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NANOMATERIALS AND COSMETICS

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SUMMARY

This review has overviewed the nanotechnology approaches and safety concerns in cosmetics. Nanotechnology based nanomaterials have been widely use in cosmetics for recent few years such as in sunscreens, hair products, skincare products, etc. However debate on their definition and insufficient quantification methods are major problems still occur in the nanomaterial field. Moreover the frequent use of cosmetics, safety of nanoscale ingredients of them has gain importance mainly by means of their dermal exposure. Although the proposed benefits that may occur by incorporating nanoparticles in cosmetics are increased efficiency, transparency, unique texture, protection of active ingredient, and overall higher consumer compliance, there still have not enough studies proved whether they are completely safe or not. As a conclusion major issues related nanomaterials such as developing, using and researching is going to increase in the near future due to their economically importance.

Key words: Nanotechnology, nanomaterial, dermal, safety, cosmetics.

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INTRODUCTION

Scope of cosmetics in general in the world is the products that are mainly use for cleansing, beautifying, perfuming, or changing the appearance of human body without causing any damage to human health. Recent years, naturel ingredients, combine clinically proven ingredients with patented delivery systems and the nanomaterials in cosmetics have been come into vogue (1-3). Among them nanomaterial containing cosmetics highly increased in the market all over the world. Although there is still an on-going debate for definition of nanomaterials, the particle size is still accepted as the main criteria with a range between 1 and 100 nm to identify them (3). In this context for a better understanding of nanomaterial objection in cosmetics, in this review initially nanomaterials by means of pharmaceutical evaluation and application are given, then nanomaterial approaches in cosmetic related researches and finally safety concerns related to nanomaterial use in cosmetics are scrutized.

PHARMACEUTICAL NANOMATERIALS

In case of particle size approaches in the range between 1-100 nm; there may be an important change in the crystal structure due to an exponentially growing number of atoms being localized at the surface and it is suggested to complement the current size range with a limiting volume specific surface area value of not less than 60 m^2/cm^3 (3,4). Also there is another suggestion that ''one-size-fits-all'' definition of nanomaterials should be abandoned altogether (3,5). Nevertheless particle size or specific surface area is that the values derived by various methods are highly dependent on the method of choice, and none of the method can be used as a best standard (3,6-8). Though there has not been any best method indicated for nanomaterial identification in cosmetics, nanomaterial characterization can be accomplished by using a variety of different techniques drawn from interdisciplinary areas. A summary of investigative methods for nanoparticle characterization is listed in Table 1 (8).

Table 1. Investigation methods for nanoparticles characterization (8).

Method or Equipment	Measurement Consideration
Laser Light Scattering System/ Particle Size Analyzer	Measurement of particle size and size distribution of nanoparticles in liquid solutions or suspensions
Zeta Potential Analyzer	Measurement of surface charge of nanoparticles in aqueous solutions or suspensions
Scanning Electron Microscope (SEM)	Examination of the consistency of nanoparticle's surface and the shape of nanoparticles
Transmission Electron Microscope (TEM)	Determination of surface property and shape morphology of nanoparticles
Atomic Force Microscope (AFM)	Measurement of the shape and surface morphology (including friction and softness) of nanoparticles with high lateral and vertical resolutions
Laser Scanning Confocal Microscope (LSCM)	Non-invasive measurement of nanoparticle's morphology in 3D, investigating the migration of nanoparticles into bio-barrier
Surface Area Analyzers and Pore Size Analyzer	Determination of single and multipoint surface-area analysis, multigas capability and full adsorption capability for nanoparticles
X-Ray Photoelectron Spectroscope (XPS, ESCA)	Providing important chemical composition (both elemental and chemical state) information on nanoparticle's surface
Fourier Transform Infrared Spectroscope (FTIR)	Assisted analytical tool for chemical composition of nanoparticle's surface
Differential Scanning Calorimetry (DSC)	Providing thermal analysis (and component interactions) of nanoparticles and related materials during fabrication process
High Performance Liquid Chromatography (HPLC)	Detection, separation and quantification of nanoparticles/ nanomaterials with different particle size

Understanding of nanomaterial interaction with the environment in combination with the route of exposure will provide useful information on nanoparticle biological fate and toxicity. For instance, the penetration of nanoparticles through the skin, their biodistribution, rate of excretion and toxicity are determined by the nanoparticle's characteristics (e.g., shape, size, surface charge, surface composition, coating, type of materials, and other

components in the nanoparticle's formulations) (8). By means of penetration and absorption of cosmetics, the stratum corneum and hair folicules are important components of the skin. Diffusion through the lipid layers of the stratum corneum has long been seen as the sole penetration pathway for topical applied substances (7) and hair follicles act as a depot for applied substances, thus increasing the storage capabilities of the stratum corneum (9,10) that can reach ten times longer within the reservoir of the follicular infundibulum than in the reservoir of the stratum corneum (9,11).

