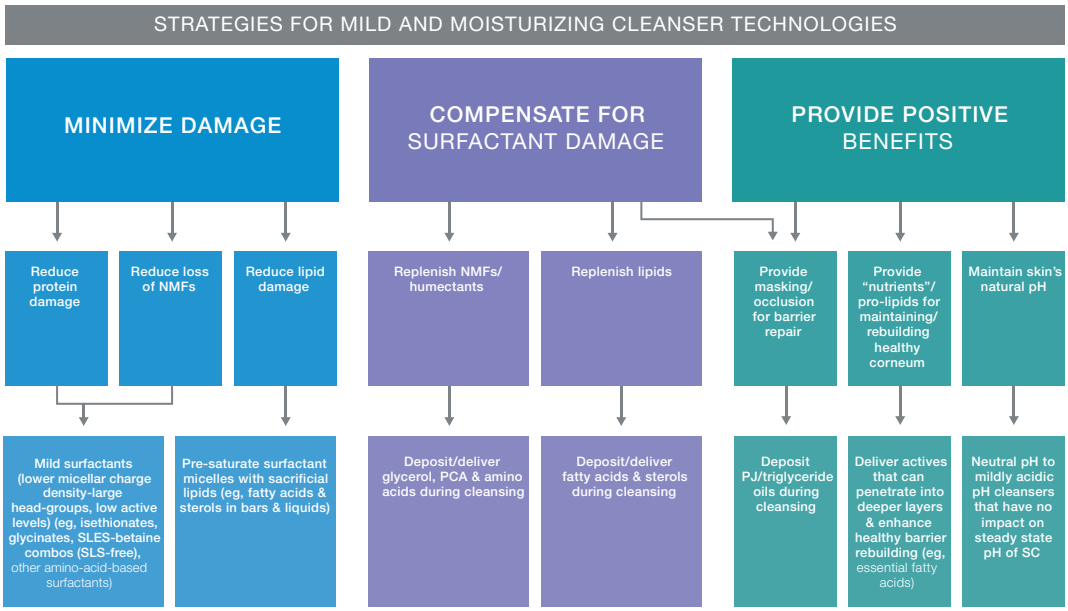
Currently available baby cleansers include both bar and liquid formats. It is well established that the neutral pH syndet cleansing bars are milder than the alkaline pH soap bars.[1,10] With regard to weakly acidic pH skin cleansing, as discussed in an earlier section, typical anionic surfactant rich bars under acidic pH conditions have a higher skin drying potential than the neutral pH syndet bars.[10] Thus, neutral pH bars may be preferable for infant cleansing.

In the liquid cleansing area, there are several options for milder surfactant combinations and additives that enhance the mildness of surfactants. Typically, the baby cleansing products have lower level of surfactants than that in adult formulations. They also tend to have higher ratios of amphoteric and/or nonionic surfactants to anionic surfactants. A balanced formula that takes into account both protein and lipid damage potential of surfactants, as discussed in the earlier section, is more appropriate for baby cleansing. In this regard, formulations containing skin lipids such as fatty acids that can mitigate some of the lipid damaging tendencies of surfactants are more appropriate for infant cleansing.

Cleansers for Sensitive Skin

Even though the percentage of self-perceived sensitive skin population has been increasing steadily in the recent past, the reasons for sensitive skin are still poorly understood.[52] A weaker skin barrier is thought to be one of the factors that results in sensitive skin in at least part of the sensitive skin subjects.[53] Therefore, the general approach has been to limit or avoid the type of ingredients that have an inherent tendency to penetrate deeper into skin and cause irritation. Specifically, this includes avoidance of harsh surfactants and fragrance and limiting pre-

FIGURE 7. Technology routes to mild cleansing and moisturizing cleanser technologies.



servatives in cleansing technologies. This area is likely to get increased attention from researchers in the coming years for a better understanding of the skin condition and for technologies specifically developed for them.

Facial Cleansing

A detailed discussion of facial cleansing is beyond the scope of this paper. Briefly, the type of products for facial cleansing vary from almost water-like non-foaming cleansers to foaming cleansers that leaves the skin with a well-stripped taught feel. Cleansers also vary significantly in their pH values all the way from highly alkaline soap like cleansers to highly acidic anti-acne cleansers. Another newer entry into the anti-acne area includes a technology using natural actives such as thymol and terpineol that has shown efficacy in clinical studies.[54] In general, unlike in body wash, "oily" emollients are not ideal for facial cleansing. Instead, humectants such as glycerol and light moisturizers are preferred.

FIGURE 8. Market trends in cleanser technologies.

