KEYWORDS: liposomes, niosomes, polymeric micelles, solid lipid nanoparticles, nanoemulsions, cyclodextrin complexes

Abstract

Delivery systems are chemical agents that carry the active compounds to the site of their action. They are used in cosmetics mainly for their ability to improve the stability of sensitive actives, their better incorporation into formulations, reduction of irritation potential, excellent penetration and sustained release properties. The most commonly used delivery systems include liposomes, niosomes, microemulsions and nanoemulsions, micro and nanoparticles, polymeric micelles and cyclodextrin complexes. Their properties and effects are different and each system is suitable for different types of compounds. Delivery systems are widely used for the incorporation of anti-aging compounds, such as whitening agents, plant extracts, antioxidants and vitamins, as well as for UV filters and fragrances.

INTRODUCTION

Delivery systems are chemical agents carrying active compounds to the site of their action. They usually contain anti-aging compounds (vitamins, whitening agents, antioxidants), UV filters or fragrances. They may also be applied in hair care cosmetics as carriers of nourishing agents, dyes, conditioners, humectants, deodorants, and as antistatic agents. They are frequently used in cosmetics because of their properties, including:

- stability improvement of the active compound (protection from sunlight or exposure to air and the compound’s improved resistance to elevated temperatures)
- a change in the active compound’s penetration properties (the controlled, sustained or delayed release of the active compound at a specific time and site and to the required depth)
- protection from the interactions with various substances in the formulation (prevention of contact between incompatible substances in the formulation)
- a change in the form of the active compound (a solution of limited solubility, incorporation or application of a substance)
- the improved tolerability of the skin to the substance (minimization of the concentration of the active compound in the epidermis and dermis, thereby reducing the risk of irritation)
- the improved aesthetics of the formulation
- the masking of unacceptable properties of the substance (a change of colour or the elimination of the unpleasant odour) (1).

The aim of this review is to present an overview of the most commonly used vehicles and carriers for cosmetic purposes.

DELIVERY SYSTEMS USED IN COSMETICS

The most commonly used delivery systems include vesicular delivery systems (liposomes and niosomes), emulsion delivery systems (microemulsions and nanoemulsions), particulate systems (microparticles, nanoparticles, polymeric micelles and solid lipid nanoparticles) and cyclodextrin complexes (2).

Liposomes

Liposomes are vesicular delivery systems with a centre consisting of an aqueous cavity which is surrounded by one or more hydrophobic bilayer membranes composed of phospholipids. The diameter of these vesicles can vary in range from 25 to 5000 nm. The main reason why liposomes are widespread in cosmetics is their ability to encapsulate both hydrophilic and hydrophobic molecules, the improvement of active ingredient absorption by the skin, and the easy method of their preparation. In addition, they can also provide controlled release profiles for many substances (3-5).

The advantage of encapsulating compounds with different solubility was employed in 2013 by Liu et al., who used two preparation methods, thin film hydration and reverse-phase evaporation, to obtain a liposome delivery system co-encapsulating the lipophilic UV filter avobenzone and the hydrophilic whitening agent arbutin. In permeation studies, it was found that arbutin permeated through the membrane into the receptor chamber while avobenzone remained in the donor chamber or accumulated in the membrane. Therefore, an ideal state was achieved – arbutin was able to reach into the deeper layers of the skin to enhance the whitening effect, while avobenzone remained at the surface to protect the skin from sunlight (6).
Efforts to encapsulate another UV filter, octyl methoxycinnamate (OMC), in the liposomal delivery system were made by Mota et al., who evaluated the efficacy and safety of this nanosystem in comparison with free OMC in the formulation. The results showed that the liposome system with OMC had no irritating effects and that the SPF [sun protection factor] was higher than the OMC free formulation. Furthermore, decreased release of OMC from the formulation and increased absorption of OMC in the upper layers of the skin occurred. Therefore, it was concluded that encapsulating UV filters delivers greater sunscreen safety and efficacy (7).

Liposomes are also able to improve the stability of certain ingredients, as shown by Lee C.H. et al. with astaxanthin, a powerful antioxidant used in cosmetics as an anti-aging agent. They encapsulated this sensitive compound into liposomes which improved its light and thermal stability and increased its possible application in cosmetics (8). As with the other delivery systems, there is an effort to keep improving and innovating liposomes as well. For instance, in 2013 Park et al. prepared and evaluated a special two-step delivery system. Ceramide liposomes were incorporated into cellulose hydrogel and a so-called liposome-in-hydrogel complex was prepared to enhance the transdermal permeation of the widely used antioxidants quercetin and rutin. It was found that rutin had better encapsulation efficiency and in vitro release properties than quercetin. However, quercetin demonstrated greater skin permeability. Moreover, the skin permeability of quercetin and rutin encapsulated in this delivery system was found to be better than the controls (9).