In general particles size of 50–500 nm is widely used in cosmetics and the concentration of nanoparticles in formulations is less than 3% (12). In addition to concentration, their dispersion in the product makes nanoparticles more active and when agglomerated their properties result from their size such as color and transparency have changed. Therefore it is important to control their agglomeration behavior and dispersed nanoparticles are needed in order to retain their specific properties for the technological applications (Figure 1) (12).

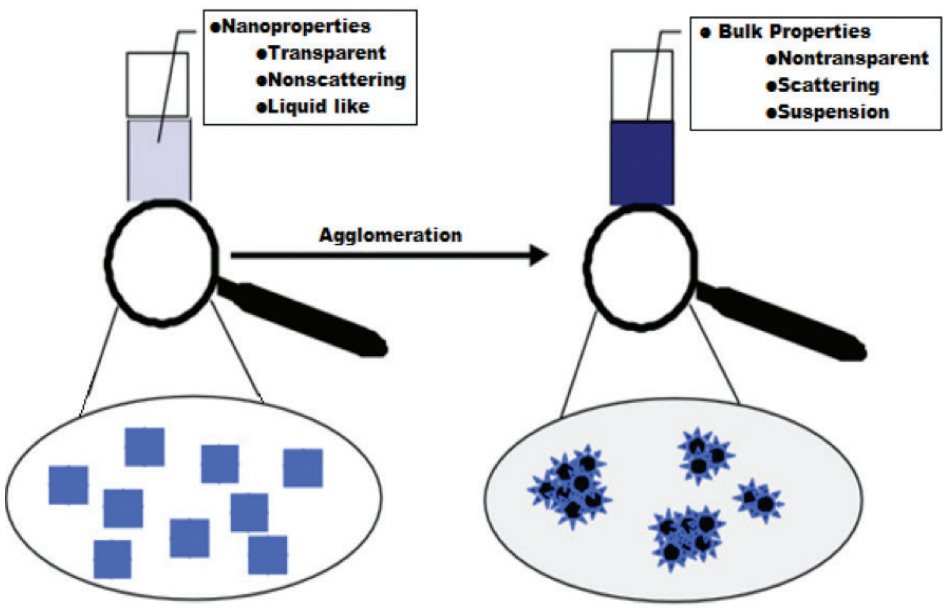

Figure 1. Dispersed nanoparticles are needed in order to retain their specific properties for the technological applications (12).

Such a technological application, widely used multiphasic nanoemulsions (micellar nanoparticle formulations in particular) prepared by mixing and milling process (high-shear or high-pressure mixing) resulted as active pharmaceutical ingredient (API) which can be an active cosmetic ingredient presents in one or more composite fractions such as solid particulates (micro/nanoparticles), micelle-associated, oil-associated or solubilized (in aqueous and/or solvent medium) (Figure 2). Following application to the skin, deposition of the micellar nanoparticle formulation within skin layers can be imagined as the model presented in Figure 3 (13). The composite structures within the micellar nanoparticle formulation are complementary to the skin structure could be this facilitates stratified positioning of the API within different skin layers (13).

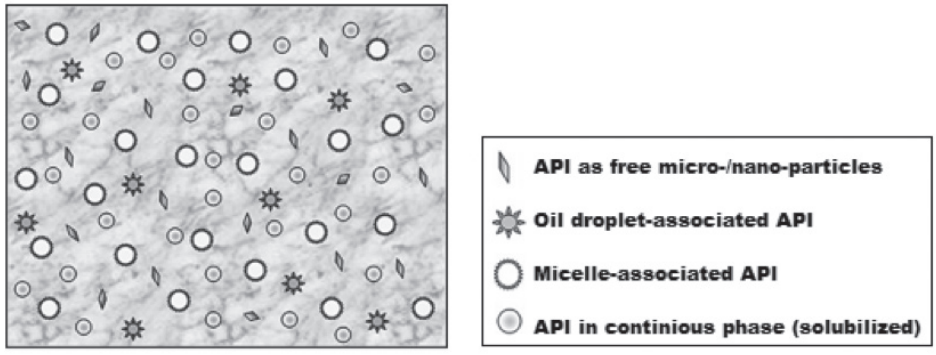

Figure 2. Schematic representation of the micro/nanostructures within a micellar nanoparticle formulation showing the different API components (13).

