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Skin Barrier Function: Effects of Moisturizers

Marie Lodén

ACO HUD AB, Upplands Väsby, Sweden

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Abstract

Moisturizing creams are used to increase skin hydration. Recent findings indicate that they also affect skin barrier function in both normal and dry skin. Not only humectants, but excipients such as lipids and emulsifiers will influence skin biochemistry and barrier function. Skin barrier function determines the susceptibility to irritants and allergens in the environment. The increased understanding of interactions between topically applied substances and the epidermal biochemistry will improve the formulation of skin care products. The present review pays attention to literature pertinent to skin barrier function and moisturizers.

Humectants, emulsifiers and commercially available moisturizers have been found to influence the barrier function in normal skin. In damaged skin, topically applied substances can both accelerate and retard normalization of the barrier function to water. Furthermore, skin susceptibility to irritants is influenced by certain moisturizers, which clearly indicates that ingredients are not as inert to the skin as previously considered. This opens up new possibilities to treat more efficiently various skin abnormalities and different body areas, and to understand various requirements among consumers. (See Figure 1.) A normalization of a defect barrier function has also been suggested to prevent persistent dermatitis by mitigation of the cytokine cascade, as shown in Figure 2.[1] The intent of this review is to present literature on moisturizers and how they can influence the skin barrier function in normal and in dry skin. The information will hopefully facilitate the development of new moisturizers tailored for different types of skin abnormalities.

Skin barrier function and dry skin

In normal skin, the epidermal permeability barrier resides in the stratum corneum (SC) and is mediated by lamellar bilayers enriched by cholesterol, free fatty acids and ceramides. The bulk of the bilamellar sheets of the lipids has been proposed to be in crystalline/gel domains bordered by lipids in a fluid crystalline state.[2] Changes in the lipid content and organization of the intercellular lipids influence the barrier function.[3-5] In dry skin and in skin exposed to organic solvents, the lipid composition and normal bilayer structure are changed.[6-11] Furthermore, cracks in the skin, resulting from a decreased softness and flexibility of the SC,[12-13] may abrogate the barrier function.

A shorter penetration pathway through the skin may also be obtained in dry skin due to a reduced projected size of the flattened corneocytes.[14-15] Clinically observed dryness of the SC may not necessarily implicate increased skin permeability, however. For example, if the dryness is confined to the outermost SC, and the major permeability barrier resides in the lower part of the SC, then

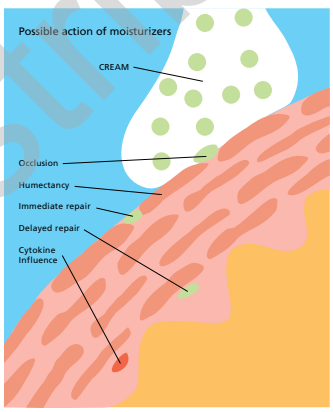

Figure 1. Possible mechanisms for the relief of skin dryness by moisturizing cream.

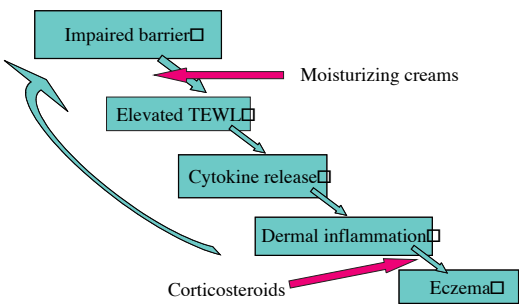

Figure 2. Topical treatments with moisturizers may prevent persistent dermatitis by reducing elevated transepidermal water loss (TEWL). Normalization of TEWL has been suggested to mitigate cytokine cascade (modified from ref 1; Elias et al. 1999).

