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Liposomal Drug Delivery – Outdated or Seminal Concept?

Keywords: Nanotechnology, Liposomal Drug Delivery

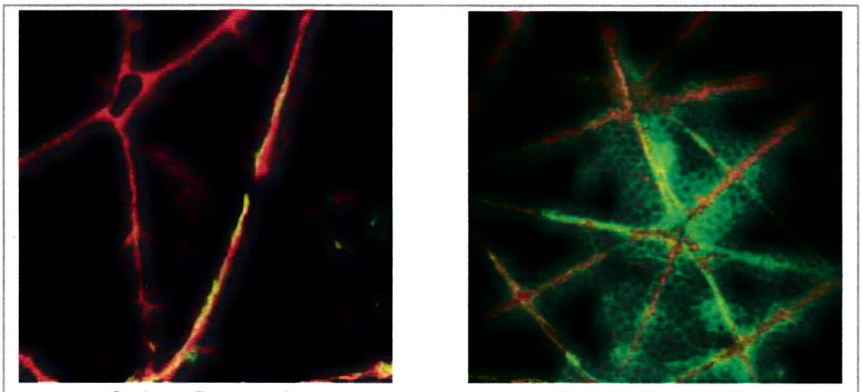
Abstract

There are countless numbers of topical cosmetical or pharmaceutical products on the market with as many active ingredients. Liposomes are commonly used in dermal applications as protective system for active ingredients and for their moisturising properties. They are spherical vesicles composed of phospholipids with an aqueous core and can either encapsulate lipophilic or hydrophilic active ingredients. Depending on their composition, they can also have the property of penetrating into the skin, carrying actives to the target site, where these molecules will be released. The efficacy of many products has been improved by liposomes due to an enhanced penetration into the skin. Since their first introduction in cosmetics (Dior, Capture, 1986) and today's controverse discussion about nanotechnology in cosmetics, it is of importance to evaluate future benefits of this delivery technology.

■ Liposomes and Nanotechnology

One type of flexible liposomes (ROVISOMEs®), describes small-sized unilamellar vesicles (50-400 nm) made of soy bean phosphatidylcholine (> 80%) with a high content of linoleic acid. They provide the skin with essential polyunsaturated fatty acids (vitamin F) which support the ceramide 1 formation and with choline which is a constituent of the NMF (natural moisturising factor). In a clinical study it was proven that these liposomes have cosmetic properties like wrinkle reduction and an increase in skin smoothness (1) and furthermore show pharmaceutical effects like decreasing efflorescences in the treatment of acne (2). In several *in-vivo* and *ex-vivo* studies those liposomes have proven the ability to penetrate the skin **(Fig. 1)**. Furthermore, the encapsulation and dermal delivery of hydrophilic and lipophilic actives with different molecular sizes increases the bio-availability and hence plays an important role in the efficacy, cost-efficiency and in the claim substantiation of the final product.

In today's discussions, there's basically no obvious distinction between various nanoscaled systems used in cosmetics. The general public awareness of nanotechnology as »new menace« (3), may lead to misunderstandings and false legislative regulations if a differentiation of »risky« nano materials and »safe« nano materials cannot be established on a clearly defined and scientific basis. Nanoparticles are overall defined as particles of which at least one dimension measures below 100nm (4). According to the afore mentioned definition, practically



Carboxyfluorescein
Dil in water/EtOH
t = 3 hours, depth: 70µm

Carboxyfluorescein
Dil in flexible liposomes
t = 3 hours, depth: 70µm

Fig. 1 Visualised Penetrability of Free Fluorescence Actives vs. Liposomally Encapsulated Fluorescence Actives
[red = Dil (lipophilic); green = Carboxyfluorescein (hydrophilic)]

almost every active used in today's cosmetics can be considered nano material, e.g. collagen fibers (3 – 30 nm in diameter) – an active widely used in cosmetics. Nowadays it is unclear if the definition range of nanoparticles should be extended to particles below 500 nm (5). Undeniably, general consumer awareness for this subject can be perceived.
Flexible liposomes, despite matching at least the SCCP-definition of nanoparticles, are able to penetrate into the deeper skin layers but without entering the blood stream. (6). In pharmaceutical products, liposomes are subject to parenteral and thus systemic application e.g. Lipofundin™ (Braun Melsungen), Intralipid™ (Kabi Pharmacia) or Arikace™, a liposomally encapsulated Amikacin used for the treatment of lung diseases. The lipid used for the production of those special liposomes is mainly phosphatidylcholine, the lipid which is constituent to the cell membranes and thus is considered as generally safe. All phospholipid based liposomes in cosmetics with a flexible membrane (e.g. ROVISOMEs®) are composed of said biodegradable material.

