CURRENT CLINICAL SOLUTIONS

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New Insights in Gentle Cleansing:

Hydrophobically-Modified Polymers Demonstrate Improved Mildness and Skin Barrier Integrity

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Qualities of Cleansers

While soap has been known to exist as far back as 2500 B.C., it was not until the second century that it is known to have been used as a body surface cleanser.[1] Since the process of saponification was a tightly guarded secret until the 1770s, the use of soap as a cleanser was limited. After the process became well known, the entire soap industry experienced rapid growth.[1] By the 1950s, new technologies for body cleansing such as synthetic detergents (syndets) were appearing which sought to remove soil and oil from the skin without the dryness and irritation typical for traditional soaps.[2] Today, there are a variety of cleanser technologies each with their own advantages and disadvantages.

One thing all of these cleansers have in common is their method of action: the use of surfactant (i.e., surface-acting-agent) molecules with both hydrophilic and hydrophobic moieties. The amphiphilic behavior of these molecules cause them to aggregate in water and form into micelles once the surfactant concentration has reached a certain concentration known as the critical micelle concentration. These micelles aid in the uplifting of soils and solubilization of oils, allowing them to be washed away while also assisting in the natural process of exfoliation of skin cells, promoting skin health.[2,3] However, surfactants also interact with proteins and lipids of the stratum corneum (SC), which can result in common side-effects of cleansers, namely barrier damage, dryness, erythema, irritation, itching and skin tightness.[3,4]

In the past, it has been assumed that once surfactants self-assemble into micelles, the resulting micellar species are too large to penetrate into the SC. However, the dose-dependent irritation response that is usually observed when surfactants are applied to skin as a function of increasing concentration suggests this is not the case. The concept of micelle penetration attempts to explain this inconsistency by suggesting that both monomeric and micellar surfactant species can contribute to irritation, thus accounting for the dose-dependent irritation response observed for many surfactant systems.[5-7]

Cleanser surfactants interact with the stratum corneum in a variety to ways, some of which are the cause of irritation to the skin. When surfactants bind to SC proteins, transient swelling and hyper-hydration occurs resulting in damage due to drying stress as water evaporates and biochemical damage as the swelling facilitates deep penetration of surfactants into the skin. Also, surfactant binding can cause a lowering of skin protein's ability to bind and hold water, resulting in a lower skin hydration following a wash.[3,8] Meanwhile, interactions of surfactant micelles with skin lipids can also adversely affect skin health because of solubilization of lipids within these micelles and SC de-lipidation.[3] In addition, lipid damage is caused by absorption and intercalation of surfactants into the SC lipid bilayers, resulting in increased permeability and destabilization of the skin.[9,10] Finally, cleanser pH also plays a role in the damage caused to the SC. Most soap-based cleansers are alkaline in nature, and these alkaline cleansers have a higher potential to irritate the skin.[11-12] This is believed to be due to the fact that SC swelling and lipid rigidity is a function of skin pH.[13] In addition, it has been demonstrated that sustained pH increases can adversely affect the skin's barrier repair mechanism.[14]