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no correlation between these parameters could be expected.[16]

A disturbance of the epidermal barrier function induces a rapid response of the keratinocytes to restore cutaneous homeostasis. The mRNA coding for pro-inflammatory cytokines, adhesion molecules and growth factors is up-regulated.[17] Likewise there is an increase in DNA synthesis leading to epidermal hyperplasi, and in lipid synthesis. [6, 18, 19]

Methodology

In assessing the effects of moisturizers on skin barrier function, the effects on diseased skin need to be distinguished from those on normal skin, (i.e., for treatment or prevention). The skin composition and properties also vary among species and body areas, making extrapolations from one area to another complicated. The selection criteria used to accept subjects into the study and the suitability of the population for its objectives should be considered. If certain subjects are excluded from the study, the general applicability of the results should be discussed.

Furthermore, application procedures and the duration of the treatment period are important for the outcome, i.e., the onset and time-course of action. Is a single application enough or should the data be based upon long-term treatment? Presence or absence of washout periods and the use of other skin care products also need to be considered. Contamination and difficulties for the test subjects to comply with the treatment may also create difficulties in evaluating the results.

A common way to monitor changes in barrier function is to measure transepidermal water loss (TEWL). The level of TEWL has been suggested to serve as an indicator of the permeability of the skin to topically applied substances.[20, 21] However, whether changes in TEWL are predictive also for the permeability to substances other than water, probably depends on the mechanism for the change in TEWL. For example, TEWL may be reduced by absorption of certain substances from the moisturizer into the SC, but this may facilitate penetration of other exogenous substances through the skin.

Table 1. Substances that have been used to test the skin barrier function in vivo.

Substance	Biologic response
Surfactants	Irritation
Alkali resistance	Burning, itching, erythema
DMSO	Urticaria
Nicotinates	Vasodilatation
Toluene	Irritation

Another method to assess the barrier function is to expose the living skin to substances with biological activity and to measure the response, as shown in Table 1. However, it is necessary to perform long-term studies under real conditions to support the results from predictive testing using surrogate parameters.

Effects on normal skin

Not only moisturizers, but also protective creams (marketed as barrier creams or invisible gloves) are promoted to be used on non-diseased skin. Protective creams are expected to prevent harmful substances from entering the skin by forming an impermeable film on the surface. Such creams may also contain substances that trap or decompose the hazardous substance. Experimental studies also show that some creams can delay contact with certain substances, while others enhance the penetration of the hazardous substance.[22-28] Treatment can also reduce skin susceptibility to chemicals such as alkali, sodium laurylsulfate (SLS) and dimethylsulfoxide (DMSO), but increase absorption of hexyl nicotinate.[29] Hence, the benefit of using protective creams in the prevention of contact dermatitis in industry or in wet working occupations is controversial.[30] In a study on metal workers, the beneficial effect from protective cream-treatment was not confirmed, whereas an ordinary moisturizer decreased the prevalence of irritation.[31] Therefore, it has been suggested that moisturizers may prevent contact dermatitis to a similar degree as barrier creams but with the possible advantage of enhanced user acceptance.[27, 32]

Despite the widespread use of moisturizers, scant attention has been paid to their influence on the permeability barrier of normal skin. Application of lipids to the skin surface will reduce TEWL, due simply to the deposition of an occlusive lipid layer on the surface and not to any deeper barrier-improving effects. This lipid layer will increase the degree of SC hydration.[33] Low-molecular-weight humectants in moisturizers (e.g. urea and glycerin) will also penetrate into the SC[34,35] and increase the degree of hydration. The increased degree of hydration may well increase the perme-

ability, since increased hydration of normal skin is known to reduce its diffusional resistance.[36,37] In vitro experiments on SC also indicate that humectants increase TEWL [38,39] and certain humectants are known as keratolytics, for instance urea and alpha-hydroxy acids.[40] Certain emulsifiers have also been reported to increase TEWL.[41]