	REGULAR	MILD	VERY MILD	ULTRA MILD
BARS	Soap bars (alkaline)	Low TFM bars, glycerol/polyol bars	Syndet bars with fatty acids	
REGULAR BODY WASH	SLES-betaine based	Milder surfactant base (eg, isethionate/glycinate/ other milder surfactants (SLS-free))	Milder surfactant base + fatty acid/lipid enriched cleanser with mild surfactants	
MOISTURIZING BODY WASH	SLES-betaine base, moisturizers	Milder surfactant base, moisturizers, humectants	Milder surfactant base + fatty acids/lipids, moisturizers, humectants	
FACIAL CLEANSERS	Alkaline soap bars and SLES-betaine liquids	Milder surfactant base, humectants, light emollients	Milder surfactant base, lipids, humectants, light emollients	Low surfactant/ low foaming/non-foaming humectants, light emollients (eg, micellar water)
INFANT CLEANSING	Alkaline soap bars, SLES-betaine based liquids	SLS–free, milder foaming cleanser	Amphoteric surfactant rich, fatty acids/lipids, humectants, moisturizers and emollients	Low surfactant/ low foaming humectants, light emollients, moisturizers
SENSITIVE SKIN		Milder surfactant base, fragrance-free	Milder surfactant base, humectants, fatty acids/lipids, emollients, moisturizers, fragrance-free	Low surfactant/ non-foaming, humectants, moisturizers, emollients, fragrance-free

The idea of low-active, water-like, low/non-foaming cleansers is highlighted by the recent growth of "micellar water" in the market place. The fact is that all conventional cleansers have "micelles" or molecular surfactant aggregates in them under conditions of cleansing and they play a significant role in the cleansing process. Micellar water is created by relatively mild, nonionic, or ultra-mild surfactants at low levels, along with low levels of solvents such as short-chain alcohols that aid in the removal of make-up and other oily materials on skin. They may also contain light moisturizers and humectants.

SUMMARY AND CONCLUSIONS

Significant advances have been made in mild and moisturizing cleanser technologies over the past 10-15 years. This includes a deeper understanding of the relative roles of SC proteins and lipids in the interaction of SC with cleanser surfactants leading to skin dryness, irritation, and erythema, and the role of co-surfactants and lipids such as stearic and palmitic acids in mitigating their effect. Typical moisturizing technologies from wash-off systems involve deposition of triglyceride oils or petrolatum during the rinse phase. The importance of cleanser base mildness even in high emollient containing moisturizing cleanser systems is now clearly established. Recent work also shows that the moisturizing technologies can move further in the direction of helping skin build better barrier by supplying actives such as fatty acids and other pro-lipids that skin can utilize in its repair process. Future trends in the cleansing area include increased use of sustainable and greener ingredients, better understanding of the skincare needs of the very elderly, and unraveling the role of skin microbiome in the context of daily skincare.

DISCLOSURE

At the time of most of this work, KP Ananthapadmanabhan was an employee of Unilever. KP Ananthapadmanabhan and JJ Leyden are consultants for Unilever. S Hawkins is an employee of Unilever.

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 ORIGINAL ARTICLE Journal of Drugs in Dermatology

Principles of Moisturizer Product Design

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ABSTRACT

Moisturizers provide significant benefit in dermatology – as adjuvant therapy for many clinical conditions, as a key player in anti-aging regimens, and as a core component in maintaining healthy skin barrier function. Although they have been a mainstay for decades, lotions and creams are no longer formulated with a one-size-fits-all approach, where thickness was the primary cue for efficacy. In fact, moisturizer design today has become an art as well as a science. Product efficacy, aesthetics, and packaging are all engineered in a variety of ways, to create an expansive market of products that meet many consumer needs. The addition of specific types of functional ingredients can make a noteworthy difference as well. This article will explore the myriad approaches for moisturizer development and debunk some of the long-standing myths that have pervaded the marketplace.

J Drugs Dermatol. 2019;18(1 Suppl):s89-95

INTRODUCTION

Moisturizers refer to a wide range of consumer products – lotions, creams, serums, and oils designed for the face, body, eyes, hands, and feet. While a primary function is to increase skin hydration, moisturizers deliver other advantages as well, such as improving skin appearance, enhancing skin softness and smoothness, and supplying benefit agents to skin.[1] Moisturizers have broad utility within dermatology and can be particularly important as adjuvant therapy for those conditions associated with skin barrier defects, such as atopic dermatitis, to help alleviate symptoms and improve barrier function.[2] Research has also indicated that early use of emollients can help reduce the rate of the development of atopic dermatitis.[3] For conditions such as acne, where treatments like retinoids and others can worsen barrier dysfunction and increase (TEWL) transepidermal water loss, concurrent moisturizer use can be beneficial.[4]

Efficacy is a top consideration when selecting a moisturizer for a patient. However, notably, product aesthetics (also known as sensory effects) have become increasingly important to consumers, especially when contemplating the use for body vs face. Consequently, a balance should be struck between efficacy and product aesthetics to encourage daily product use.