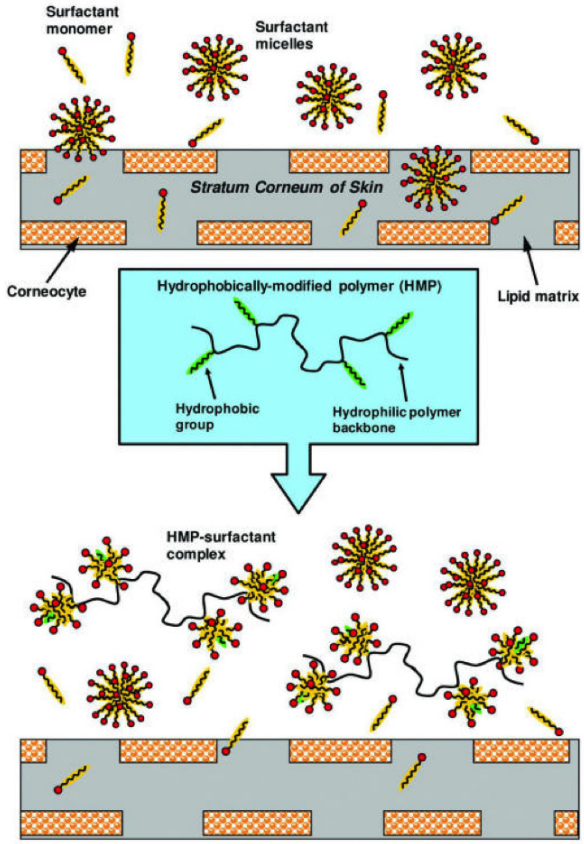
All of these contributors to skin damage become even more pronounced when a person has compromised skin. Atopic dermatitis (AD) can be worsened by a loss of intracellular lipids due to solvent removal (typically by cleansers), resulting in a red and scaly appearance. Exposure of dermal nerve endings result in itching, burning and pain for subjects with this condition.[15] Facial rosacea is also associated with an overly permeable skin barrier that can allow irritants to reach the viable parts of the epidermis and dermis, causing vasodilation and inflammation. As a result, subjects with facial rosacea can appear flushed and have a lower tolerance to many skin care products and cosmetics. [15]

Because of the damage that traditional cleansers can cause to the skin, researchers are constantly attempting to find less irritating cleanser technologies that remain effective at removing soil and oils from the skin. To this end, hydrophobically-modified polymers (HMPs) have been developed as an advanced technology for reducing damage associated with cleanser use by binding to micelles species formed by traditional surfactant cleansers and halting their penetration into the skin and minimizing their interaction with skin molecules.

Qualities of Cleansers with Hydrophobically-Modified Polymers (HMPs)

Due to micelles contributing to irritation, methods designed to limit micelle penetration have emerged as a new approach in mild cleanser formulation. One such method involves the use of water-soluble polymers to bind surfactants via polymer-surfactant association, creating polymer-surfactant complexes that are too large to penetrate into healthy living tissue and lowering the concentration of free micelles in solution (Figure 1).

FIGURE 1. Schematic representation of polymer-surfactant association using HMPs to reduce micelle penetration.



The efficacy of surfactant binding is determined by both polymer and surfactant chemistry, with the electrostatically charged anions and cations and the hydrophobic areas of each species being the most critical variables. The binding affinity of a polymer for a given surfactant may be enhanced by including functionalities that promote surfactant association, such as hydrophobic domains, oppositely-charged ionic groups, or dipolar moieties. HMPs are hydrophilic, water-soluble polymers that contain hydrophobic moieties (Figure 1). These polymers are particularly efficient at binding surfactants due to the strong propensity for aggregation of hydrophobic surfactant tail groups with the hydrophobic domains of the HMP. In some cases, the hydrophobic interactions driving HMP-surfactant association are so prevalent that charged HMPs will efficiently bind surfactants of like charge, despite the repulsive electrostatic interactions.

In order to demonstrate the benefits of HMPs in preventing surfactant penetration into the skin and maintaining skin barrier integrity, both in vitro and in vivo tests were carried out. In one study, porcine skin samples were exposed to either a facial cleanser formula incorporating HMP or a commercially available benchmark cleanser (both foaming and non-foaming varieties). After the treatment, a lipophilic fluorescent dye (Nile Red, NR) was applied to the skin, which would penetrate deeply into a damaged skin barrier. Two-photon fluorescence microscopy (TPM) was used to visualize the morphology of the skin barrier, and the benefits provided by HMP technology could be seen directly. Figure 2 shows several of these 2-photon fluorescent microscopy images of skin. Figure 2a shows an image of skin treated with a buffer solution while Figure 2b shows skin treated with 1% sodium lauryl sulfate solution (SLS) as a negative control. While there is limited NR penetration into the normal, intact skin, NR penetrates deep into the skin treated with the negative control, indicating severe barrier damage. Figures 2c, d and e depict skin