The use of moisturizers with urea has been questioned, with reference to the risk of reducing the chemical barrier function of the skin to toxic substances.[42] Urea is easily absorbed into the skin[34,35] but appears to have no influence on the lipid matrix of the murine SC.[43] Moreover, no changes in the binding forces within SC have been found after 6h occlusive exposure of human skin to 10% urea.[35] In vitro measurements on piglet SC suggest that urea markedly decreases TEWL (44). Some single-application studies show that urea may act as a penetration-enhancer,[45-49] but other studies do not support these results.[45,50,51] No influence on TEWL has been observed after a few applications of 5% and 10% urea moisturizers to normal skin,[52] whereas repeated applications (10-20 days) reduce TEWL.[52-54]

Another humectant, glycerin, has been suggested to influence the crystalline arrangement of the intercellular bilayer lipids,[55] but no change in TEWL was observed after 10 days treatment with 20% glycerin in a placebo-controlled study.[56] This is in accordance with a previous single-blind study on a cream containing 7% glycerin.[52] Also, in several other studies, TEWL was not increased by repeated application of moisturizers although the treatment appeared to significantly increase skin hydration.[33,57-59]

In vivo TEWL measurements have also been combined with evaluation of the skin response after exposure to a vasodilator (nicotinates) or to an irritant (SLS) to further elucidate changes in barrier function due to treatment with moisturizers.[30, 52, 53, 56, 60] Single exposure to sodium lactate, sodium pyrrolidone carboxylic acid and sorbitol show these to reduce the penetration of benzyl nicotinate.[61] Furthermore, an increased resistance to SLS-induced irritation has been found after treatment with Alpha-hydroxyacids.[60] No change in SLS-sensitivity has been found after repeated application of a moisturizer with 20% glycerin compared to its placebo.[56] However, increased skin susceptibility to irritation has been shown after treatment with a moisturizer without any humectant.[30]

Effects on impaired barrier function

Increased skin hydration will increase the elasticity of a dry and brittle SC, reducing the risks of cracking. However, increased hydration may also enhance the degradation of the desmosomes, facilitating the corneocyte loss from the skin surface. This reduces the degree of scaling, which is an important feature of skin dryness. Excessive hydration of the SC layer may also create interfacial defects in the lipid bilayer[62] and reduce its diffusional resistance.[37] Thus, an increase in TEWL may

reflect a decreased or an increased level of hydration.

Treatment of dry skin with moisturizers containing humectants, such as urea or glycerin, has been found to reduce TEWL in ichthyotic,[63,64] atopic,[65] dry[54] and irritated skin.[53, 66] Treatment with urea also seems superior to glycerin in lowering TEWL in dry skin of atopic patients.[67] Single application of glycerin to tape-stripped and acetone treated skin has been reported to decrease skin sensitivity to alkali, sodium lauryl sulphate (SLS) and dimethylsulfoxide, but to increase bioavailability of hexyl nicotinate.[29] However, a moisturizer without humectant[68] and another with ammonium lactate as humectant[69] had no effect on TEWL, despite clinical improvement. Furthermore, in a recent study it was found that a moisturizer with lactic acid and propylene glycol actually increased TEWL in ichthyotic skin.[70]

Traditionally, lipids have been incorporated into topical formulations on the basis of their technical and sensory properties rather than for their possible deeper effect on the epidermis. However, topically applied substances might reduce the mitotic activity and increase cell differentiation.[71] With a larger corneocyte area, the tortuous lipid pathway gives a longer distance for penetration, which reduces permeability.[14, 15]

Lipids may also penetrate the skin and affect its barrier properties.[7, 72-74] For instance, petrolatum is absorbed into the outer layer of delipidized SC.[73] Canola oil and an unsaponifiable enriched fraction gave similar effects as a hydrocortisone cream in SLS-damaged human skin.[75] Moreover, sunflower oil, rich in linoleic acid, has been found to reduce abnormally high rates of TEWL in sodium laurate-irritated rat skin[76] and borage-oil-normalized TEWL in infantile seborrheic dermatitis.[73]

