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### Comments concerning the legal framework for the use of liposomes in cosmetic preparations

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#### Introduction

Lecithins and their individual components, the phospholipids, in their natural and hydrogenated forms are experiencing a renaissance at the present time in the form of liposomes in cosmetics. There are many reasons for this: Liposomes are a new type of formulation of two-phase aqueous-lipophilic systems beside the well-known emulsion. Liposomes or their chemical constituents penetrate into or through the surface of the skin and thus form a transport system for themselves, as active cosmetic agents, and for stored cosmetic agents («loads») [1]. Therefore, reference is often also made to a «deep effect» and a potentiation of the effect of the cosmetic agent employed as the load. In the case of the unsaturated, especially vegetable phospholipids the body is provided through the skin with «essential» fatty acids in chemically bonded form. These essential fatty acids are normally constituents of a balanced diet. Orally administered (foodstuffs) or topically absorbed (cosmetics), unsaturated phospholipids are eventually metabolized in a natural manner. Furthermore, the linoleic acid released by phospholipases is transformed into arachidonic acid (5,8,11,14-C<sub>20:4</sub>) and its metabolites via  $\gamma$ -linolenic acid (6,9,12-C<sub>18:3</sub>) and di-homo- $\gamma$ -linolenic acid (8,11,14-C<sub>20:3</sub>),  $\alpha$ -linolenic acid (9,12,15-C<sub>18:3</sub>) is transformed into docosahexaenoic acid (4,7,10,13,16,19-C<sub>22:6</sub>) and its metabolites [2] via eicosapentaenoic acid (5,8,11,14,17-C<sub>20:5</sub>).

#### Issues

In view of these physiologically highly active metabolites of the essential fatty acids the question immediately arises as to whether one is not balanced on an incalculable knife-edge between cosmetics and pharmacy. The discussions concerning antiperspirants, antiacne agents, hair growth agents and antiwrinkle agents spring to mind [3].

However, a glance at the fatty acid patterns of the triglycerides and phospholipids of mammals is reassuring: 10–20% of the total fatty acids already consist of linoleic acid. Thus, absorbed essential fatty acids and their precursors (phospholipids) are first stored and then the major proportion oxidatively metabolized. Hence, systemic effects after possible topical absorption can be excluded with certainty. Negligible amounts are taken up in comparison with the amount already intrinsically present. Many years' experience with phospholipids (lecithins) and highly unsaturated natural oils in cosmetics confirms these findings. On the other hand, it is the excellent local effects that are exploited in cosmetics: influence on transdermal moisture loss, regulation of sebaceous gland function etc. [1]. What is the legal framework in connection with liposomes as a novel phospholipid formulation?

#### General considerations

1. Concerning the penetration of liposomes, we know from experience that this is dependent on various parameters including chemical composition, size, lamellarity and other components in the formulation. As far as cosmetics are concerned, the mechanism of degradation of the liposome, as such, in the body is of less interest than the distribution, metabolism and biological effects of its components. However, this does not represent a new situation, since the components of other previously well-known formulations penetrate more or less into the deeper layers of the skin and can even be detected in the plasma [4, 5].

2. The EEC Guidelines for Cosmetics and, thus, the German Cosmetic Regulation derived from them [6] do not differentiate between various application forms such as solutions, emulsions, suspensions etc. with respect to the

size, shape and penetration behaviour, degradation and metabolism of the formulated particles. Hence, there are no restrictions for liposomal formulations in this respect.

3. The oral and topical administration of essential components of the human body (water, minerals, vitamins, essential amino acids, essential fatty acids and their derivatives) are covered in the Federal Republic of Germany by the Food Law and the Cosmetic Regulation appended to it. Thus, in order to prevent symptoms of deficiency which result or could result from insufficient intake of such essential substances (unbalanced diet), it is permissible to take compensatory or preventative measures e.g. the addition of vitamins to foodstuffs, the enrichment of cosmetics with these substances. The increasing use of native oils and highly unsaturated phospholipids in cosmetic confirms this trend. Of their nature some of the cosmetic effects of these substances are only possible if these penetrate sufficiently deeply into the skin, so that they can be referred to as deep effects.

4. Finished cosmetic products containing empty liposomes of phospholipids from natural sources with the intrinsic cosmetic properties described and the equivalent liposomes carrying loads whose kinetics and safety following possible transdermal absorption are known, are subject to the usual safety tests [7]. Thanks to their essential components these products can be employed optimally and without restriction. They may be regarded as a preventive medical measure which is what the legislator wishes [8]. Furthermore, because of their unobjectionable nature the WHO has not laid down ADI levels (acceptable daily intake) for lecithins as a foodstuff [9]; the FDA has given lecithins a GRAS status (generally recognized as safe; CFR No. 182.1400/184.1400) [10]; there are no restrictions on the use of lecithin as an ingredient in foodstuffs in the Federal Republic of Germany and the EEC [11, 12].

5. Non-natural liposome raw material, e.g. liposome formers not based on natural substances, the frequently employed stabilizers and potential liposome loads, whose effects on possible topical absorption are unknown (e.g. animal and vegetable extracts, protein fractions), in turn, must be precisely standardized and investigated for unwanted biological effects, both before and after processing to liposomes. Hydrogenated phospholipids as liposome raw material are regarded as being unobjectionable owing to their chemical composition; yet, they do not possess the cosmetic effects of the esterified essential fatty acids.

#### Advertising claims

The above considerations are not a contradiction of the respective regulations of the other European states or of the USA (FDA) [13, 14] so that a cosmetic liposome formulation tested according to the state of the art is unproblematical as such. On the other hand, advertising claims for finished cosmetic products are problematical. They may not contain promises which cannot be fulfilled [15], nor may

they contain (misleading) statements which fall under the concept »drug« employed in the various states [16, 17]. The aim, therefore, should be to argue clearly in order not to bring very desirable – desirable from the point of view of the consumer too – technology and the new group of preparations resulting from this into unnecessary discussion. This applies to the liposome manufacturer (responsible for the chemical composition and physical properties of the liposomes), the creator of the cosmetic (choice of the type of formulation and its ingredients; furnishing the demonstration of cosmetic efficacy of the final formulation) and to marketing (advertising statements concerning the finished product). There is a distinct danger here that in the euphoria concerning the boom-like development of the market, claims will be made which even extend beyond the manifold possibilities offered by the field of liposomes.

#### Summary

Concerning cosmetics the same application criteria are valid for liposome formulations as for other comparable forms of application. The advertising claims for a deep-acting liposome preparation must not be extended into the »drug« field. The argumentation becomes much simpler if highly unsaturated natural phospholipids are employed as raw material for the liposomes.

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#### Brief biography of the author

Dr. Hans Lautenschläger, born 1947, studied chemistry at the Free University Berlin from 1967 to 1973, awarded doctorate in organic chemistry 1976 and appointed laboratory manager in the Chemical Research Division of A. Nattermann & Cie GmbH in Cologne in 1977. From 1978 as department head he was responsible for drug and natural product synthesis in the indication area lipid metabolism and inflammation. In 1987 he was appointed head of the application research laboratories of Nattermann Phospholipid GmbH.