

CURRENT GALENICAL RESEARCH CHALLENGES IN HUMAN DERMATOLOGY: APPLICATION FOR THE DEVELOPMENT OF PRODUCTS FOR SENSITIVE AND ATOPIC SKIN

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Introduction

Essential clinical features of atopic dermatitis are pruritus, eczema, associated with lichenification and skin dryness, frequently superinfected by bacterial or fungal infections. Atopic dermatitis skin is characterised by a hyperreactivity to many factors and an inflammation. This dermatitis predisposes to sensitive skin.

Sensitive skin presents a tendency to hyperreact to topical agents with symptoms of dry skin such as erythema and scaling and also different forms of discomfort such as stinging, burning and itching.^{1,2}

Atopic and sensitive skins are both characterised by a disrupted barrier function. The lack of intercellular lipids such as cholesterol, ceramides, essential fatty acids -organised in multilayered lipid structures between the corneocytes in the intact barrier- causes enhanced transepidermal water loss, and an inadequate stimulation of nerve endings resulting in heightened neurosensory input. It also contributes to enhanced immune reaction through altered percutaneous absorption. As a matter of fact, the development of epithelial microfissures into xerosis allows entry of skin allergens and pathogens.³

A local treatment will have to fight these deficiencies and the effectiveness of dermocosmetics for atopic and sensitive skin is related to the overall formulation. Therefore, the formulation of topical products for atopic and sensitive skins is based on a number of criteria:

- presence of specific active ingredients: cutaneous antiseptics, emollients, local anti-inflammatory or immunomodulating agents and/or local antibiotics,
- development of specific galenic forms: limitation of the transepidermal water loss, film formation properties, which influences bio-availability and local tolerance,
- absence of irritant ingredients and allergenic compounds,
- choice of the excipients: high quality, pure materials, free of contaminants, must be selected. Surfactants and other potentially irritating agents (preservatives, fragrances, antioxidants...) should be carefully selected.⁴

We shall first consider the significance of new galenical forms for skin care and then describe the recent developments in the therapeutic approach to atopic skin.

I- New galenical forms for toiletry and skin care

More than just a hygiene practice, personal care products now include skin care and pleasure of use.⁵

Solid soaps are still much appreciated by customers for their convenience, adaptability to family use and mildness. Based on fatty acid esters derived from animal sources (suet) or plants (olive, coconut, soy), they are enriched with jojoba oil, shea butter or glycerine to improve their lipid-replenishing and moisturising properties. Translucent and transparent formulas are now developed to diversify and optimise foaming, cleansing and mildness.

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Liquid products such as **syndets** are increasingly popular thanks to their advantages over soap. They consist of synthetic detergents and are less alkaline and consequently less harsh on the skin. **New formulas contain extra-mild cleansing agents** (isethionates, acyl-glutamate, acyl-amphoacetate, undecylamido propyl betaines, alkyl polyglucosides, etc.), **vitamins, minerals for sensitive skins, oils and proteins for a moisturising effect**. Several laboratories offer 2-in-1 milky moisturising shower gels. Rich in plant oils (coconut, sesame), with ingredients close to the natural substances of the skin (lactates), their objective is to reduce the drying effect of surfactants. In addition, to adopt skin care positioning, some cleansing products present colorant-free formulas and physiological (5.5) or neutral pH. This parameter is very important, because there are still products recommended for sensitive or dry skin that have an irritant effect, which has been correlated to the pH of the product.⁶

A new generation of cleansers has recently emerged. These are products with well tolerated surfactants that do not require rinsing. There are two kinds of galenic forms. Firstly, **emulsions** are an interesting form for cleansing sensitive skin, solubilising both aqueous and oily dirt. The originality of these cleansing emulsions is that they have no ionic or amphoteric surfactants. They essentially contain non-ionic surfactants (**both emulsifiers and cleansers**), emollient esters and also anti-irritant and soothing ingredients such as oat extract (Sensifluid, Pierre Fabre) or Acteoside (cleansing milk, Actidia). **These systems can be very fluid and used as sprays (Allermyl lotion, Sebomild P lotion, Virbac).**

The other innovation consists in **micellar solutions**. Completely aqueous, free of oil, they develop micelles of non-ionic biocompatible surfactants, which can microemulsify dirt. These lotions (Innovance gelée micellaire and Crealine TS H2O, Bioderma or Pureté Thermale, solution micellaire démaquillante, Vichy) also prevent skin irritation thanks to their rich content in active ingredients such as glycerine, oligosaccharides or rose phytophenol. They gently clean the skin while respecting its hydrolipidic balance and are especially appropriate for sensitive and atopic skins.

Today, skin care formulations must be increasingly effective and maintain tolerance and aesthetic properties. New galenical concepts have been designed to protect fragile active ingredients, acting as controlled delivery systems or targeting an action area while supporting the barrier function of the skin. Nanodispersed systems, multiple emulsions, microemulsions are proposed to succeed in skin treatment and comfort.