In contrast to these findings, an inverse relationship was found between recovery of normal TEWL and the amount of sunflower seed oil in emulsions used for treatment of SLS-induced irritation in man.[74] Moreover, applications of individual ceramides, linoleic acid and a variety of other fatty acids delay barrier recovery in acetone-treated murine skin. Likewise, two-component mixtures of fatty acid plus ceramide, cholesterol plus fatty acid, or cholesterol plus ceramide delay barrier recovery.[8] The only treatments that allowed normal barrier recovery were applications of complete mixtures of ceramide, fatty acid and cholesterol, or pure cholesterol.[8]

In a recent double-blind human study, a physiological lipid mixture in petrolatum failed to show superiority compared to its placebo regarding normalization of detergent and tape-stripped skin.[77] One possible reason for the failure might be the content of oleic acid, which is known to act as a penetration enhancer in other emulsions. Other commercially available moisturizers have been found to reduce elevated TEWL-values in acetone-treated mice skin compared to untreated areas during a 24h test period.[78] Interestingly, not only lipids but also emulsifiers can reduce TEWL in surfactant irritated human skin.[41]

Discussion and conclusion

Dermatologists have always realized that moisturizers have a steroid-sparing effect and are important treatment adjuncts in inflammatory skin disorders, but the exact mechanism behind the beneficial effects in various disorders is not fully understood. (See Figure 1.) The findings that moisturizers can affect barrier homeostasis clearly illustrate that ingredients are not as inert to the skin as was previously considered. It is obvious that a reduction in TEWL may be due to a simple deposition of lipid material to the surface and not to any deeper effects in the skin. Another explanation is increased skin hydration, which increases SC elasticity and decreases the risks of cracks and fissures. Interference with the lipid layer around the corneocytes may also help to retain the moisture content in the corneocytes and prevent cracking of the SC. [6, 9, 73, 79]

Other mechanisms, such as anti-inflammatory actions, are also conceivable explanations for the benefits of moisturizers on the skin.[80] It is possible that the applied moisturizer decreases the proliferative activity of the epidermis, increasing the size of the corneocytes. Topically applied lipids may also penetrate deeper into the skin and interfere with the endogenous lipid synthesis, which may in turn change barrier recovery in damaged skin. [8] Furthermore, other substances in the creams may influence the composition of the SC lipids. Lactic acid, for example, has been found to stimulate the production of ceramides by keratinocytes in vitro.[81]

A number of different mechanisms behind the barrier-improving effects of moisturizers are summarized above. More efficient study designs such as using randomization and control treatment (placebo and/or reference product) will facilitate detection of the mechanisms and discrimination between formulations.

In conclusion, we can foresee an increased understanding of the interactions between topically applied substances and the epidermal biochemistry, which will improve the formulation of future skin care products (82). The use of new techniques will allow us to monitor treatment effects more closely, and we can expect new devices with the ability to non-invasively diagnose specific skin abnormalities.

References

Address correspondence to Marie Lodén, c/o Editor, *Cosmetics & Toiletries* magazine, 362 S. Schmale Road, Carol Stream IL 60188 USA.