FIGURE 2. 2-photon fluorescent microscopy images of skin samples depicting (a) control skin and (b) skin treated with SLS, demonstrating the low amount of NR that penetrates healthy skin (a), while a damaged skin barrier results in a much higher amount of NR diffusion, shown by the much greater intensity. Skin treated with a foaming benchmark cleanser, a non-foaming benchmark cleanser and a cleanser containing HMP are shown in (c), (d) and (e), respectively. Of the three, (e) the cleanser with HMP depicts the lowest NR intensity and, thus, the least skin barrier damage.

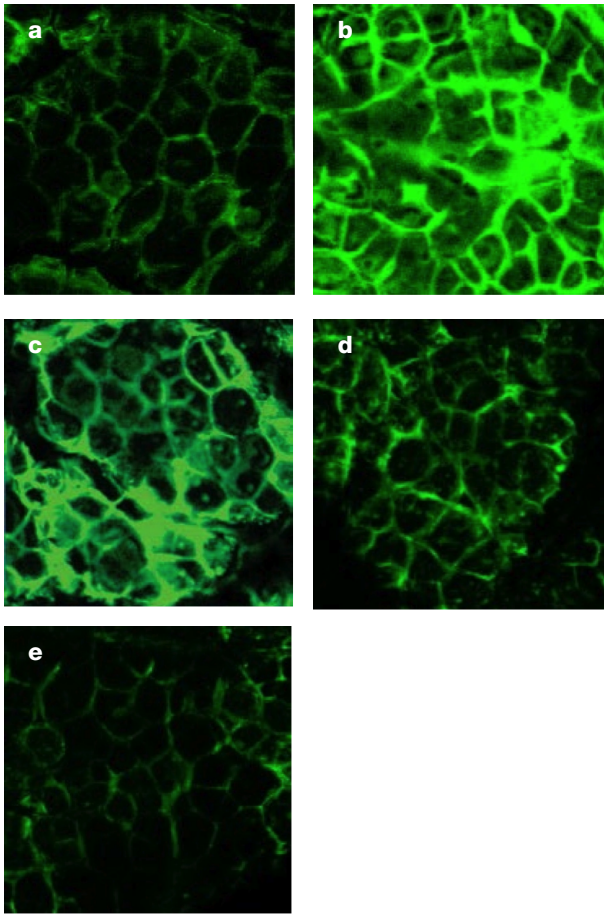
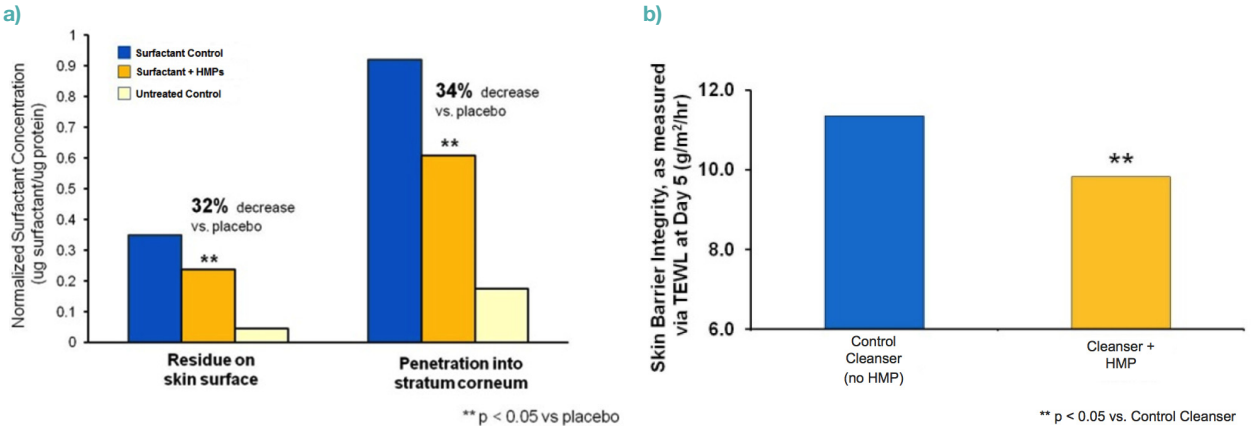


