RELATA TECHNICA

International journal on dermopharmacological research,
dermopharmaceutical technology and related cosmetic subjects

# ACTIVITIES OF EXCIPIENTS FOR TOPICAL SKIN CARE FORMULATIONS

Published on Relata Technica Web Site
http://www.relata.info

# Activities of Excipients for Topical Skin Care Formulations

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**Reading Time: 15'**

## ABSTRACT

The optimal skin care excipient is the one that allies the capabilities to provide excellent rheological and sensorial qualities with the most appropriate octanol/water partition coefficient for helping active ingredients to reach their site of action, i.e. to penetrate the epidermis if they act on cells (e.g. anti-oxidants, vitamins, epigenetic factors) or to stay on the surface if they have to act on the stratum corneum (e.g. sunscreens, moisturizing factors, self-tan actives). Three excipients endowed with these properties are: Xalifin-15, Nesatol and Cetacene. This paper describes their safety and efficacy as well as their rheological, sensorial and physical chemical properties and points out some actives they can conveniently be associated with, to help them penetrating or remaining on the top of the skin, according to what is needed.

## INTRODUCTION

Far from being inactive bystanders of the pharmacological activity, excipients can play relevant roles in skin care products. Aesthetically pleasing emulsions owe their light touch or sensual feeling to carefully selected excipients able to improve spreadability without diminishing viscosity and to provide a sensation of immediate adsorption while leaving the stratum corneum moist and the skin protected.

The sensory characteristics are associated to well-defined physical-chemical parameters, such as the capability of reducing the surface tension and of modifying the viscosity of the formulation; expert physical-chemists know how to select the excipients for a topical product to achieve the required sensory properties.

Things become more complicated when the product for topical application is required not only to provide a specific sensation, but also to deliver "actives" to help the stratum corneum and the epidermis to achieve a specific function, for instance to scavenge Reactive Oxygen Species, or to deliver vitamins for DNA repair, or to stimulate the production of a natural component, such as filaggrin, or to trigger the anti-stress response via the induction of Heat Shock genes or to inhibit melanin synthesis, or only to keep the sun-filters from penetrating the epidermis (thus becoming totally useless).

At risk of appearing schematic, we could say that the excipients can favor or hinder the penetration of "actives", and that the ultimate goal of skin care is to provide the consumer with Delivery Systems able to release the actives by topical application while providing the most pleasurable sensation.

To do so one could use the so-called pro-penetrants, that disrupt the lipid structure of the stratum corneum, but this is not a recommended methodology.

The way to follow is to realize that the selected excipients must have the capability to modulate viscosity as well as surface tension and have octanol/water partition coefficient (Log Kow) that are compatibles with the ones of the actives to be delivered.

The ideal situation is encountered when the "active" has a Log Kow (active) similar to the Log Kow of the stratum corneum and the aesthetically pleasant excipient has a

$$\log \text{Kow (excipient)} > \log \text{Kow (active)} + 5$$

After the introduction of silicones in cosmetics, this became more of a problem because the log Kow of silicones is intermediate between the ones of water-soluble and the ones of lipid-soluble molecules so that many silicones clinch to "actives" thus hindering their delivery to the skin.

This frustrates the efforts of the pharmacologists and the biochemists who discover actives, and the activity of physical -chemists who try to prepare formulations able to offer excellent sensorial qualities.

In this paper we shall review the properties of some excipients remarkable both for their aesthetic properties and for their capability to help delivering "actives".

## ELEGANT EXCIPIENTS WITH PHYSICAL-CHEMICAL ACTIVITIES

### Xalifin-15

A mixture of esters obtained by reacting polyethylene glycol (PEG) and a calibrated blend of fatty acids (among others stearic acid, isostearic acid or palmitic acid), named Xalifin-15, is a particularly appropriate example of this category of excipients. Because of their amphiphilic structure, the esters in Xalifin-15 have great rheological properties in spite of containing fully saturated aliphatic chains and this makes Xalifin-15 an ingredient of choice for products aiming at providing excellent sensorial qualities.

The absence of double bonds ensures that the components of Xalifin-15 are free from adventitious oxidation and are therefore more stable when they are added to commercial formulations.

The safety of Xalifin-15 has been ascertained by topical applications on the skin and on genital mucosa in human volunteers. Histological analysis of biopsy samples after a month of daily application of Xalifin-15 revealed the absence of reactive or pathological phenomena both in the epidermis and in the dermis.

The oral toxicity of Xalifin-15 is nil: when fed with food added with Xalifin-15, young rodents did grow and acquire weight in a indistinguishable manner from the control group fed without Xalifin-15.

As for the "active" behavior of Xalifin-15, it has been shown in vivo that Xalifin-15 is an excellent vehiculant. Two preparations, one consisting of an emulsion of Xalifin-15 and water and the other consisting of a mixture of lanolin and petrolatum[(1)], both containing a radioactive labeled substance, were applied to the skin of 35 volunteers.