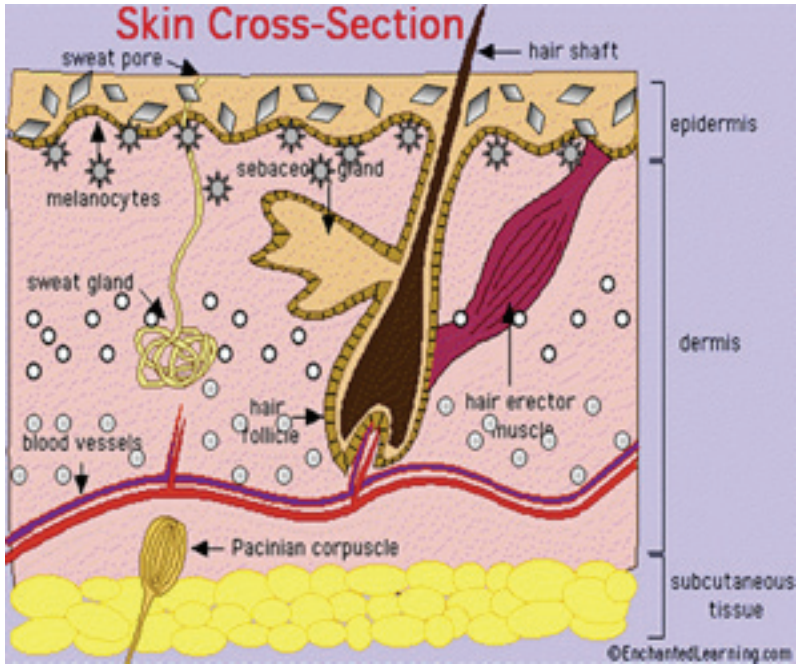

Figure 3. Schematic representation of deposition and disposition of micellar nanoparticle structures within skin layers showing stratification of API (13).

Based upon cosmetics incorporating nanotechnology has appeared considerably on the consumer market over the past few years (6-8), many manufacturers of the skincare products (e.g. creams, lotions, beauty essences, etc.) use ultra-high-pressure emulsification and other techniques to make their active ingredients down to tens of nanometers, which are smaller than the gaps between the skin cells in the corneum layer (70 nm), with an attempt to improve their skin permeability and absorbability (7). Nanoparticles used in drug delivery systems are of interest to the cosmetic industry. Examples include nano-encapsulation vesicular delivery systems, nanoemulsions and nanocrystals, liposomes and niosomes, micelles, polymeric nanocapsules, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC), carbon nanotubes and fullerenes, and dendrimers, etc. (8). Some of the proposed benefits that may occur by incorporating nanoparticles in cosmetics are increased efficiency, transparency, unique texture, protection of active ingredient, and overall higher consumer compliance (6). Furthermore

nanoparticles provide improved stability of chemically unstable active ingredients, controlled release of active ingredients, pigment effect and improved skin hydration and protection through film formation on the skin. Due to their good physical stability and compatibility nanoparticles can be added with other ingredients to cosmetic formulations without any problem. Accordingly by using nanotechnology amount of molecular sunscreen could be decreased by 50% while maintaining the protection level as compared to a conventional emulsion. (1,14). Such an example, larger particles of titanium dioxide and zinc oxide are white and opaque but at the nanoscale, these substances become transparent thus enables their use in moisturizers and foundations having sunscreen effect. As another example nanoparticles of aluminum oxide provide a ‘‘soft focus’’ effect that disguises wrinkles and used in high-end concealer sticks, foundations, and face powders. Carbon ‘‘fullerene’’ nanoparticles are used in anti-ageing creams and moisturizers partly because these tiny nanoparticles penetrate skin so effectively. Hereby, cosmetics industry uses nano-scale ingredients routinely (6).

