

# Microvesicle Formulations Used in Topical Drugs and Cosmetics Affect Product Efficiency, Performance and Allergenicity

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Attempts to improve the formulations of topical products are continuing processes (ie, to increase cosmetic performance, enhance effects, and protect ingredients from degradation). The development of micro- and nanovesicular systems has led to the marketing of topical drugs and cosmetics that use these technologies. Several articles have reported improved clinical efficacy by the encapsulation of pharmaceuticals in vesicular systems, and the numbers of publications and patents are rising. Some vesicular systems may deliver the drug deeper in the skin as compared to conventional vehicles, or even make transdermal delivery more efficient for a number of drugs. Vesicular systems may also allow a more precise drug delivery to the site of action (ie, the hair follicles) and thereby minimize the applied drug concentration, reducing potential side effects. On the other hand, this may increase the risk of other side effects. Few case reports have suggested that microvesicle formulations may affect the allergenicity of topical products. This article gives an overview of the current knowledge about the topical use of microvesicular systems and the dermatoallergologic aspects.

THE DEVELOPMENT of new formulations for topical products is a continuing process. The encapsulation of product ingredients into different carrier molecules (such as liposomes) may improve product efficiency and is a promising tool for dermal and transdermal delivery of drugs and cosmetic ingredients. The encapsulation technology has been used since the late 1960s, and several topical products marketed today claim benefits from this technology. This review focuses on the use of different types of encapsulating technologies in topical drugs and cosmetics and describes their possible effects on product allergenicity.

## Encapsulation Technology Used in Topical Drugs and Cosmetics

One advantage of encapsulating a drug into liposomes is the possibility of delivering the drug directly to the site of action in the skin at a higher concentration and obtaining a decreased percutaneous absorption at the same time. The penetration pattern is determined by the composition of the

liposome and the encapsulated compound. It is difficult to get approval from health service authorities for topical drugs using encapsulation technology because it is problematic for the manufacturer to prove the presence and stability of the microvesicles in the product. Some pharmaceutical products using microvesicle carriers are commercially available; examples are Pevaryl Lipogel (Cilag Corp., Schaffhausen, Switzerland), which is econazole encapsulated in liposomes, and a local anesthetic formulated in liposomes (LMX4, Ferndale Pharmaceuticals Ltd, UK). Estrasorb (Graceway Pharmaceuticals, Exton, PA) is estradiol encapsulated in micelles in a nanoemulsion for transdermal drug delivery; it is used for reducing hot flares in menopausal women.<sup>1</sup>

Several clinical trials have shown improved biologic effects of products with microvesicle formulations as compared to products with conventional formulations (for treatment of herpes simplex, psoriasis, acne, xerosis, atopic dermatitis, vitiligo, and superficial thrombophlebitis<sup>2-5</sup>). An example is 5-aminolevulinic acid formulated in 50 nm liposomes, which gives a more precise drug delivery that allows a 40% reduction in the amount of active ingredient when used to treat acne with photodynamic therapy. The liposomes concentrate in the pilosebaceous units, thereby reducing side effects and opening doors for new treatment modalities.<sup>6</sup> Another example is the topical administration of methotrexate (MTX), which is hydrophilic and present in dissociated form at physiologic

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hydrogen ion concentration (pH); its capacity for passive diffusion is thus limited. Clinical trials have shown better efficacy of MTX encapsulated in liposomes when compared to placebo and marketed MTX gel, probably owing to increased bioavailability.<sup>2</sup>

The carrier particles themselves are all considered safe for topical use, but the interaction between the carrier particle and the active ingredient may cause biologic effects due to altered skin penetration, release profile, and deposition of the active ingredients.