The percentage of radioactivity remaining on the surface of the skin was monitored versus time and it was observed the rate of penetration. The study has shown that the decrease of the radioactivity applied by the emulsion containing Xalifin-15 and water was four time faster than the radioactivity applied by a preparation containing lanolin and petrolatum.

It has also been shown that the speed rate of the release of a bacteriostatic agent from a drop of a preparation layered on the top of an agar plate inoculated with bacteria was larger when the base of the preparation was the emulsion of Xalifin-15 in water.

From these results it can be expected Xalifin-15 to be an excellent vehiculant of actives. Considering that the molecules in Xalifin-15 are composed of a water-soluble head (PEG) with log Kow~ 4 and of a lipophilic tail (the fatty acid) with log Kow ~ 7, it can be expected that Xalifin-15 favors the penetration into the skin of substances with log Kow between 0 and 3 (e.g. hydroquinone, niacin or salicylic acid). Xalifin-15 can be expected to be an excellent additive for sunscreens insofar as it can strongly bind to sunfilters with log Kow larger than 6 (such as for instance butyl-octyl-salicylate or octocrylene) and therefore hinder their penetration across the stratum corneum.

### Nesatol

Another "active" excipient is Nesatol, a synthetic poly-tri-glyceride obtained with stearic (C18), palmitic (C16), myristic (C14) and lauric (C12) acids combined together to make it "sebumsimilar". It is therefore a saturated oil with chains whose lengths are the same as the ones of the chain of natural vegetal oils.

This confers specific properties to Nesatol, which is endowed with all the advantages of vegetal oils, as such as emolliency and undisputed safety, without being prone to rancidification or acidification. As confirmation of this, the rate of oxidation of Nesatol at 110°C under a stream of purified air is seven times smaller than that of soja oil or peanut oil, and fifteen to thirty times smaller than that of olive oil.

Nesatol is as pleasant as animal oils when topically applied, but it does not release any unpleasant odors and do not present any health hazard. In addition to that, it is an excellent solubilizer for lipophilic actives, such as for instance vitamins or fragrances.

The safety of Nesatol has been proven beyond any doubt by showing that the topical application on scarified skin and on conjunctive mucosa is perfectly well tolerated and does not lead to pathological signs of irritation or intolerance. Intra-peritoneal injections of Nesatol have shown that the LD50 is 15 g per kilogram of body weight in rats.

The necroscopic analysis in organs such as spleen, lungs, liver, kidney and heart indicated that the effects of Nesatol did not differ from the results obtained with equal quantities of olive oil or coconut oil or peanut oil.

The "active" behavior of Nesatol has been put to an advantage for the release of antipyretic drugs administered via the rectal route.

Dimethylaminophenazoneguyacolglycolate (DAG) and Mefenamic acid (MA) have been separately formulated in two sets of suppositories, in one of which 20% of the excipients were replaced by Nesatol (these were called DAGN and MAN).

Four groups of rabbits were inoculated with lipopolysaccharides and administered with DAG, MA, DAGN and MAN after the temperature increase had stabilized. In the first hour after administration, the temperature of the rabbits treated with DAGN suppositories dropped twice as quickly than the temperature of the rabbits treated with DAG suppositories, and the same was true also for the rabbit treated with MAN versus MA.

Thirty minutes after the administration of the suppositories, the concentration of free mefenamic acid in blood was 2.5 times higher in the group of rabbits receiving Nesatol-containing suppositories[2]. The same was qualitatively true for the other drug, albeit to a lesser quantitative extent.

These results indicate that Nesatol could be used in products for topical application in skin care, to enhance the penetration in the skin of active ingredients with

log Kow (active ingredient) < log Kow (Nesatol) - 2

**Cetacene**

Esthetically pleasing molecules like Cetacene (Acetylated Glycol Stearate, AGS) can be extremely helpful in the formulation of stable organo-gel nanoparticles.

These semisolid droplets with a diameter between 100 and 500 nm can be prepared by homogenizing at temperatures above the gelling temperature (Tgel) vaseline oil and/or almond oil with a stabilizer such as hydroxystearic acid (HSA) and/or acetylated glycol stearate (AGS), while the aqueous phase contains Sodium Hyaluronate and Poly Vinyl Alcohol [3].

The homogenate is then dispersed in water at temperatures below the gelling temperatures (Tgel) and so nanoparticles are obtained. Nanoparticles can be prepared to contain sunscreens and it has been observed that the presence of a stabilizer such as hydroxystearic acid (HAS) results in SPF values at least twice as large as when the nanoparticles are prepared without the stabilizer [3]. It is important to realize that the calculated partition coefficients of HSA and of AGS are

Log Kow (HSA) = 6.45 and Log Kow (AGS) = 8.23

and that therefore AGS is more appropriate to be used with sunscreens with Log Kow~8, such as Drometrizole Trisiloxane (Mexoryl XL) whereas HSA will be more conveniently used with sunscreens having Log Kow ~ 6, such as Nomcort-X and Ethylhexyl methoxycrylene.