Nanodispersed systems involve liposomes, nanocapsules, nanoemulsions and lipid nanoparticles⁷. They are used as delivery systems but their own structure may have an effect on the skin hydration.

-Liposomes are formed with mono- or multilamellar bilayers, produced by dispersion of phospholipids in water. They can encapsulate hydrophilic substances in their aqueous core. Liposomes can favour the disposition of encapsulated ingredients in the outermost skin layers, but it has also been demonstrated that in case of empty liposome application, the presence of highly skin-compatible lipids such as phospholipids and sphingolipids increases skin moisture. **New multilamellar vesicles tend to substitute to liposomes.** **Micro or nanocapsules** are composed of multiple concentric bilayers of surfactant, separated by a polar liquid medium, generally water in which the hydrophilic additives can be incorporated. Their lipid core allows to encapsulate lipid additives. Moreover, their multilamellar (lipid/water) structure creates good skin affinity leading to cutaneous penetration and good hydration.

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-Nanoemulsions, also called sub-micron emulsions (SMEs) or mini-emulsions, are oil-in-water emulsions with an average droplet size ranging from 100 to 500 nm. This allows very good stability and these emulsions do not undergo phase separation during storage. Usually, SMEs require high-pressure homogenisation and contain 10 to 20 per cent of oil stabilised by non-ionic surfactants (often phospholipids). They have a liquid lipophilic core and are appropriate for lipophilic compound transportation. Many studies show the appropriateness of SMEs for increased cutaneous penetration of active ingredients, and reduced transepidermal water loss, which confirms support in the barrier function of the skin⁸. Nanoemulsion viscosity is very low, which is interesting because they can be produced as sprays, an innovative presentation that will be discussed later. Regarding emulsions, several alternatives are developed to eliminate the negative effects of surfactants. The most attractive alternatives are polymeric emulsifiers such as copolymers of acrylic acid or hydroxypropylcellulose, on the one hand, and solid particles such as alumina, silica or titanium dioxide packed in the interface, on the other hand. This can lead to a stable interfacial film with a good protection against coalescence. These systems are called **surfactant-free emulsions**.

-In solid lipid nanoparticles⁹ (SLNs), droplets are made by solid lipids. Their sizes range from 50 to 1000 nm. They can also be stabilised by surfactants or polymers. SLN structures depend on the chemical nature of active ingredients and excipients. There are mainly three structures: Homogeneous matrix, drug-enriched shell and drug-enriched core. It has been demonstrated that these systems present advantages over other dispersed systems: they can protect active components against chemical degradation and modulate compound release. These properties will depend on the nature of lipids and surfactants used in the formulation. SLNs also present occlusive properties thanks to the formation of a film on the skin. This film formed by lipid fusion is supposed to be a pore-less film with improved skin hydration and protection properties. Depending again on their composition, different penetration profiles can be obtained and SLNs can be very efficient in promoting penetration into the stratum corneum.

Multiple emulsions^{10,11} are another interesting system for application in cosmetics. W/O/W emulsions consist in the dispersion of a W/O emulsion in an aqueous phase under several conditions. One can incorporate different water soluble ingredients (even if they are incompatible) and also oily soluble additives. Like SLNs, these substances will be protected and release sustained by controlling droplet breakdown. These systems can have high oily phase contents (65%, Trixera, Bain emollient, Avène) and thus present good hydration. Their efficacy has been demonstrated in dermatology to treat stretch marks (Trieffadiane, CS Dermatologie).

Microemulsions¹²: these formulations have been shown to be superior for cutaneous delivery compared to other conventional vehicles. These systems are identified as transparent mixtures of water, oil and surfactants. They are thermodynamically stable and optically isotropic. Microemulsions are spontaneously produced in a narrow range of oil-water-surfactant composition, represented on pseudo-ternary diagram phases. They are dynamic systems with continuously fluctuating interfaces. Their good dermal and transdermal delivery properties could be attributed to their excellent solubilising properties. Lipophilic components are mainly involved, but hydrophilic active substances can also benefit from microemulsion application. Their high solubilising properties improve bioavailability and thus reduce the efficient dose, increasing tolerability. Furthermore, their restructuring effect on skin and hair (due to their high lipid content) make microemulsions formulations adapted to altered skin and hair conditions (Hair Sensation, Lancôme, Allermyl Shampoo, Virbac).

II- Therapeutic approach to atopic dermatitis

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We are now going to develop recent progress in the therapeutic approach to atopic skin.

As mentioned above, the presence of active ingredients such as emollients, cutaneous antiseptics, local anti-inflammatory agents and/or local antibiotics is important for solving atopic skin problems.

The role of **moisturising treatments** in restoring the barrier function by reconstituting the hydrolipidic film of the skin area has been proved¹³. Moisturisers are fairly numerous and can be classified in two categories¹⁴.