Ethosomes, phospholipid-based elastic nanovesicles with high ethanol content (20-45 percent), are a new type of liposomes. Their advantage consists in increasing of the skin penetration of drugs and active cosmetic ingredients and in increasing of the stability and reduction of the skin irritation of problematic cosmetic chemicals. Ethosomes could be potential delivery systems for antioxidants such as vitamins, which are usually very unstable, mainly due to the light exposure. Koli et al. prepared special ethosomes containing vitamins, like vitamin A, C and E in their aqueous core and lipid bilayer. These ethosome formulations provided complete protection from oxidation and increased photo-stability under UVB irradiation (10, 11).

**Niosomes**

Niosomes are structurally very similar to liposomes. The difference lies in their preparation - niosomes are prepared from non-ionic surfactants which have lower toxicity and irritant potential. This property makes them good candidates as potential penetration enhancers for use in transdermal delivery. Niosomes are also more stable than liposomes, they can easily release the compounds they carry, increase the stability of encapsulated compounds, and improve the bioavailability of poorly absorbable compounds (2, 5). The penetration potential was proved by Tavano et al., who developed niosomal formulations containing the common cosmetic lipophilic antioxidants resveratrol, alpha-tocopherol and curcumin. Besides the in vitro percutaneous permeation profiles of this niosomal complexes, the effects of co-encapsulation and their antioxidant properties were investigated. The results showed that all niosomal formulations had potential in the transdermal delivery of antioxidants molecules; in vitro percutaneous permeation of antioxidants appeared to be improved with respect to the free solutions. Moreover, it was demonstrated that antioxidant combinations promoted ability to reduce free radicals. Therefore, they could be potentially used in cosmetics for the prevention of diseases caused by oxidative stress (12).

**Microemulsions**

Microemulsions are transparent, thermodynamically stable and usually low viscous dispersions of water, oil and usually surfactant and co-surfactant. The size of particles ranges between 10 and 100 um. Therefore, microemulsions appear as isotropic, optically clear liquids or gels. They are more stable than common emulsions, placing them among attractive cosmetic delivery systems. On the other hand, a higher concentration of surfactants and co-surfactants (20-25 percent) is needed for their preparation, which can cause increased irritation of the skin (13). As microemulsions demonstrated transdermal permeation, they are used in formulations for topical applications, such as skin or body care moisturizers, hair care formulations or clear gel antiperspirants and deodorants. Due to their non-sticky, easily spreadable and good permeation properties they are suitable vehicles for sunscreen agents, such as 4-methylbenzylidene camphor and octylmethoxycinnamate, as proved by Carlotti et al. (14). Microemulsions were also shown to be suitable vehicles for the whitening agent hesperidin. A hesperidin-loaded microemulsion reported enhanced in vitro permeation, a significant topical whitening effect, and diminished skin irritation (15). In addition, also vitamins can be incorporated into microemulsions, as was shown earlier with sodium ascorbyl phosphate. In this study, the stability of o/w and w/o microemulsions containing this vitamin was evaluated and compared to the stability of ascorbyl palmitate. After its incorporation, sodium ascorbyl phosphate was found to be stable in both types of formulations and had better permeation properties (16).

**Nanoemulsions**

Nanoemulsions are clear, kinetically stable isotropic mixtures of oil, water, surfactant and co-surfactant, with a droplet diameter of less than 100 nm. They are characterized by good sensorial and biophysical properties. The advantage of nanoemulsions is that they need a lower quantity of surfactants for preparation (only 5-10 percent) than microemulsions. On the other hand, the nanoemulsion manufacturing process is more expensive, because special techniques and equipment are needed. Nanoemulsions are mainly used in the preparation of skin care and hair care products, where their ability to improve transdermal and dermal penetration is used (2, 3). This effect was confirmed by Mahdi et al., who developed a nanoemulsion cream for the topical delivery of 30 percent ethanolic dried extract from Phyllanthus urinaria, which is used as skin anti-aging agent, and evaluated in vitro release and its radical scavenging activity. The results showed that the prepared nanoemulsion can penetrate the skin easily to deliver P. urinaria extract and can neutralize reactive oxygen species, and therefore counteract oxidative injury induced by ultraviolet radiation (17). Regarding hair care formulations, Hu et al. investigated the stability of possible o/w nanoemulsion containing...
silicone oil and its effect on improving deposition on the hair surface, because it is difficult for silicones to be directly absorbed on the hair due to their hydrophobicity. This effect is important mainly because of their ability to provide conditioning benefits for hair. It was demonstrated that the deposition of the silicone oil on hair was greatly improved by oil-in-water nanoemulsions. Thus, these nanoemulsions can be promising formulations for hair care applications (18).