For decades, moisturizers have been perceived to be formulated in just two ways. Lotions were thinner and known to contain more water; they absorbed faster and were not greasy or unctuous, and thus believed to be less efficacious. Creams, on the other hand, were thicker, oilier, and more dramatically altered the visual appearance of dry skin immediately. As a result, creams were believed to be more moisturizing. However, moisturizer formulation design has become an art as well as a science, and the adage that creams are simply better than lotions because of their consistency is outdated and no longer true. In today's market, with an explosion of product formats and new scientific techniques for combining ingredients with novel packaging, efficacy, the way a product feels, and what it can deliver to skin can be manipulated in a variety of ways. For example, through the careful selection of emulsifiers, polymers, or thickeners, moisturizer consistency is easily transformed to be thinner or more viscous. With the inclusion of key actives in combination with other moisturizing ingredients, efficacy can be dialed up or down.

It should also be noted that price may not be indicative of the degree of effectiveness. Our own internal studies have shown that the clinical efficacy of $100 creams is parity to or even inferior to mass market products containing similar ingredients. Price is most often set by the brand appeal and consumer willingness to pay, rather than the efficacy of the product.

This article will discuss the myriad ingredients that are utilized in moisturizers, describe the ways in which formulas can be engineered to create specific, desired outcomes, and debunk some of the long-standing myths that have pervaded the industry. This understanding is crucial for those who are recommending products to consumers or patients.

Moisturizers 101: The INCI

Differentiating between moisturizers starts with understanding the key components, which can be found on the ingredient label. This label lists the ingredients, by INCI (International Nomenclature Cosmetic Ingredient), in the order of percentage inclusion in the formulation (in most markets). An exception to this rule is that in the US, for ingredients whose inclusion levels are less than 1%, the INCI can be listed in any order irrespective

FIGURE 1. Typical INCI for **(A)** a body lotion[5] and **(B)** a high occlusive/emollient cream.[6]

(A) **INGREDIENTS:** WATER(AQUA), PETROLATUM, CAPRYLIC/CAPRIC TRIGLYCERIDE, STEARIC ACID, GLYCERIN, SODIUM HYDROXYPROPYL STARCH PHOSPHATE, GLYCOL STEARATE, PEG-100 STEARATE, GLYCERYL STEARATE, CETYL ALCOHOL, PHENOXYETHANOL, METHYLPARABEN, ISOPROPYL MYRISTATE, ALKYL ACRYLATE CROSS POLYMER, DISODIUM EDTA, CEDROL, TOCOPHERYL ACETATE, TITANIUM DIOXIDE (CI77891)

(B) **INGREDIENTS:** WATER(AQUA), GLYCERIN, STEARIC ACID, ISOPROPYL PALMITATE, GLYCOL STEARATE, PEG-100 STEARATE, MINERAL OIL, DIMETHICON, GLYCERYL STEARATE, PETROLATUM, CETYL ALCOHOL, PHENOXYETHANOL, ACRYLATES/C10-30 ALKYL ACRYLATE CROSSPOLYMER, METHYL-PARABEN, TRIETHANOLAMINE, PROPYL PARABEN, STEARAMIDE AMP, DISODIUM EDTA, ISOPROPYL MYRISTATE, CEDROL.

of its actual inclusion level. Figure 1 shows the ingredient lists of a standard body lotion and a high oil body cream.

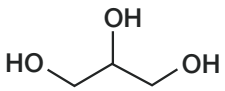
Whereas deciphering the ingredient levels from an INCI is not easy, insights into a formula can be gained by understanding certain principles that apply to all moisturizers. First, in both lotions and creams, water is often the first ingredient. Typically, a lotion contains more water-soluble moisturizers, which are typically humectants. In a cream, occlusives and emollients tend to be the primary moisturizers. Though this is generally the case, it is not always. For example, the first three ingredients of a highly recommended body cream, CeraVe™ Moisturizing Cream, are: purified water, glycerin, ceteareth-20, and cetearyl alcohol. This product is not a cream in the above sense since oils and occlusives do not fall among the first four ingredients on the INCI. This is one example among many that demonstrate that just because a product is labelled a cream and is in a jar, it should not be assumed to be high in occlusive and emollients, and as described below, it is not necessarily more moisturizing. The INCI needs to be examined to gauge whether the product truly meets the need for which it is being recommended.