1. PM Elias, LC Wood and KR Feingold, Epidermal pathogenesis of inflammatory dermatoses, *Am J Contact Derm*, 10 119-126 (1999)
2. B Forslind, A domain mosaic model of the skin barrier, *Acta Derm Venereol (Stockh)* 74 1-6 (1994)
3. PM Elias, Lipids and the epidermal permeability barrier, *Arch Dermatol Res* 270 95-117 (1981)
4. PM Elias, J Goerke and DS Friend, Mammalian epidermal barrier layer lipids: Composition and influence on structure, *J Invest Dermatol* 69: 535-546 (1977)
5. PM Elias, ER Cooper, A Korc and BE Brown, Percutaneous transport in relation to stratum corneum structure and lipid composition, *J Invest Dermatol* 76 297-301 (1981)
6. KR Feingold, M Mao-Qiang, GK Menon, SS Cho, BE Brown and PE Elias, Cholesterol synthesis is required for cutaneous barrier function in mice, *J Clin Invest* 86 1738-1745 (1990)
7. G Imokawa and M Hattori, A possible function of structural lipids in the water-holding properties of the stratum corneum, *J Invest Dermatol* 84 282-284 (1985)
8. M-Q Man, KR Feingold and PM Elias, Exogenous lipids influence permeability barrier recovery in acetone-treated murine skin, *Arch Dermatol* 129 728-738 (1993)
9. G Imokawa, A Abe, K Jin, Y Higaki, M Kawashima and A Hidano, Decreased level of ceramides in stratum corneum of atopic dermatitis: An etiologic factor in atopic dry skin, *J Invest Dermatol* 96 523-526 (1991)
10. B Melnik, J Hollmann, G Plewig, Decreased stratum corneum ceramides in atopic individuals – a pathobiochemical factor in xerosis, *Br J Dermatol* 119 547-548 (1988)
11. A Yamamoto, S Serizawa, M Ito and Y Sato, Stratum corneum lipid abnormalities in atopic dermatitis, *Arch Dermatol Res* 283 219-223 (1991)
12. IH Blank, Factors which influence the water content of the stratum corneum, *J Invest Dermatol* 18 433-440 (1952)
13. IH Blank, Further observations on factors which influence the water content of the stratum corneum, *J Invest Dermatol* 21 259-271 (1953)
14. RO Potts and ML Francoeur, The influence of stratum corneum morphology on water permeability, *J Invest Dermatol* 96 495-499 (1991)
15. A Rougier, C Lotte, P Corcuff and HI Maibach, Relationship between skin permeability and corneocyte size according to anatomic site, age, and sex in man, *J Soc Cosmet Chem* 39 15-26 (1988)
16. G Imokawa, S Akasaki, Y Minematsu and M Kawai, Importance of intercellular lipids in water-retention properties of the stratum corneum: Induction and recovery study of surfactant dry skin, *Arch Derm Res* 281 45-51 (1989)
17. BJ Nickoloff and Y Naidu, Perturbation of epidermal barrier function correlates with initiation of cytokine cascade in human skin, *J Am Acad Dermatol* 30 535-546 (1994)
18. E Proksch, WM Holleran, GE Menon, PM Elias and KR Feingold, Barrier function regulates epidermal lipid and DNA synthesis, *Br J Dermatol* 128 473-482 (1993)
19. GK Menon, KR Feingold, AH Moser, BE Brown and PM Elias, De novo sterologenesis in the skin. II. Regulation by cutaneous barrier requirements, *J Lipid Res* 26 418-427 (1985)
20. K Aalto-Korte and M Turpeinen, Transepidermal water loss and absorption of hydrocortisone in widespread dermatitis, *Br J Dermatol* 128 633-635 (1993)
21. D Dupuis, A Rougier, C Lotte, DR Wilson and HI Maibach, In vivo relationship between percutaneous absorption and transepidermal water loss according to anatomic site in man, *J Soc Cosmet Chem* 37 351-357 (1986)
22. M Lodén, The effect of 4 barrier creams on the absorption of water, benzene, and formaldehyde into excised human skin, *Contact Dermatitis* 14 292-296 (1986)
23. A Boman, JE Wahlberg and G Johansson, A method for the study of the effect of barrier creams and protective gloves on the percutaneous absorption of solvents, *Dermatologica* 164 157-160 (1982)
24. JE Wahlberg, Anti-chromium barrier creams, *Dermatologica* 145 175-181 (1972)
25. T Fischer and I Rystedt, Skin protection against ionized cobalt and sodium lauryl sulphate with barrier creams, *Contact Dermatitis* 9 125-130 (1983)
26. RR Lauwerys, T Dath, J-M Lachapelle, J-P Buchet and H Roels, The influence of two barrier creams on the percutaneous absorption of m-xylene in man, *J Occup Med* 20 17-20 (1978)
27. AM Grunewald, M Gloor, W Gehring and P Kleezs, Barrier Creams. Commercially available barrier creams versus urea- and glycerol-containing oil-in-water emulsions, *Dermatosen* 43 69-74 (1995)
28. W Schlüter-Wigger and P Elsner, Efficacy of 4 commercially available protective creams in the repetitive irritation test (RIT), *Contact Dermatitis*

