

Krafft Temperature of Surfactants in Vehicles for Roflumilast and Pimecrolimus Cream and Effects on Skin Tolerability

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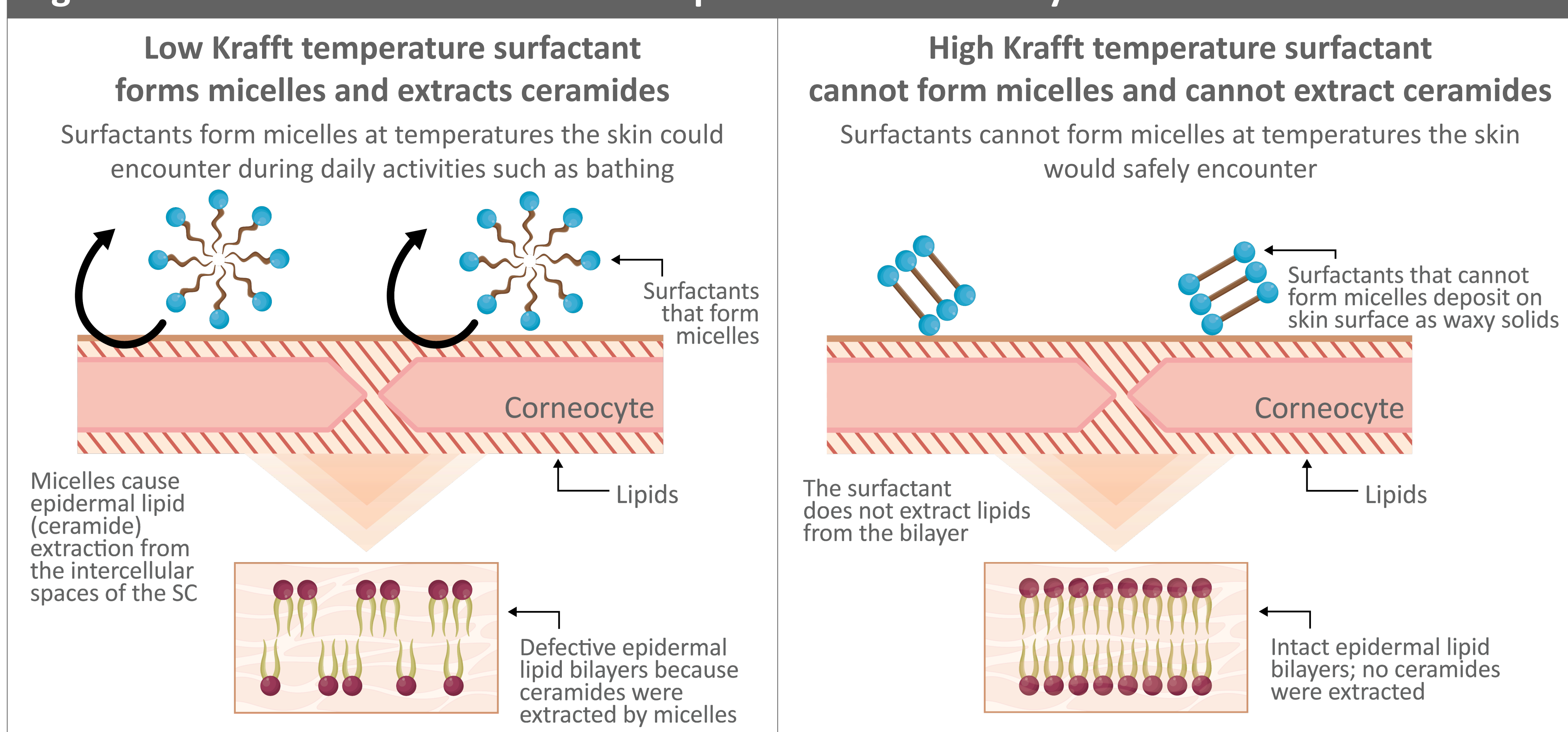
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INTRODUCTION

- Creams, foams, and lotions are typically applied delivery forms that, to date, have used surfactants (specifically emulsifiers) to reduce surface tension and manufacture a physically stable moisturizing vehicle
- The minimum temperature required for an anionic emulsifier to form micelles, which can cause lipid extraction from skin and result in irritation, is known as the Krafft temperature (T_K)
 - A cream, foam, or lotion formulated with emulsifiers having a T_K above safe water temperatures ($\sim 50^\circ\text{C}$) cannot irritate skin resulting from epidermal lipid extraction by those emulsifiers
 - Knowing normal human skin surface temperature is 32°C and the maximum safe bathing water temperature is 48°C , the principles of T_K can be used in formulations of topical therapies¹
- The ability of surfactants to solubilize lipids in the skin stratum corneum (SC) and cause irritation is important in the formulation of topical treatments (Figure 1)
 - Skin barrier protection is particularly important in patients with atopic dermatitis (AD) because decreased ceramides in the SC have been linked to an increase in disease severity²

Figure 1. Effect of Surfactant Krafft Temperature on Corneocytes



SC: stratum corneum.