Another general guide is that polymers, fragrances, preservatives, colorants, and dyes are often present at levels <1%. Since many functional ingredients are efficacious at levels >1%, if a product promotes an ingredient, a user may be well served by ensuring that the promoted ingredient is listed before these ingredients on the INCI. While this is a general rule, there are exceptions such as retinol, which is typically formulated at around 0.1%.

Common Ingredients: Benefits and Issues

In a standard moisturizer, one can find several classes of ingredients: moisturizing ingredients, emulsifiers, polymer/thickeners, sensory modifiers, and preservatives. In addition to these ingredients, there are often advanced benefit ingredients as well, such as anti-oxidants, vitamins, lipids, or sunscreens. In the sections below, we elaborate on these ingredients with details on usage levels and conditions required for efficacy and watch-outs.

FIGURE 2. Chemical structure of glycerin (or glycerol).



Moisturizing Ingredients

There are three key classes of moisturizing ingredients: humectants, occlusive, and emollients.

Humectants are hygroscopic conditioning agents containing multiple hydroxy (-OH) functionalities (Figure 2). By their chemical nature, they attract and bind water. They are water soluble, which means that while they are key moisturizing ingredients in leave-on formats, they are not easily retained on the skin from wash off products like cleansers. The most common humectant is glycerin.

Glycerin can be found in most moisturizers – whether face or body, lotion, or cream. The level ranges generally from 1% to 25% or more with the maximum improvement in hydration seen between 20% to 40% depending on the chassis.[7,8] Beyond hydrating the skin surface, glycerin has been proven to aid in barrier recovery including the stratum corneum integrity, cohesion (UL), and mechanical properties.[7] Glycerin has also been shown to enhance desmosomal degradation.[9]

Occlusive ingredients in skin care products help regulate water in the stratum corneum by preventing excessive water loss from the surface of the skin to sustain a moisturized environment. They are by nature not 100% occlusive but allow for the transfer of water that is necessary for normal skin function.[10] A consequence of this increased water content is that it accelerates barrier recovery.[10] Most occlusives do not contain hydroxy functionalities in their chemical structure, so they cannot bind water. However, since they form uniform hydrophobic films, they effectively seal moisture into skin.

The most common occlusive is petrolatum or petroleum jelly. Petrolatum is a highly refined blend of short and long-chain alkanes (Figure 3), microcrystalline wax, and mineral oils, and is a semi-solid at RT. When rubbed onto skin, petrolatum liquifies and penetrates the stratum corneum where it re-crystallizes forming a strong *interstitial* occlusive system (*not as superficial* as is commonly thought), substantially decreasing transepidermal water loss.[10] At the same time, according to our testing on Vaseline jelly, petrolatum is non-comedogenic. Other occlusives include high molecular weight mineral oils and dimethicones (Figure 4).

Emollients are materials such as oils and lipids that are water insoluble but do not form an occlusive film. In some cases,

the difference between an emollient and an occlusive is the molecular weight of the material. Examples of this are low molecular weight hydrocarbons and dimethicones that spread and absorb easily. They are often used for their ability to soften and smooth skin and impart a silky skin feel. Other classes of emollients include fatty alcohols and triglycerides, which are a key source of fatty acids for the skin. Examples of these include cetyl or cetearyl alcohol, cetylcaprylic/capric triglyceride, or oils such as grapeseed, soybean, or sunflower seed oil (Figure 5). Sunflower seed oil (SSO) is a triglyceride precursor to alpha-linoleic acid, an essential fatty acid that is incorporated into stratum corneum ceramides. The type and level of emollient is determined by the consumer needs – the relevant benefit and the clinical need as well as the desired sensory.

The efficacy of a basic moisturizer is determined by the levels of humectants, occlusive, and emollients. A good moisturizer needs a balance of the three. High humectant lotions restore moisture levels to skin but cannot immediately decrease trans-epidermal water loss. High emollient or occlusive creams can immediately reduce TEWL but it takes some time for the skin hydration levels to be restored. It should, therefore, not be assumed that a cream containing high levels of occlusives or emollients is automatically more efficacious. A combination of these ingredients at adequate amounts is necessary to replenish moisture and maintain it creating an environment where the skin barrier can be repaired. This combination can be designed in a cream or a lotion since the thickness can be manipulated independent of efficacy. A final point to be made is that glycerin, petroleum jelly, and dimethicone are amongst the most commonly used, safest, and most beneficial ingredients for the skin.