34 278-283 (1996)
29. J Bettinger, M Gloor, C Peter, P Kleesz, J Fluhr and W Gehring, Opposing effects of glycerol on the protective function of the horny layer against irritants and on the penetration of hexyl nicotinate, *Dermatology* 197 18-24 (1998)
30. E Held, S Sveinsdottir and T Agner, Effect of long-term use of moisturizers on skin hydration, barrier function and susceptibility to irritants, *Acta DermVenereol (Stockh)* 79 49-51 (1999)
31. CL Goh and SL Gan, Efficacies of a barrier cream and an afterwork emollient against cutting fluid dermatitis in metalworkers: A prospective study, *Contact Dermatitis* 31 176-180 (1994)
32. H Zhai and HI Maibach, Moisturizers in preventing irritant contact dermatitis: An overview. *Contact Dermatitis* 38 241-244 (1998)
33. M Lodén, The increase in skin hydration after application of emollients with different amounts of lipids, *Acta Derm Venereol (Stockh)* 72 327-330 (1992)
34. K Wellner and Wohlrab, Quantitative evaluation of urea in stratum corneum of human skin, *Arch Dermatol Res* 285 239-240 (1993)
35. M Lodén, P Boström and M Kneczke, The distribution and keratolytic effect of salicylic acid and urea in human skin, *Skin Pharmacology* 8 173-178 (1995)
36. HLGM Tiemessen, HE Boddé and HE Junginger, A silicone membrane sandwich method to measure drug transport through isolated human stratum corneum having a fixed water content, *Int J Pharm* 56 87-94 (1989)
37. IH Blank, J Moloney, AG Emslie, I Simon and C Apt, The diffusion of water across the stratum corneum as a function of its water content, *J Invest Dermatol* 82 188-194 (1984)
38. MM Rieger and DE Deem, Skin moisturizers. II. The effects of cosmetic ingredients on human stratum corneum, *J Soc Cosmet Chem* 25 253-262 (1974)
39. LM Lieb, RA Nash, JR Matias and N Orentreich, A new in vitro method for transepidermal water loss: A possible method for moisturizer evaluation, *J Soc Cosmet Chem* 39 107-119 (1988)
40. M Lodén, Keratolytics. In: *Dermatopharmacology of topical preparations* B Gabard, C Surber C, P Treffel and P Elsner eds, Heidelberg, Springer-Verlag, pp 255-280 (1999)
41. E Bárány, M Lindberg and M Lodén, Unexpected skin barrier influence from nonionic emulsifiers, *Int J Pharm* 195 189-195 (2000)
42. L Hellgren and K Larsson, On the effect of urea on human epidermis, *Dermatologica* 149 89-293 (1974)
43. MVLB Bentley, ERM Kedor, RF Vianna and JH Collett, The influence of lecithin and urea on the in vitro permeation of hydrocortisone acetate through skin from hairless mouse, *Int J Pharm* 146 255-262 (1997)
44. R McCallion and ALW Po, Modelling transepidermal water loss under steady-state and non-steady-state relative humidities, *Int J Pharm* 105 103-112 (1994)
45. J Beastall, GH Guy, J Hadgraft, I Wilding, The influence of urea on percutaneous absorption, *Pharm Res* 3 294-297 (1986)
46. AC Allenby, NH Creasey, AG Edginton, JA Fletcher and C Schock, Mechanism of action of accelerants on skin penetration, *Br J Dermatol* 81 suppl 4, 47-55 1969
47. CK Kim, J-J Kim, S-C Chi S-C and C-K Shim, Effect of fatty acids and urea on the penetration of ketoprofen through rat skin, *Int J Pharm* 99 109-118 (1993)
48. W Wohlrab, The influence of urea on the penetration kinetics of vitamin-A-acid into human skin, *Z-Hautkr* 65 803-805 (1990)
49. W Wohlrab, The influence of urea on the penetration kinetics of topically applied corticosteroids, *Acta Derm Venereol (Stockh)* 64 233-238 (1984)
50. JE Wahlberg and G Swanbeck, The effect of urea and lactic acid on the percutaneous absorption of hydrocortisone, *Acta Dermatovener (Stockh)* 53 207-210 (1973)
51. G Stüttgen, Penetrationsförderung lokal applizierter Wirkstoffe durch Harnstoff, *Hautarzt* 40 suppl 9, 27-31 (1989)
52. Lodén, Urea-containing moisturizers influence barrier properties of normal skin, *Arch Dermatol Res* 288 103-107 (1996)
53. M Lodén, Barrier recovery and influence of irritant stimuli in skin treated with a moisturizing cream, *Contact Dermatitis* 36 256-260 (1997)