## CONCLUSION

The best kept secret in the science of skin care is that inert excipients (in the chemical sense of the term) do indeed exert relevant actions on the physical-chemical properties of a formulation, on its stability and on its sensorial characteristics as well as on the behavior of the active ingredients, that have to be kept on the surface such as the sun-filters in a sunscreen, or that have to penetrate in the epidermis to scavenge free radicals, provide moisturizing factors, trigger repair or induce the expression of specific genes.

The reasons for this secret might well be the American legislation and the FDA guidelines. They are so worried to protect the consumer and the pharmaceutical companies, that every claim describing an action whatsoever will bring ipso facto the product exerting that action out of the realm of cosmetics into the realm of hard core drug-pharmaceutical industry.

The consequences are that it is impossible for a serious manufacturer of cosmetic products to justify in easily understandable words, why its products are better then the ones of the competitors. Nevertheless, it is not forbidden to test one's ingredients and to select the ones that do indeed exert a favorable action, as along as that action is not discussed in the advertising.

In this paper we have reviewed the remarkable properties of Xalifin-15, Nesatol and Cetacene, three notable ingredients available on the market, already largely used in the dermopharmaceutical field, and we have proposed a physical-chemical approach to extending their utilization in cosmetic formulations according to their affinity for other active ingredients on the basis of the similarities or strong differences of the octanol/water partition coefficients

The relevance of the partition coefficient in the biochemical behavior of liposomes anew has been recently pointed out [4].

This concept can easily be applied to products for topical application and transdermal delivery, on the basis of the assumption that actives with a partition coefficient similar to, or slightly larger than, the one of stratum corneum will penetrate more easily when the formulation contains excipients with a much larger partition coefficient.

Conversely, when a formulation contains actives that have to be maintained on the top of the skin, such as sunscreens or keratolytic agents, the excipients to be used should ideally have a partition coefficient equal to the one of the active ingredients.

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## WHAT IS RELATA TECHNICA?

Starting from the beginning of the human story numberless substances have been applied on the skin to favour wound healing, for the management of skin diseases, or simply and perhaps more often for cosmetic aims. In sharp contrast, only in recent years, and with a great delay as compared with otherfields of pharmacology, the study of the effects of chemicals on the skin moved from art to science; now it is soundly based on a rational approach. Regulatory Authorities classify substances and formulations to be applied on the skin in two distinct categories: drugs and cosmetics. This in order to prevent that harmful or extremely active chemicals, contained in cosmetic preparations, are used without medical control.

Nevertheless, all pharmacologists know that in its widest meaning drug is every substance capable of modifying cell function, and it is difficult to admit that chemicals used in cosmetic preparations are devoid of any influence on biochemical mechanisms of epidermal cells, in particular in the case of long-term treatments. Thus dermopharmacology and cosmetology are at least overlapping disciplines, and there is no doubt that the same methodology should be employed in both fields.

Over the years Relata Technica has achieved a wide readership; at present its aim is to broaden the journal to make it a truly comprehensive dermopharmacology research journal in which articles in all of the most interesting and exciting areas of modern skin care have their forum. As a consequence, Relata Technica should attract manuscripts concerning the pharmacokinetic behaviour and the pharmacodynamic activity of old and new chemicals used to control skin diseases or to prevent skin aging, as well as studies providing insights on which to base rational development of new compounds for medicinal or cosmetic use.

Investigations on the various aspects of the interaction of chemicals with the skin can be analysed by the use of several experimental models: the intact animal, fragments of surviving skin, keratinocytes cultures or the more sophisticated in vitro reconstructed human skin, subcellular fractions and pure enzyme systems. The end point examined in the study may be the macroscopic appearance of the skin, its histological, histochemical or ultrastructural features, and a biochemical or molecular marker.

An important aspect of dermopharmacology, and even more of cosmetology, is safety assessment. Therefore the journal will be also very interested in publishing the results of research dealing with the local and systemic tolerability of new compounds. In this respect, one of the major goals of Relata Technica is to promote studies on the use and validation of the so called alternative assays which should have the final aim of substituting, at least for cosmetics, the use of laboratory animals in the assessment of systemic toxicity, local irritant activity and, in a broader sense, of any possible adverse effect.

Finally, Relata Tecnica should be the natural publication outlet for manuscripts concerning the formulation of dermopharmaceutical and cosmetic preparations, and in particular for those which analyse the influence of the vehicle and other ingredients on the efficacy and tolerability of the active substance.

It is essential that the quality of papers published in Relata Technica be good and, on the other hand, it is important for the journal to process and publish papers promptly. We will make every possible effort to improve and shorten the review process, and I believe that Relata Technica will become a preeminent journal in the field of dermopharmacology.

Stampato da Vevy Europe S.p.A.
Autorizzazione del Tribunale di Genova 31/84, del 18/6/84.
Iscrizione al Registro Operatori di Comunicazione (ROC) al n. 6411 del 10.12.01.