Emulsifiers and Polymers

Moisturizers are usually emulsions or kinetically stabilized colloidal suspensions of two immiscible liquids meaning there is no appreciable phase separation and the in-use experience remains consistent over the product's usable lifetime. Emulsions require the use of emulsifiers for stability. Emulsifiers can range from simple monomeric surfactants to much larger polymeric surfactants, particles, and lamellar liquid crystal aggregates.

An interesting property of emulsifiers is that they usually have long carbon chains like skin lipids, which makes it possible for an emulsifier to also impart skin benefits. In fact, the closer the chemistry of the emulsifier is to skin lipids, the more skin benefit can be imparted. Long chain emulsifiers, identified on an ingredient label as "palmitic" or "cetyl" (16 carbons or C16), "stearic" or "stearyl" (C18), and "behenic" or "behenyl" (C22), are compatible with and beneficial to skin, help maintain emulsion stability, and are not irritating. Stearic acid, a fatty acid with a C18 chain and carboxylic acid head group, is a good example of an emulsifier with skin benefits that Unilever uses extensively. Fatty acids are an integral component of the lipid matrix, and topically applied stearic acid has been demonstrated to incorporate into the lipid matrix improving the quality of the stratum corneum.[11, 12]

Another class of materials used to improve the stability, impact thickness and texture, and modify sensory feel of moisturizers is polymers. These could include synthetic polyacrylate type polymers or natural ones like starch (a polysaccharide based polymer). The feel and look of emulsions changes dramatically depending upon the polymer and emulsifier used. For example, culinary enthusiasts are aware that using a starch versus gelatin results in radically different textures. Similarly, in cosmetics, availability of novel polymers and emulsifiers have provided the formulator with a unique ability to modulate the feel and texture of moisturizers independent of its efficacy.

FIGURE 3. Chemical structure of a simple alkane chain. Higher alkanes, with 9 carbons or more, such as nonane shown here, are the basis of mineral oil.

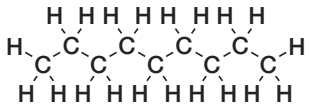


FIGURE 4. Chemical structure of a simple dimethicone showing the siloxane (-SiO-) backbone.

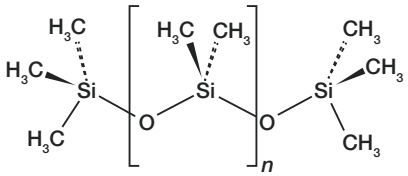


FIGURE 5. Chemical structure of an example triglyceride with 3 carbon chains attached to a glycerin backbone.

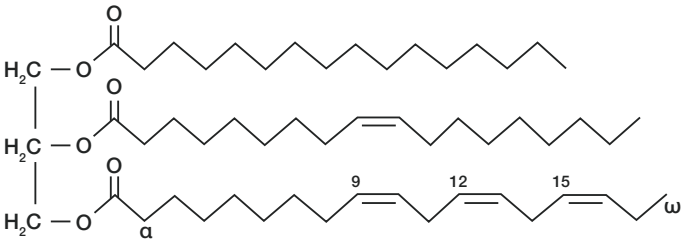


FIGURE 6. Chemical structure of stearic acid.

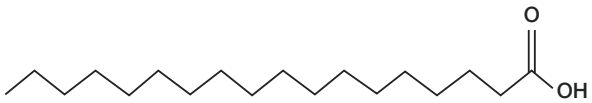
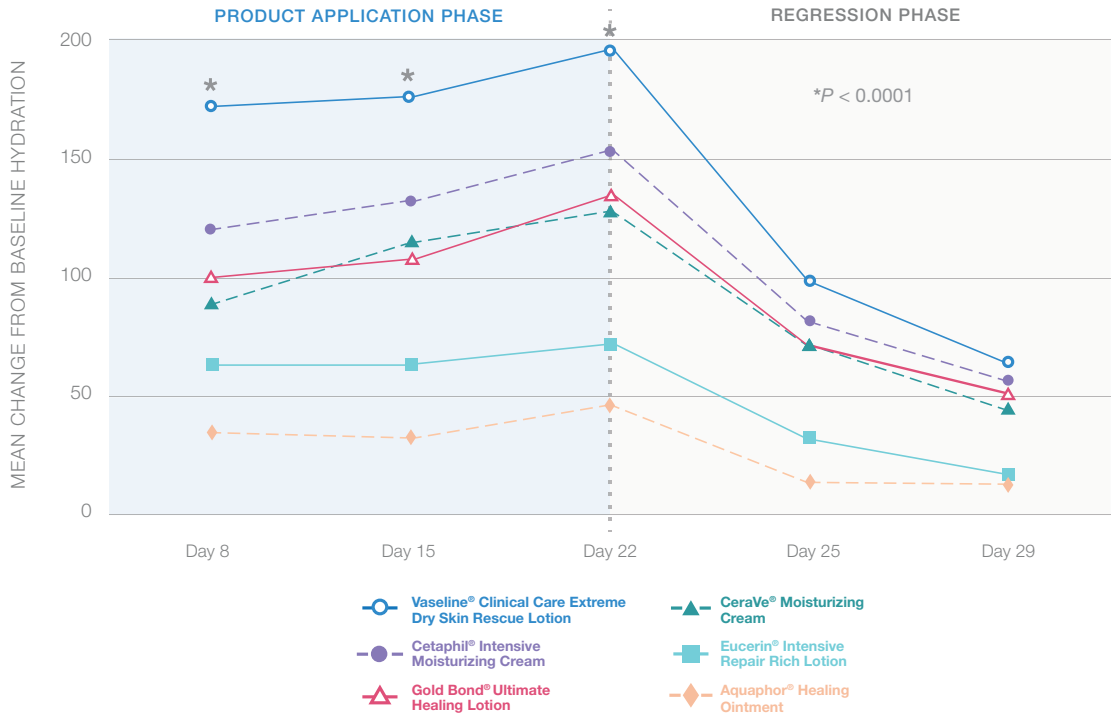