54. J Serup, A double-blind comparison of two creams containing urea as the active ingredient. Assessment of efficacy and side-effects by non-invasive techniques and a clinical scoring scheme, *Acta Derm Venereol (Stockh)* Suppl 177 34-38 (1992)
55. CL Froebe, A Simion, H Ohlmeyer, LD Rhein, J Mattai, Cagan RH et al, Prevention of stratum corneum lipid phase transitions in vitro by glycerol - An alternative mechanism for skin moisturization, *J Soc Cosmet Chem* 41 51-65 (1990).
56. M Lodén and C Wessman, The influence of a cream containing 20% glycerin and its vehicle on skin barrier properties, *Int J Cosm Sc* 23 215-220 (2001)in press.
57. T Frödin, P Helander, L Molin and M Skogh, Hydration of human stratum corneum studied in vivo by optothermal infrared spectrometry, electrical capacitance measurement, and evaporimetry, *Acta Derm Venereol (Stockh)* 68 461-467 (1988)
58. R Bimczok, A Ansmann, S Bielfieldt, D Billek, H Driller, G Feistkorn, F Heinze, R Hüttinger, B Komp, H Lautenschläger, M-C Leneveu, L Motitschke, L Pohl, A Reng, HJ Schulze, B Thomaskamp, K Tolkiehn, H Tronnier, HU Wekel and KP Wittern, A multicenter comparison of different test methods for the assessment of the efficacy of skin care products with 368 human volunteers, 17th Int IFSCC Congr, Yokohama, October 13-16, vol 3, 1241-1266 (1992)
59. J Serup, A Winther and CW Blichmann, Effects of repeated application of a moisturizer, *Acta Derm Venereol (Stockh)* 69 457-459 (1989)
60. E Berardesca, F Distante, GF Vignole, C Oresajo and B Green, Alpha hydroxyacids modulate stratum corneum barrier function, *Br J Dermatol* 137 934-938 (1997)
61. BC Lippold and D Hackemüller, The influence of skin moisturizers on drug penetration in vivo, *Int J Pharm* 61 205-211 (1990)
62. DA Van Hal, E Jeremiasse, HE Junginger, F Spies and JA Bouwastra, Structure of fully hydrated human stratum corneum: A freeze-fracture electron microscopy study, *J Invest Dermatol*, 106 89-95 (1996)
63. FM Pope, JK Rees, RS Wells and KGS Lewis, Out-patient treatment of ichthyosis: A double-blind trial of ointments, *Br J Dermatol* 86 291-296 1972
64. K Grice, H Sattar and H Baker, Urea and retinoic acid in ichthyosis and their effect on transepidermal water loss and water holding capacity of stratum corneum. *Acta Dermatovener (Stockh)* 53 114-118 (1973)
65. M Lodén, A-C Andersson, and M Lindberg, Improvement in skin barrier function in patients with atopic dermatitis after treatment with a moisturizing cream (Canoderm®), *Br J Dermatol* 140 264-267 (1999)
66. GP Serban, SM Henry, VF Cotty and AD Marcus, In vivo evaluation of skin lotions by electrical capacitance: I. The effect of several lotions on the progression of damage and healing after repeated insult with sodium lauryl sulfate, *J Soc Cosmet Chem* 32 407-419 (1981)
67. M Lodén, A-C Andersson, C Andersson, T Frödin, H Öman and M Lindberg, Instrumental and dermatologist evaluation of the effect of glycerine and urea on dry skin in atopic dermatitis, *Skin Res & Technol* 7 00-00 (2001)
68. L Halkier-Sørensen and K Thestrup-Pedersen, The efficacy of a moisturizer (Locobase) among cleaners and kitchen assistants during everyday exposure to water and detergents, *Contact Dermatitis* 29 266-271 (1993)
69. J Vilaplana, J Coll, C Trullás, A Axón and C Pelejero, Clinical and non-invasive evaluation of 12% ammonium lactate emulsion for the treatment of dry skin in atopic and non-atopic subjects, *Acta Derm Venereol (Stockh)* 72 28-33 (1992)
70. A Gånemo, M Virtanen and A Vahlquist, Improved topical treatment of lamellar ichthyosis: A double blind study of four different cream formulations, *Br J Dermatol* 141 1027-1032 (1999)
71. S Tree and R Marks, An explanation for the 'placebo' effect of bland ointment bases, *Br J Dermatol* 92 195-198 (1975)
72. A Tollesson and A Frithz, Transepidermal water loss and water content in the stratum corneum in infantile seborrhoeic dermatitis, *Acta Derm Venereol (Stockh)* 73 18-20 (1993)
73. R Ghadially, L Halkier-Sorensen and PM Elias, Effects of petrolatum on stratum corneum structure and function, *J Am Acad Dermatol* 26 387-396