Lipid vesicles, solid lipid nanoparticles, and polymeric nanoparticles are used in cosmetic formulations to increase bioavailability in stratum corneum and to protect light- and oxygen-sensitive cosmetic ingredients against degradation.<sup>7</sup> Cosmetic ingredients such as retinyl palmitate may cause physiologic changes of the skin but are not claimed to treat skin diseases. Examples of encapsulated cosmetic ingredients are numerous (eg, coenzyme Q<sub>10</sub>, ascorbyl palmitate, tocopherol [vitamin E], and retinol [vitamin A]).<sup>8,9</sup> The types of nanoparticles and microparticles discussed below are components of marketed cosmetics.

### Liposomes

Liposomes are produced in sizes ranging from 25 nm to several micrometers. They consist of a single or multiple lipid double layer (unilamellar or multilamellar vesicles). Liposomes are capable of carrying amphiphilic active ingredients either in the lipid layer or in the hydrophilic core. They are believed to protect the active ingredients from degradation. Liposomes tend to break down into their constituent components when in contact with the skin. Therefore, liposomes at best can modulate drug transport to stratum corneum, but penetration will require more-stable carriers such as solid lipid nanoparticles or Transfersomes.<sup>10</sup> The concentration of active ingredients in the epidermis may be up to five times greater with liposome formulations than with formulations that use more-conventional vehicles.<sup>11</sup> Liposome formulation in water can easily be incorporated in an aqueous cream for better cosmetic performance. In the cosmetic industry, examples of active ingredients incorporated in liposomes are antioxidants, vitamin A derivatives, and vitamin E.

### Transfersomes

Vesicles produced by adding different amounts of so-called edge activators to the bilayer of classic liposomes (eg,

cholesterol or sodium cholate and a small concentration of ethanol) are called Transfersomes and Flexosomes. The edge activators destabilize the membrane, creating a more flexible structure, and have been shown to penetrate in stratum corneum better as compared to classic liposomes, thereby delivering their encapsulated ingredients deeper in the epidermis but not to the blood circulation.<sup>12</sup> The mechanism of enhancement of skin penetration has not been completely elucidated, but because of their flexibility, Transfersomes are believed to squeeze between the corneocytes, driven by an osmotic force due to the difference in water content of the relatively dehydrated epidermis and the viable dermis.<sup>13</sup> Because of that theory, Transfersomes should not be applied under occluded conditions, which abolishes the osmotic effect. Several drugs encapsulated in Transfersomes (eg, nonsteroidal antiinflammatory drugs [NSAIDs] and local anesthetics) have been tested in animal experiments and showed increased dermal delivery and clinical effect when compared to conventional formulations.<sup>12</sup>

### Ethosomes

Ethosomes are nanocarriers made of phospholipids, ethanol at a high concentration (20–50%), and water. They can deliver drugs to the deep skin layers and the systemic circulation. Ethosomes have a much higher loading capacity of lipophilic drugs as compared to classic liposomes. A clinical trial showed that treatment with ethosomal encapsulated acyclovir significantly improved a herpetic infection when compared to treatment with the traditional Zovirax (GlaxoSmithKline, Brentford, UK) cream with the same concentration of active drug. Insulin-loaded ethosomes have been found to be suitable for systemic transdermal delivery, and the antibiotic bacitracin has likewise been encapsulated in ethosomes and reaches the deep layers of the skin in animal experiments. Ethosomes may play a role in future transdermal drug delivery.<sup>14</sup> Examples of cosmetics using ethosomes are Lipoduction (Osmotics, New York, NY) and Noicellex (Novel Therapeutic Technologies, Inc., Wilmington, DE).

### Niosomes

Niosomes consist of non-ionic surfactant vesicles and are an alternative to liposomes. They can entrap both hydrophilic and hydrophobic chemicals, enhance delivery to the skin, and sustain the release of the drug. A phase I and II study in psoriasis patients concluded that MTX-