FIGURE 7. Comparison of moisturization between marketed "therapeutic" creams and lotions (SKICON hydration scores, CFB; 2016).



Moisturization Efficacy: Cream or Lotion?

It is a widely held belief that creams are more moisturizing than lotions, and hence more effective in treating dry skin, for example. While this may have been true when such consumer products first appeared in the market, this is not the case anymore. Today, the difference between creams and lotions is largely related to the types of moisturizers and the consumer sensory expectations. Creams tend to be thicker; however, this can be easily modified by using the right combinations of polymers and emulsifiers. Creams can contain more oils than lotions as in the case of emollient creams, and lotions can contain more humectants, for example, Vaseline™ Intensive Care Deep Moisture Jelly Cream and Vaseline™ Intensive Care Advanced Repair Unscented (See Figure 1 above), respectively. However, this is not always the case. In determining moisturization efficacy, the total level and combination of moisturizers in the product is the most important factor. This is clearly demonstrated in Figure 7, where hydration scores from a 3-week moisturization efficacy study with a 2-week regression phase were compared across different marketed cosmetic therapeutic creams (represented by dashed lines) and lotions (represented by solid lines). There was no direct relationship found between the format and efficacy, in fact, the most efficacious product in the study was a lotion. The entirety of the formulation is responsible for the product efficacy, but this data does suggest that glycerin and total moisturizer levels is a better indicator of performance than product format.

If there is no clear relationship between product format and efficacy, how does one select the right product? There are multiple considerations. First, it should be ensured that the product contains the right moisturizer combinations and levels (per INCI understanding as described earlier in this article) to address the patient's moisturization needs. Second, functional ingredients to address a patient's secondary skin concerns should be considered and, based on personal experiences, specific ingredients that are not suitable for their skin or have caused issues or reactions in the past such as fragrances, should be avoided. Several key functional ingredients are described in more detail below. Finally, consumers should choose a product that meets their personal sensory preference and price tolerance so they can easily incorporate the product into their daily routine as using a product every day is a key factor to full realization of efficacy.

Functional Ingredients

In addition to the core skin lotion and cream ingredients described in the sections above, it is common to include one or more bioactive ingredients that target specific pathways in the stratum corneum and underlying epidermis.

Niacinamide (Vitamin B3)

Niacinamide (Figure 8) is the physiologically active form of vitamin B3. This water-soluble vitamin has a variety of dermato-

logical therapeutic benefits and is often included in many good moisturizers.

Niacinamide stimulates ceramide synthesis,[13] reduces hyperpigmentation,[14,15] provides anti-inflammatory and anti-bacterial benefits,[16] and contributes to anti-aging benefits like appearance of facial fine lines and wrinkles as proven at the concentrations used in the products (roughly 3%). One potential side effect of products containing niacinamide is flushing, particularly in consumers of Asian descent. The culprit ingredient is niacin, which is another form of vitamin B3 and can occur as a contaminant if the quality of the raw material is not properly controlled. Manufacturers of quality topical products know to screen raw materials for this contaminant.