(1992)
74. R Blanken, MJT van Vilsteren, RA Tupker and PJ Coenraads, Effect of mineral oil and linoleic-acid-containing emulsions on the skin vapour loss of sodium-lauryl-sulphate-induced irritant skin reactions, *Contact Dermatitis* 20 93-97 (1989)
75. M Lodén and AC Andersson, Effect of topically applied lipids on surfactant-irritated skin, *Br J Dermatol* 134 215-220 (1996)
76. C Prottey, PJ Hartop, JG Black and JI McCormack, The repair of impaired epidermal barrier function in rats by the cutaneous application of linoleic acid, *Br J Dermatol* 94 13-21 (1976)
77. M Lodén and E Barany, *Acta Derm Venereol* 80 412-415 (2000)
78. CG Mortz, KE Andersen and L Halkier-Sørensen, The efficacy of different moisturizers on barrier recovery in hairless mice evaluated by non-invasive bioengineering methods. A model to select the potentially most effective product, *Contact Dermatitis* 36 297-301 (1997)
79. JD Middleton, The mechanism of water binding in stratum corneum, *Br J Dermatol* 80 437-450 (1968)
80. LE Rhodes, Essential fatty acids, In: *Dry Skin and Moisturizers: Chemistry and Function*, M Lodén and HI Maibach, eds, Boca Raton: CRC Press, (2000) pp 311-325.
81. AV Rawlings, A Davies, M Carlomusto, et al, Effect of lactic acid isomers on keratinocyte ceramide synthesis, stratum corneum lipid levels and stratum corneum barrier function, *Arch Dermatol Res* 288 383-90 (1996)
82. M Lodén and HI Maibach, *Dry Skin and Moisturizers: Chemistry and Function*, Boca Raton: CRC Press (2000)

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