Future Perspective of Liposomal Drug Delivery

In contrary to the afore mentioned discussion, it is worth considering the major benefit of flexible liposomes which is the targeted administration of actives to the living cells. For instance, technological advances in pharmaceuticals have lead to an increasing potential for individual disease analysis. Today it is absolutely possible to combine diagnostics and therapeutics in order to stop just treating disease-symptoms, but to understand and cure the »biology of the disease«. It is estimated that in the year 2030 personalised therapeutics account for a 25% market share (7). As an example echogenic liposomes (ELIP) can be mentioned which contain both gas and fluid/drugs. With antibody conjugation, these liposomes can be used as novel targeted diagnostic and therapeutic drug delivery system in cancer therapy (8).
Among others, future perspectives in cosmetics will be specific drug targeting to special cell layers in the skin. Therefore, it is of interest whether there's a correlation between the phase transition temperature of liposomes and the penetration profile of drugs (depth) in different skin layers. In a study it was shown that flexible liposomes in the liquid state can penetrate into the very deep skin layers, DMPC-liposomes (liquid to gel state) accumulate in the stratum corneum and the upper skin layers, whereas hydrogenated liposomes (gel state) accumulate on top of the skin (CF-fluorescently marked liposomes - 3 hours - confocal laser scan miscroscopy). Depending on the chain length of the fatty acids liposomes consisting of phosphatidylcholine will reach different layers of the skin **(Fig. 2)**.

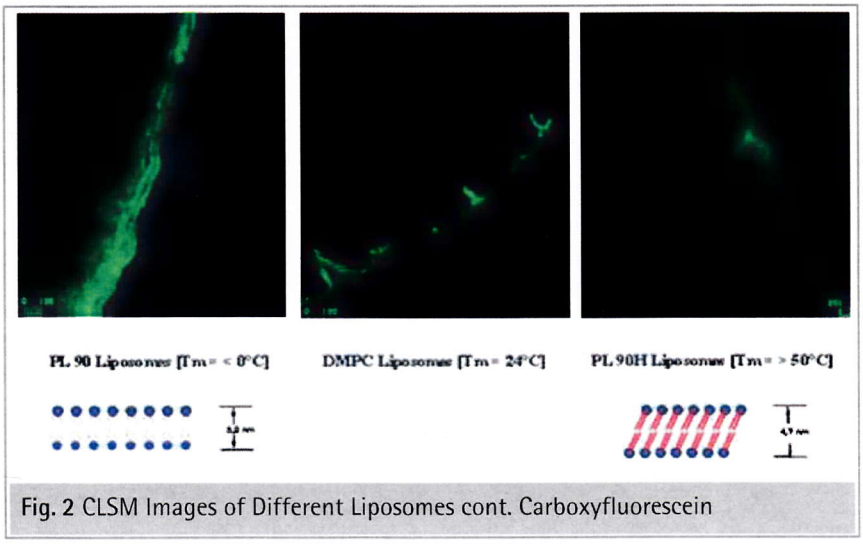


Fig. 2 CLSM Images of Different Liposomes cont. Carboxyfluorescein

Another future perspective is the development of environmentally sensitive liposomes reacting to different external stimuli like heat, pH or light. Furthermore, the development of »intelligent liposomes« exclusively reaching certain target sites within the skin represents a future challenge for the industry.

Conclusion

It is obvious that despite or even because of the current discussions and trends well-designed liposomal drug delivery is far from being outdated. There are numerous future fields of application and design in this area of expertise which will serve both the industry's needs and the consumers' benefit. It is just a matter of how the old image of the liposome is renewed and transformed into modern claims.

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