loaded niosomes are more efficacious than marketed MTX gel.<sup>2</sup>

### Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) were developed in the 1990s and are produced by replacing the liquid lipid in an oil-in-water emulsion with a lipid that is solid at both room and body temperature. The incorporation of pharmaceuticals and cosmetics in SLNs is feasible and can easily be formulated in a cream.<sup>15</sup> An advantage of SLNs compared to conventional creams is an increase in skin hydration owing to a better occlusive effect by SLNs.<sup>16</sup> Burst or sustained release of incorporated ingredients has been reported, as well as increased percutaneous absorption as compared to conventional formulations; this is probably due to the unique composition of the SLN and incorporated ingredient. Examples of pharmaceuticals formulated in SLNs are podophyllotoxin, antimycotics, NSAIDs, psoralen, and topical glucocorticoids. No human studies with pharmaceuticals incorporated in SLNs have been performed yet, but more than 30 cosmetic products containing SLNs were marketed in 2008.<sup>17</sup> No side effects have been reported.

### Nanoemulsions

Nanoemulsions consist of two phases, with droplets of 50 to 100 nm in the external phase. Emulsifiers that are used to bind together oil and water in products such as hair conditioners and makeup removers yield a less oily mixture when they are broken down into nanoparticles. Nanoemulsions are used in both rinse-off and stay-on products. Opposing results are obtained on the relation between emulsion droplet size and the depth of dermal penetration of the active ingredients. Nanoemulsions increase the transdermal bioavailability of vitamin E,<sup>18</sup> but penetration of tetracaine from nanoemulsion is not affected by a droplet size of 100 to 3,500 nm on the skin.<sup>19</sup> Different emulsion components have been used, and other authors have found increasing transdermal penetration with decreasing droplet size. There is so far no simple relationship between chemical, particle size, and penetration, and each new emulsion carrying different active ingredients must be investigated separately to ascertain its skin penetration pattern.

### Nanospheres

Nanospheres are produced from different polymers (eg, polycaprolactone, a biodegradable product widely used in

the cosmetic industry). When produced, the polymer wraps around itself, creating lipo- and hydrophilic spaces. Several drugs have been incorporated in nanospheres,<sup>20</sup> as have cosmetic ingredients.<sup>21</sup> L'Oréal (Paris, France) has developed a nanocarrier system called Nanosome, which consists of the biodegradable polymer polycaprolactone; other cosmetic companies have developed similar products. Polycaprolactone nanoparticles loaded with the lipophilic dyeing agent nile red showed enhanced penetration of the molecule into the stratum corneum layers (up to 60  $\mu\text{m}$ ) as compared to non-nanoparticle formulations.<sup>22,23</sup> The distribution of another topically applied nanosphere nile red formulation was studied in human cadaver skin with cryosectioning and fluorescence microscopy by Sheihet and colleagues.<sup>24</sup> Permeation analysis revealed that the nanospheres delivered nine times more nile red to the lower dermis than a control formulation using propylene glycol did. Few articles have been published about penetration and absorption in skin and the clinical effect of carrier molecules manufactured by cosmetic companies.

### Dermatitis Related to Exposure to Products Containing Microvesicles

Few case reports have suggested that microvesicles in topical products may have been involved in the development of allergic contact dermatitis. Propyl gallate incorporated in liposomes has been suggested to boost the allergic potential of propyl gallate in 13 patients; however, patch tests with and without the liposomal formulation were not performed.<sup>25</sup> Another case report described a woman who developed severe allergic contact dermatitis from an antiwrinkle cream containing retinyl palmitate encapsulated in polycaprolactone.<sup>21</sup> Polycaprolactone is a polymeric drug delivery system capable of encapsulating lipo- and hydrophilic agents. Retinyl palmitate is a rare contact allergen, and diagnostic patch tests revealed that the patient reacted more strongly to encapsulated retinyl palmitate than to retinyl palmitate in petrolatum, even though the retinyl palmitate concentration was much lower when formulated in polycaprolactone when compared to the petrolatum formulation (Fig 1).