**Microparticles**

Microparticles are solid polymeric particles ranging in size from 1 to 100 μm. They are formed from a core and membrane consisting of organic polymers, fats, proteins, polysaccharides, etc. They can be used in cosmetics for the protection of sensitive compounds from the environment, as proved by Scalia and Mezzena with photo unstable agents (19); and for compatibility improvement and unfavourable-odour reduction. According to Jain et al. (20) microparticles are suitable delivery systems for sunscreen agents. This was shown by Scalia et al., who used lipid microparticles as vehicles for the most widely used combination of UVA and UVB filters, ethylmethoxycinnamate (EHMC) and butyl methoxydibenzoylmethane (BMDBM). An in vivo evaluation was conducted to determine whether the encapsulation of these sunscreen agents could affect the percutaneous penetration. The results showed that the incorporation of BMDBM and EHMC UV filters into lipid microparticles decreased their penetration into the stratum corneum when compared with the non-encapsulated controls. This effect preserves the protective capacity of the UV filters by retaining them on the skin surface, and also limits potential toxic reactions. Moreover, encapsulation means that a lower concentration of UV filters is required in the formulation (21).

**Polymeric micelles**

Polymeric micelles, with typical diameters ranging from 10 to 100 nm, are nanoscopic core-shell structures formed by amphiphilic block copolymers. The inner core is composed of hydrophobic regions of amphiphiles, where the lipophilic drugs are being solubilized. The core region is surrounded by a palisade or corona composed of hydrophilic blocks of amphiphiles. Polymeric micelles are often composed of polyesters or polyamin acids covalently bonded to a biocompatible hydrophilic block, typically PEG (polyethylene glycol) (22).

In order to achieve the increased safety of delivery systems, innovative polymeric micelles are being developed. An example might be novel micelles composed of modified hyaluronic acid (HA), with joined hydrophobic functional groups which allow loading of small molecules of hydrophobic compounds. The advantage of these micelles is their ability to deliver the agent to the required site and to increase hydration of the skin due to their HA nature (23).

**Solid lipid nanoparticles**

Solid lipid nanoparticles (SLN) are novel colloidal carriers with a particle size ranging from about 40 to 1000 nm. They were developed as an alternative carrier system to emulsions, liposomes and polymeric micelles. They are composed of 0.1 percent to 30 percent solid lipid dispersed in an aqueous medium and are stabilized by 0.5-5 percent surfactant. Second-generation nanoparticles are called nanostructured lipid carriers (NLC). They were developed to overcome potential limitations associated with SLN, which are lower loading capacity for active compounds, higher water content of the particle suspension or increased potential to expulsion of active compounds during storage. In cosmetics, NLC provide controlled release profiles for many substances. Due to their lipid composition, they exhibit low toxicity and cytotoxicity, which translates into excellent tolerability. Their small size ensures close contact with the stratum corneum and can increase the amount of the drug penetrated into the skin. Moreover, they are able to improve the chemical stability of compounds sensitive to light, oxidation and hydrolysis. Lipid nanoparticles also have occlusive properties, which can increase the skin hydration effect (24). Therefore, nanoparticles are suitable carriers for various cosmetic compounds, such as UV filters, as shown by Nikolic et al. They developed and evaluated sunscreen formulations based on lipid nanoparticles. Increased SPF values of organic UV filters incorporated into NLC were demonstrated. Furthermore, a lower concentration of UV filters in the formulation was needed, which diminished the irritation potential. The synergistic effect of NLC and incorporated sunscreens depended on the solid state of the lipid and on its type (25).

**Cyclodextrin complexes**

Cyclodextrins are cyclic α-1,4-glucans composed of six to more than 100 glucose units. A cyclodextrin molecule has a hydrophilic outer surface and hydrophobic internal cavity. As a result, inclusion complexes can be formed with a wide range of molecules, however very highly aqueous soluble substances cannot be included (26, 27). Cyclodextrins and their derivatives can increase the solubility and stability of drugs, they protect against oxidation, photolytic and thermal degradation and decrease the risk of compound incompatibility in a formulation (27). Cyclodextrins are particularly suited for UV filters. It was proved that they helped to decrease penetration of sunscreen agent butyl methoxydibenzoylmethane into the stratum corneum which enhances its protection and limits potential toxic reaction (28). Cyclodextrins might be used also as vesicles for anti-acne agents, like isotretinoin. The results showed the significant reduction in skin irritation potential in comparison to free drug (29). Using cyclodextrins for fragrances demonstrated Numanoglu et al. The results showed that inclusion complexes of linalool and benzyl acetate with 2-hydroxypropyl-β-cyclodextrin significantly increased the water solubility of these materials. The controlled release and increased stability of compounds was also achieved. Moreover, through the complexation process, liquid fragrances could be obtained in powder form, which improved their handling properties (30).

**CONCLUSION**

The use of various types of delivery systems in cosmetics is becoming ever more popular, primarily on account of growing efforts to achieve the greatest possible effect of the active compounds. Developments in this area are making rapid headway. Efforts are focusing on the
development of entirely new systems and on innovating or combining some existing systems. Thus, compounding the resultant effect of the loaded substances is more increased. One of the greatest benefits of the delivery systems is that they are able to penetrate the stratum corneum in the case of carrying an active compound that needs to reach deeper layers of the skin. At the same time, they have the capacity to retain other substances that are not intended to penetrate the skin’s surface. Therefore due to such properties their safety and biocompatibility need to be achieved.

REFERENCES AND NOTES