-Substances forming an occlusive film on the skin (passive hydration mechanism). They consist in lipophilic substances such as hydrocarbons, wax or fatty alcohols and are now less used due to their greasy feeling and partial tolerability.

-Substances that maintain water in the stratum corneum (active hydration mechanism). These are hygroscopic substances (glycerol, sorbitol, lactates, AHA or urea and lactic acid), substances that maintain the skin barrier function (ceramides, glycoceramides, and polyunsaturated fatty acids) and hydrophilic compounds (biological macromolecules, polysaccharides and chitosanide), which are hygroscopic and non-occlusive film formers.

Topical corticoids are commonly used for severe attacks of atopic dermatitis. Adults can be treated with high potency dermocorticoids (class II) and children or babies with moderate potency (class III). Side effects are mainly related to conditions of use, e.g. period of use and cutaneous area treated. New corticosteroids such as mometasone, hydrocortisone aceponate or fluticasone exhibit good efficiency and tolerability, and should reduce side effect risks such as cutaneous atrophy. Moreover, well used topical corticosteroids (for a short period and with localised surface treatments) reduce systemic effect risks and are a good alternative to systemic treatments.

Topical corticoid treatment can be supported by **local antibiotherapy and cutaneous antiseptics**. When patients are colonised by *Staphylococcus aureus*, the presence of this microorganism can exacerbate the inflammation by super-antigen secretion. Antistaphylococcal antibiotics such as fusidic acid, mupirocin and silvered sulfadiazine and cutaneous antiseptics such as chlorhexidine, hexomedine, and metallic derivatives based on copper sulfate and zinc can help treat atopic dermatitis¹⁵. Anyway, the actual challenge is to find substances to reduce antiseptic quantities in topical products. The possibility of using substances that limit microorganism adhesion on the skin (monosaccharides or certain surfactants) is an interesting alternative to improve antiseptic action. Furthermore, it seems that the association of corticoids with antiseptics is more interesting than the association with antibiotics because it does not entail any risk of resistance to antibiotic molecules.

With atopic dermatitis, one can also observe the occurrence of fungal contamination by *Malassezia furfur* requiring the use of antifungal agents³.

New topical **immunomodulatory therapies** may offer an attractive alternative for treating atopic dermatitis. Tacrolimus is a new macrolide that has a high inhibitor potential of T-lymphocyte activation and can penetrate the skin to provide local immunosuppression. Pimecrolimus is a macrolactame derived from Ascomycine. It has the same mechanism of action as Tacrolimus. 0.1% and 0.03% Tacrolimus ointments (Protopic®, Fujisawa Sarl) and 1% Pimecrolimus cream¹⁶ have shown to be both effective and safe in adults and children. With an efficiency similar to that of dermocorticoids, these molecules represent an attractive alternative in controlling inflammatory skin diseases.

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Other molecules present an immunomodulator effect on the cutaneous inflammatory process. The regulation of immune reaction by endogenous glycans leads to using **monosaccharides or oligosaccharides** as active ingredients for limiting and weakening the inflammatory process. Their suppressing properties for allergic contact dermatitis¹⁷ and cell-mediated immune reaction have been proven. These properties are interesting for sensitive skin and atopy. These saccharides are α -L-fucose, galactose, galacturonic acid, rhamnose or α -D-glucose¹⁸ (Innovance crème soie, Bioderma).

Conclusion:

Although choosing active components and galenic vehicles is crucial to develop toiletry and skin care products, a good appreciation of the product by the patient and its ease of use will ensure better compliance with the treatment. The market offers several original and new presentations of topical products that improve this important aspect. Firstly, creams or lotions can be presented with **unidoses or mini-doses** (2 to 5 ml). These formulations for allergic and hyperreactive skin contain formulas with the least possible ingredients, and no preservatives, fragrances or surfactants. Ingredients and manufacturing are sterile. The dose must be used in one or three times (Lait nettoyant et crème Tolérance extrême, Avène, Respectissime, La Roche Posay).

Sprays are also very useful. They are easy to apply, even on large areas, dosage is easy to control, and there is no contamination. Sprays were initially used for solutions only but with the development of sprayable emulsions, they offer interesting possibilities for lipophilic active substances or emollients for skin **cleansing and care** the with new sensory aspects and textures (A-derma Epitheliale, Ducray, Pierre Fabre and, for Veterinary applications, Allermyl and Sebomild P Lotions, Virbac).

Lastly, **cleansing wipes** (Deep Clean, Neutrogena, Lingettes démaquillantes, Roc) are gaining shares in the toiletries market. They ensure effective cleansing of the face and eyes in one easy step. Tissues, pre-impregnated with emulsions or lotions, provide hydration and deep cleansing, without rinsing. They are quick and convenient as well as safe and well tolerated. The only inconvenience is that they are still rather expensive, but with a growing market, they will soon spread.

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