Alpha Hydroxy Acid (AHA)

Alpha hydroxy acids (AHAs) are a class of organic carboxylic compounds including naturally-derived glycolic acid, lactic acid, malic acid, citric acid, and tartaric acid (Figure 9).[17] AHAs have been used at various concentrations to enhance desmosomes resolution and stimulate desquamation, with positive benefits for the epidermis and dermis.[18,19,20] At lower concentrations (5-10%), AHAs are available in over-the-counter products that can be used daily for improved barrier function and to improve the appearance of skin related to sun-damage, wrinkling, and hyperpigmentation benefits. At higher concentrations (20-70%), AHAs are used as chemical peels by dermatologists, beauty, and health spas.[18]

PPARs

Peroxisome proliferator-activated receptors (PPARs) are well recognized for their effects on skin barrier development and maintenance,[21,22] and on increasing keratinocyte differentiation.[23,24,25] They enhance the production of barrier important lipids such as ceramides and fatty acids,[26,27] and increase epidermal thickness and filaggrin synthesis leading to anti-aging benefits such as reduction in appearance of overall photodamage, mottled hyperpigmentation, and fine lines and wrinkles.[28,29]

PPAR ligands are often naturally occurring unsaturated fatty acids such as conjugated linoleic acid (CLA). Such compounds are unstable, rapidly oxidize when exposed to air, and lose efficacy. Hence, historically, PPAR ligands have required the use of airless pack for stability leading to a higher cost product. In 2015, Unilever successfully introduced 12-hydroxy stearic acid (12-HSA) as a stable, gentle, and inexpensive PPAR ligand for the mass market (Figure 10). 12-HSA contains no unsaturated bonds obviating the need for high cost, airless packaging.

Vitamins C and E

The skin barrier is altered when exposed to external oxidative stresses such as UV irradiation and pollution.[30] Vitamin C (ascorbic acid) and E (α-tocopherol) are two of the most important antioxidants to protect skin from these external oxidative stresses. Although these are powerful ingredients, vitamins C and E are extremely unstable upon exposure to air. More stable forms of these vitamins like magnesium ascorbyl phosphate and vitamin E acetate are available; however, these need to be absorbed and converted into the active form within the skin. It is important to recognize that not all vitamin C and E formulas have similar physiological activities active.

Hyaluronic Acid (HA), a disaccharide polymer (Figure 11), is an integral component of the extracellular matrix where it plays

FIGURE 8. Structure of niacinamide.

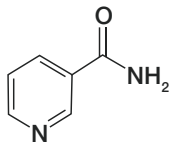
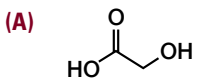


FIGURE 9. Example AHA structures. **(A)** glycolic and **(B)** lactic acids.



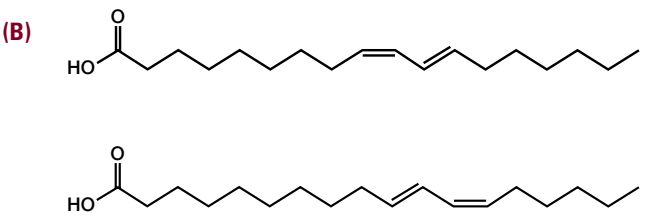


FIGURE 10. Structures of **(A)** 12HSA and **(B)** CLA.

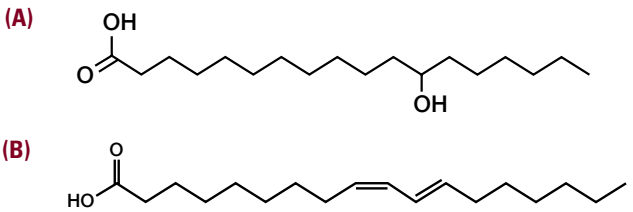


FIGURE 11. Chemical structure of hyaluronic acid.