FIGURE 3. (a) Normalized Surfactant Concentration measured from ten consecutive tape stripes taken from subjects after a 4-hour exposure of diluted cleaning solutions. (b) Transepidermal water loss (TEWL) was used to evaluate skin barrier integrity between subjects treated with a placebo cleanser and a cleanser using HMPs.



samples treated with a commercial foaming benchmark cleanser (c), a commercial non-foaming benchmark cleanser (d) and the facial cleanser with HMP (e). As can be seen, the cleanser incorporating HMP prevented changes in SC permeability, indicating a protective effect on the barrier properties of the skin.

In a separate study which combined in vitro and in vivo models, surfactant penetration into the stratum corneum was measured on human adult subjects (n=10) after a 4-hour exposure of diluted cleansing solutions (a surfactant control, a surfactant with HMP and an untreated control) under an occlusive patch. The patches were removed and ten consecutive tape strips were taken from each subject; levels of surfactant and total protein were measured via colorimetric detection of each tape. Meanwhile, in vitro studies were conducted utilizing a skin equivalent model (EpiDermTM from MatTek Corporation (Ashland, MA, USA), measuring the release of pro-inflammatory mediator IL-1α after exposure to 10% diluted cleansing systems. Also, a patch-testing model of human adult subjects with clinically diagnosed atopy (n=25) was utilized to evaluate the effect of diluted cleansing systems on skin barrier integrity. Subjects were exposed to four consecutive 24-hour patches on the volar forearm. Skin condition, including skin barrier integrity—as measured via transepidermal water loss (TEWL)—was evaluated at baseline and Day 5. Figure 3 demonstrates the results of these procedures.

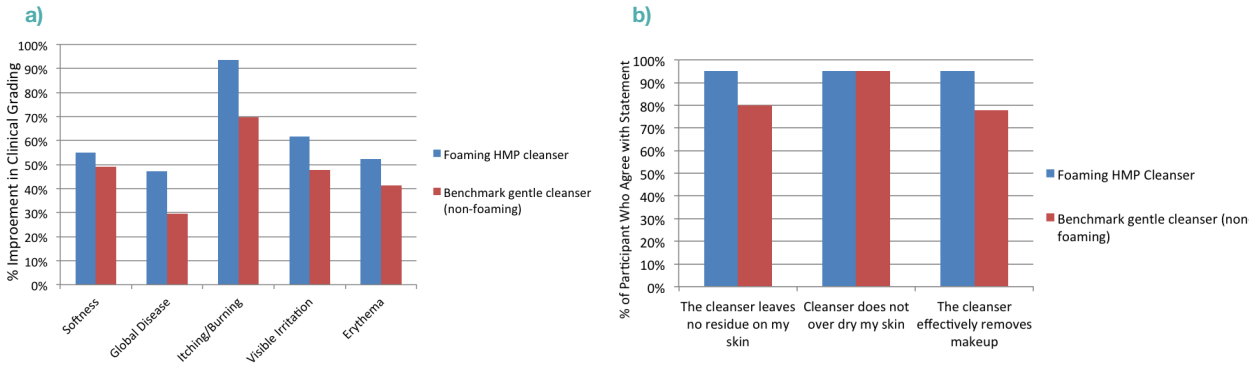
Total levels of both surfactant and proteins were measured from ten subjects, and these figures were used to determine the Normalized Surfactant Concentration. Figure 3a demonstrates how incorporating HMPs into the surfactant system results in decreased levels of surfactant penetration into the stratum corneum ($p<0.05$ vs. placebo), which is highly correlated to the amount of polymer-surfactant complexes within the system.[16] In Figure 3b, a significant improvement ($p<0.05$ vs. placebo) in skin barrier integrity (as measured via TEWL) for the HMP containing cleanser, was observed after 4 consecutive 24-hour patch exposures to a diluted cleanser solution.[16] Furthermore, it was also found that there is a significant improvement ($p<0.05$) in cleanser irritation potential as measured via release of IL-1α, with a 43% reduction in skin irritation potential, as compared to placebo (data not shown).[16] All these results support that a cleanser formulation containing HMPs result in less surfactant penetration, less cleanser irritation potential and greater skin barrier integrity.