There are many types and shapes of materials such as polymers, lipids, metals and ceramics have been used to produce nanoparticles. Nanoparticles can be divided into organic and inorganic or they can be classified according to their shape, size, surface charge and physicochemical properties. Nevertheless, from the point of view of particle interactions with biological surfaces and barriers like skin, it may be useful to distinguish between soft and rigid particles. In general, soft particles are made of organic materials (e.g., lipids, proteins, polymers) and can temporarily alter their shape by stress or contact with surfaces, while rigid particles are made of inorganic materials and are not deformable. It might seem that any kind of a nano-sized particle, be it of “simple organic” (e.g. a dendrimer), complex organic (e.g. an aggregate made of amphipaths), or inorganic (e.g. a metallic or mineral particle) origin can meet the above mentioned criterion (15).

Some of the most common soft and rigid nanoparticles proposed in dermal applications and cosmetics are described below.

Soft particles

Oils and amphipaths in polar solvents (including water) spontaneously form a plethora of structures: micelles, cubic phases, microemulsions, hexagonal phases, vesicles, etc. (15) as soft particles. Liposomes are typical soft deformable particles. They are vesicular structures composed of a

phospholipid bilayer and a hydrophilic core. Hydrophilic and lipophilic substances can be integrated into the core or the shell, respectively and liposomes penetrate deeper into the hair follicle canal than other non-particulate formulations (9,16). Conventional pharmaceutical liposomes have stiff bilayers (to prevent undesirable active substance leakage), are nearly spherical and normally have an average diameter above 75 nm. Conventional fluid bilayer liposomes therefore cannot trespass pores <30 nm (15).

SLN and NLC were developed to create more stable systems. They lack the micelle structure of the liposomes and are therefore more stable in hydrophilic as well as lipophilic environments, allowing the safe transport and delivery of various substances to skin both for pharmaceutical and cosmetic purposes (9,17-21).

Fullerene derivatives (22,23) and dendrimers (24,25) are supramolecular structures with dimension of few nanometers and therefore can be considered as nanoparticles. Fullerenes have been investigated for their ability to absorb UV light and their radical scavenging properties (22,23). Dendrimers were first synthesised in 1978 and are essentially nano-sized. Because of their excellent carrier properties, dendrimers have utility in cosmetics and personal care products such as hair-styling gels, shampoos, sunscreens, and anti-acne products (25). Star-burst like macromolecules as skin permeation enhancers that seem lower generation cationic dendrimers enhance skin permeability better than large dendrimers (15,26). Poly(amidoamine) dendrimers have also been used as skin penetration enhancers (9,26).

Nanoemulsions are emulsions having small droplet size (20–300 nm). Nanoemulsions containing droplets above 100 nm look white, whereas dispersions around 70 to 100 nm appear opaque and below that become transparent (1,27). A nanoemulsion can nonetheless “survive” long before changing, e.g. into a coalesced form. Shearing, especially in the high concentration range, accelerates physical deterioration of any nanoemulsion. This may be problematic if a concentrated nanoemulsion is squeezed through a nano-porous membrane, such as skin (28). Multiple nanoemulsions are in the nano range and allow the application of several incompatible substances at the same time (1,29).

Nanocrystal technology is an attrition process that large micron size crystals are media milled in a water-based stabilizer solution and generates physically stable dispersions consisting of nanometer-sized substance

crystals. It can be utilized for development of cosmetic formulation of flavonoids, sunscreens, etc. (1,30-32). Nanocrystals are reported that they can increase the penetration of poorly soluble cosmetic substances into skin due to increased saturation solubility increases the concentration gradient (33,34).

Cubosomes are bicontinuous cubic phases, consisting of two separate, continuous and periodic structures results in a very high viscosity of the bulk cubic phase. However, cubosomes prepared in dispersion maintain a nanometer structure identical to yield a much lower, water-like viscosity. Compared with liposomes, cubosomes have much higher bilayer area-to-particle volume ratios. The cubic phase is strongly bioadhesive; thus, it may find applications in flavor release. Even more recent patent activity by points to cubosome used in personal care products as varied as skin care, hair care, cosmetics, and antiperspirants (35). They have ability to incorporate lipophilic, amphiphilic, and watersoluble cosmetic molecules (1, 35, 36).