### Enhanced Allergenicity of Compounds Encapsulated in Microvesicle Formulations

Increased sensitization response was found by local lymph node assay (LLNA) when dinitrochlorobenzene and isoeugenol encapsulated in ethosomes were compared to

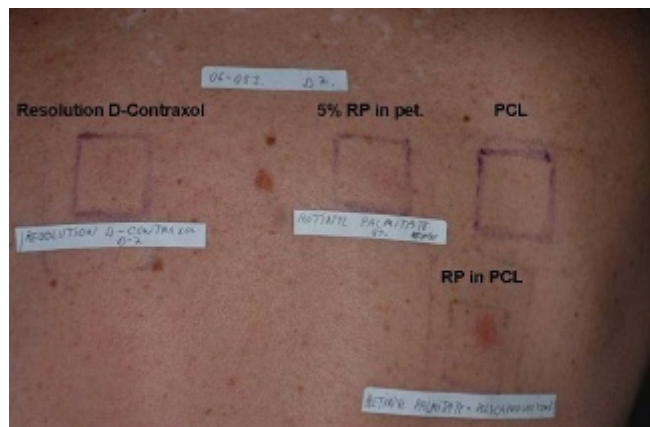


**Figure 1.** Patch-test results of retinyl palmitate in petrolatum, encapsulated retinyl palmitate in polycaprolactone, and pure polycaprolactone. Retinyl palmitate 5% in petrolatum yielded a + reaction; polycaprolactone, a negative reaction; and retinyl palmitate in polycaprolactone, a ++ reaction. Note that retinyl palmitate in polycaprolactone is at a lower concentration than retinyl palmitate in petrolatum. Encapsulating retinyl palmitate in polycaprolactone increased the strength of the patch-test reactions. (PCL = polycaprolactone; pet = in petrolatum; RP = retinyl palmitate.)

formulations without ethosomes.<sup>26</sup> Controlled patch-test experiments in selected sensitized volunteer patients and using ethosomes loaded with methyldibromoglutaronitrile or isoeugenol showed enhanced patch-test responses in comparison to patch tests with the same allergens in ethanol and water (4:6) formulations, making the vesicles the only difference.<sup>27</sup> Vehicle effects on both sensitization and elicitation responses in experiments using LLNA and human volunteers as test subjects were previously reported.<sup>28,29</sup> However, the effect of new encapsulating vehicles on product allergenicity is rarely studied. The particles in these experiments exceeded the 100 nm size limit for nanoparticles. However, particles larger than 100 nm also may show size-specific properties; for example, liposomes of 120 nm penetrate human skin to a greater extent than do liposomes of 810 nm.<sup>30</sup> So far, no reports have suggested that vesicles of nanosize range increase the skin penetration of encapsulated compounds as compared to similar formulations without the nano-sized vesicles.

## Conclusion

The dermatotoxicologic risk from skin exposure to micro-vesicle carrier systems is considered to be low. No general rules can be determined from the reported experiments, and risk assessment should be done on a case-by-case basis. Given the limited information available, it is important that dermatologists be aware of the use of encapsulation technology in products that cause contact dermatitis as

encapsulation of product ingredients may affect allergenicity in some cases. Whether a product contains micro-vesicles may be difficult to ascertain if it is not mentioned on the label. Words such as “nanosphere,” “liposome,” and “encapsulated” can be looked for, but often these words appear not on the label but rather in the marketing folder. Based on information from the manufacturers or other sources, the Web site <[www.nanotechproject.org](http://www.nanotechproject.org)> lists consumer products that use nanotechnology and different carrier technologies. The list is far from complete but can be helpful. Dermatologists investigating patients with allergic reactions to consumer products that use encapsulation technology should consider the risk of false-negative results when testing with ingredients in conventional patch-test vehicles. It is important to collaborate with the manufacturer; manufacturers can sometimes provide dermatologists with samples of encapsulated compounds for patch testing.<sup>21</sup> Whether these new formulation systems really pose a risk for consumers in regard to allergic skin reactions from the use of topical products using this technology is not documented so far, but experimental data show that such a risk is possible. Dermatologists are urged to look for dermatitis patients with possible allergic skin reactions from topical products using nano- or microvesicle technology and to be aware of the importance of patch-test vehicles.

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