In addition to providing the benefit of enhanced mildness, HMPs can also improve the lathering and foam quality of cleansing products, improving patient perception of the products. The idea that a surfactant-binding HMP will improve foaming may seem counter-intuitive, since polymer-surfactant association would seemingly decrease the availability of free surfactant for foam generation. However, both HMPs and HMP-surfactant complexes exhibit the ability to stabilize newly formed air-water interfaces, and are also capable of increasing the thickness and viscosity of foam. As a consequence of these qualities, thicker, denser, longer-lasting foams can be generated by surfactant-based cleansers that incorporate HMPs.

Use of HMPs to Reduce Irritation Associated with use of Surfactant-Based Cleansers

Having established that HMPs show promise in reducing the skin damage that is commonly associated with cleansing products, a clinical study was initiated to demonstrate the efficacy of a surfactant-based

FIGURE 4. In the clinical assessment of the facial cleansers done at three weeks, the foaming HMP cleanser displayed significant improvement for several of the hallmark signs of sensitive skin (a). Also after three weeks of use, subjective assessment after using the HMP-based facial cleansers showed a high level of agreement with statements about cleansing efficacy. (b)



cleanser with HMP both in its ability to remove soil and oils as well as its gentleness to the skin. To this end a three-week double blinded study was done that compared a foaming facial cleanser featuring the HMP against a commercially available, non-foaming benchmark gentle cleanser with each patient being randomly assigned one cleanser to use.[17] To ensure adequate sensitivity, all patients used for this study were previously diagnosed with mild-to-moderate eczema, rosacea, atopic dermatitis or active acne. Skin attributes evaluated by a dermatological investigator during this study included cleanser induced itching/burning, visible irritation and erythema. Meanwhile, patients self-assessed the cleaner effects including ability to remove make-up and presence or absence of residue. Investigator and patients assessments were captured using an ordinal 5-point scale.

As can been seen in the following figure, the HMP facial cleanser formulation provided exceptional tolerability among the clinically diagnosed sensitive skin patients (Figure 4a). They were shown to provide strong cleansing efficacy, even effectively removing make-up, while rinsing away completely (Figure 4b). Also, the HMP facial cleanser provided significant improvement in skin condition according to the patients' self-assessment.[17]

The results of this clinical study showed that HMP-based gentle cleansers were very well tolerated by this challenging sensitive-skin population, with no safety-related adverse effects noted. HMP technology offers a new cleansing option capable of superior hygiene, without inducing barrier compromise due to its ability to effectively manage the concentration of free micelles that can potentially penetrate the skin and cause skin irritation. The principle benefits of HMP technology for irritation mitigation are two-fold. First, HMPs enable previously unattainable levels of mildness in facial cleansing products for improved health and beauty. Second, HMPs allow for the use of higher cleanser concentrations for increased foam performance without concomitant increase in irritation potential. These qualities are particularly important to patients with sensitive skin due to dermatologic diseases. These patients require cleansers that are particularly gentle yet still effective at removing excess sebum from the skin. HMP cleansing technology provided dermatologists with a new level of mildness and efficacy for their patients with sensitive skin.

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