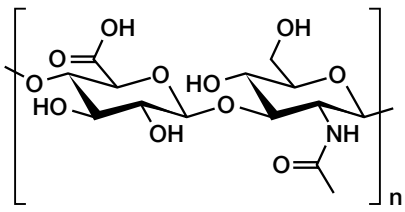
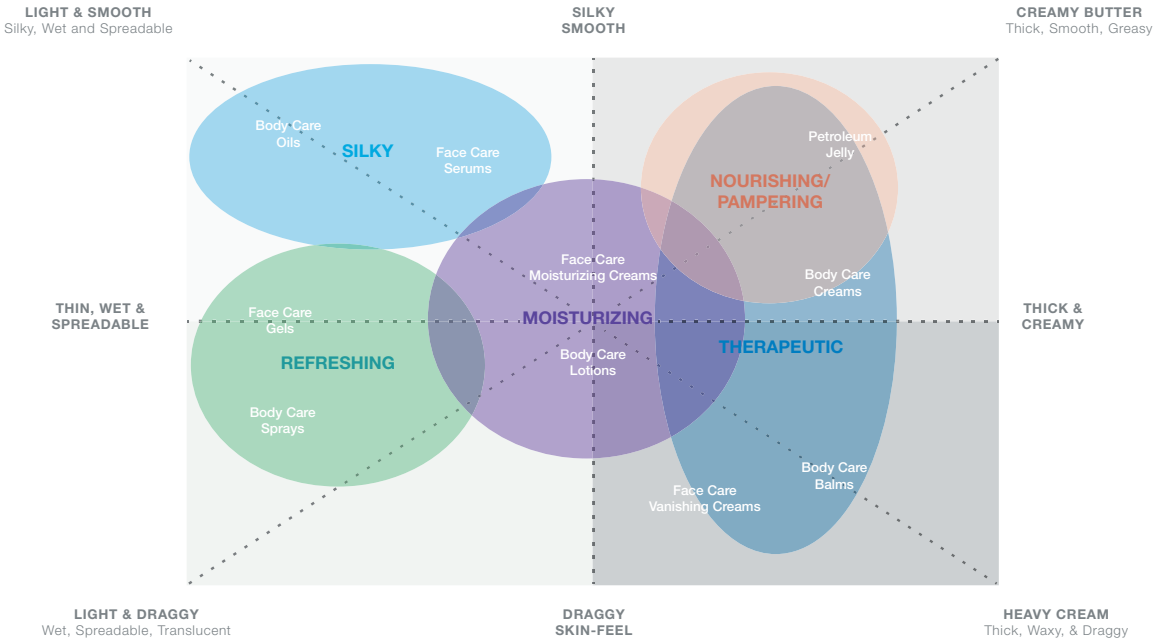


FIGURE 12. Generalized map of face and body moisturizer formats indicating typical sensory domains.



a key role in keratinocyte proliferation, migration, and wound repair. Because of the numerous -OH moieties, HA is exceptionally hygroscopic and is often touted as a wonder ingredient in skin-care products. However, due to its large molecular weight, topically dosed hyaluronic acid may not penetrate sufficiently into the skin for biological effects.

Product Sensories

Today, consumer experiences vary widely across moisturizing products. Also, most possible combinations of ingredients are available in almost any product format. In Figure 12, we have mapped different products and formats by their typical skin feel sensories as well as by the perceived consumer benefits associated with the different sensory domains.

Products in the center of this map are designed for normal dry skin and daily use. They are typically easy to apply, absorb quickly, and *feel* moisturizing. Formulations on the right side of the map are thicker, creamier products and are associated with consumer benefits such nourishing and pampering. Thicker, creamier aesthetics also suggest to the consumer that the products will provide more therapeutic benefits such as longer-lasting moisturization and efficacy for drier skin. These formulas generally use higher levels of solid based emulsifiers and polymers to achieve their thicker texture. High emollient creams fall here with thick, smooth textures and greasier after-feel. Because these aesthetics strongly suggest superior efficacy (whether clinically true or not), products for people with very dry skin and its associated symptoms tend to fall in this space in the sensory map.

Compositions spanning the left side are typically thinner, wetter, and spread more easily. These are often polymer-structured liquids with a lower level of liquid-based emulsifiers. The lower left quadrant is associated with refreshing and hydrating benefits and includes gel and spray formats. These are especially suited for hot, humid climates. On the other hand, most face care products tend to lie in the upper quadrants because they often contain silicones and silicone elastomers to impart a silky skin feel.

It is important to note that it is entirely possible to create any possible experience on this map by simply altering the type of emulsifiers, polymers, sensory modifiers, and emollients. Moisturizing ingredients and actives play a role in sensory, but not as overwhelmingly as is often believed.

CONCLUSION

This article is intended to describe the art and science of moisturizer product design and to start a conversation about long-standing beliefs about cosmetic products, specifically that some pre-conceived relationships between experience and efficacy and cost may not always be accurate. For example, it is erroneously assumed that creams are more efficacious than lotions. Clinical studies performed by Unilever and others using many creams and lotions have disproven this myth. In fact, cosmetic moisturizers covering a wide variety of formats can give the consumer their personally desired combination of efficacy and hedonics. Price is not often a guarantor of product efficacy and the best strategy is to examine the INCI, be armed with information, and seek expert advice.

DISCLOSURE

Christine Lee, John Bajor, Teanoosh Moaddel, Vivek Subramanian, Jian-Ming Lee, Diana Marrero, and Sheila Rocha are employees of Unilever R&D.

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