- Roflumilast is a selective and highly potent phosphodiesterase-4 (PDE-4) inhibitor with greater affinity for PDE-4 than apremilast or crisaborole and approximately 25- to >300-fold more potent based on in vitro assays³
 - Topical roflumilast is being investigated in cream and foam formulations as a once-daily, nonsteroidal treatment for various dermatologic conditions, including AD, seborrheic dermatitis, and scalp and body psoriasis
 - In a phase 2, proof-of-concept, randomized clinical trial for topical roflumilast in patients with AD, 45 patients who applied the vehicle cream once daily for 4 weeks had a 55.8% reduction (improvement) in Eczema Area and Severity Index (EASI) score compared with baseline⁴
 - On investigator-rated local tolerability, more than 97% of patients in each group had no signs of irritation at Weeks 1, 2, or 4
 - One patient (2.2%) in the roflumilast 0.5% group and 1 (2.2%) in the vehicle group reported an application-site adverse event during the trial
 - In contrast, in a randomized trial of pimecrolimus cream (which is approved for the treatment of AD), children with AD treated once daily with the vehicle for pimecrolimus cream for 4 weeks experienced a 1% increase (worsening) in EASI^{5,6}
 - In this study, 10.4% of patients receiving pimecrolimus cream 1% and 12.5% of patients receiving vehicle reported a transient and mostly mild-to-moderate severity burning sensation when the cream was applied⁵
 - Since both the roflumilast cream vehicle and the pimecrolimus cream vehicle contain anionic emulsifiers with cetyl (C16) and stearyl (C18) alkyl chain lengths, it was hypothesized that the differences in tolerability between the roflumilast and pimecrolimus vehicles may be because of differences in T_K between the vehicles for these creams
- This poster presents results of a study to determine T_K of the 2 primary surfactants used in the vehicle for roflumilast cream (dicetyl phosphate, ceteth-10 phosphate) and pimecrolimus cream (sodium cetostearyl sulfate)

METHODS

- Dicetyl phosphate, ceteth-10 phosphate, and commercial grade sodium cetostearyl sulfate 0.0012% (wt/wt) solutions (near but not below the critical micellization concentration of the alkyl phosphate emulsifiers) were mixed in 20-mL glass scintillation vials
- Each vial was placed into a water bath and the temperature was increased by $1\text{--}2^\circ\text{C}$ until the solid emulsifier completely dissolved and foam was visible after shaking
- The T_K was fine-tuned by returning the samples to ambient condition, observing precipitation of the solid emulsifier, placing them in a water bath just below the previously observed T_K , and increasing temperature by 0.5°C increments
 - Each sample was equilibrated at each temperature for at least 2 hours

RESULTS AND DISCUSSION

- At the T_K listed in Table 1, the readily visualized surfactant particles dissolved and the samples foamed
- Since the surfactants used in the vehicle cream for roflumilast have T_K values (53°C and 58°C) above the maximum safe bathing water temperature (48°C),¹ these surfactants cannot extract epidermal lipids from the SC. The T_K for the surfactant used in the vehicle cream for pimecrolimus is below the maximum safe water temperature, so the surfactant may be able to extract epidermal lipids when skin is exposed to water $>40^\circ\text{C}$

Table 1. Krafft Temperatures of the Surfactants in the Vehicles for Roflumilast and Pimecrolimus Creams

Anionic Surfactant in Water (No pH Adjustment)	Approximate CMC (%)	Krafft Temperature ($^\circ\text{C}$)
Roflumilast cream vehicle		
Dicetyl phosphate (0.017% wt/wt)	0.0012	58
Ceteth-10 phosphate (0.012% wt/wt)	0.0012	53
Pimecrolimus cream vehicle		
Sodium cetostearyl sulfate (0.014% wt/wt)	0.0056*	41

*Critical micellization concentration value for sodium n-octadecyl sulfate at 40°C was 0.16 mMolar = 0.0056% (wt/wt).⁷

CONCLUSIONS

- The surfactants evaluated in this study provide insight on the link between emulsifier T_K and potential skin environments that could promote epidermal lipid extraction
 - Specifically, the two particular anionic phosphate surfactants in the vehicle for roflumilast cream (which are also used in the vehicle for roflumilast foam) have T_K higher than the temperature range that human skin experiences during the activities of daily living
- Since its specific anionic emulsifiers cannot function as surfactants and form micelles below their T_K , it is impossible for the roflumilast cream (or roflumilast foam) vehicle to extract epidermal lipids from the SC
- Since skin will not safely encounter environmental temperatures above 50°C , a cream or lotion formulated with emulsifiers having $T_K >50^\circ\text{C}$ cannot form micelles, and therefore the roflumilast vehicle cannot irritate the skin due to epidermal lipid extraction no matter the skin environment

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DISCLOSURES

David Berk and David Osborne are employees of Arcutis Biotherapeutics, Inc. Additional disclosures may be provided on request.