Rigid particles

Typical rigid particles are colloidal structures of various shapes and made of various materials such as metals (e.g.,gold, silver), metal oxide (e.g., iron oxide) or ceramics (e.g., silica). The encapsulation of active substance in the nanoparticle core or their adsorption on nanoparticle surface allows the transfer and delivery of them avoiding metabolism and degradation in tissue. Quantum Dots (e.g.,CdSe) are new nanocrystalline semi-conductor materials with unique spectroscopic and optical properties can be used for detection and imaging of mentioned nanostructures (9,37). Surface functionalization of particles improves particle properties such as surface charge and colloidal stability, bioavailability as well as active substance carrying and targeting abilities (9).

Metallic nanoparticles are naturally long-lived. Moreover such particulates are monodisperse and mechanically hard. Nanoparticles therefore cannot cross pores comparable to or smaller than their own diameter. If exposed to dryness they tend to coalesce and then, or otherwise, may shed their stabilizing surfactants into ambient solution (15,38).

Deliberate epicutaneous use of nanoparticles dates back at least to the introduction of the first modern sun-blockers several decades ago. Epicutaneous pharmacological applications that are all based on organic

particles sometimes focus on minimising the depth of cutaneous penetration as well (15,38-40), but otherwise seek to enhance skin permeation (15,20), mainly via a (semi)occlusive superficial film formation (15,21,41,42).

NANOMATERIALS USE IN COSMETICS

By the reason of sun exposure and UV radiation have been correlated with the increased incidence of epithelial skin cancer and melanoma, sunscreens have become important skin cancer prevention tools and their protective effect against UV radiation-induced oxidative stress make them important components of cosmetic anti-aging products. In this respect available photoprotecting methods can be use of antioxidants, stimulators of repair mechanisms and physical photon blockers (9,43).

In case of photon blockers (44-47), liposomes or SLN can be used in sunscreen formulations for this purpose and also used as penetration enhancers (44,45). Using SLN and NLC having high loading capacity as ultraviolet (UV) protector enhancers provide high sun protection factor (SPF). For NLC, UV protective efficacy of the lipid particles is indicated that depend on the nature of lipid and UV wavelength (45). In a study investigated the protection efficacy of topically applied substances showed that particle size is important and increase the homogeneity of distribution and, thus, the protection efficacy is significantly increased (46). Influence of nonhomogeneous distribution of topically applied UV filters on sun protection factors has been investigated by Lademann et al. and it was reported that direct correlation of homogeneity of distribution with the SPF opens up the possibility to increase the SPF by optimizing the formulation, thus homogeneity of the distribution on skin surface is a necessary for increasing SPF (47).

Barrier function of the stratum corneum reported that could be insufficient in protecting the skin and frequent exposure to water is an important risk factor for the development of irritant hand eczema. Therefore emulsions have been used so far to satisfy protection and the better homogeneity of substances' distribution achieved with the use of particulate formulations. Enabling the coverage of the skin with a thin protective film nanoparticles have been used in new generation cosmetics (9). Early studies had already proved that particulate barrier creams are more effective than moisturizers

with high lipid content in protecting the skin from water loss and thus minimizing the potential irritations resulted as hand eczema (48). The better distribution of the solid microparticle formulation on skin surface might have resulted in a better occlusive effect than those achieved by using moisturizers (9).

Carboxyfullerenes reported that act as free radical scavengers in many cell settings and prevent apoptosis in vitro and in vivo, for this reason Chirico et al. have been clarified protection ability of carboxyfullerenes for normal human keratinocytes from UVB induced apoptosis and results indicate that carboxyfullerenes penetrate human keratinocytes, localize within mitochondria where they act both by scavenging free radicals and by protecting cells from apoptosis by using confocal laser microscopy and transmission electron microscopy (22). Certain nanoparticles possessing antioxidative properties have been proposed as components of anti-aging cosmetic products. Such a nanoparticle, fullerene-C60 was prepared in squalene to obtain LipoFullerene and it has been tested for its anti-wrinkle efficacy with a clinical trial. Obtained results showed that LipoFullerene could be used as an active ingredient for wrinkle-care cosmetics. (23).

Combination of a film-forming polymer with a dendritic polymer allowed the inventors to develop a low-viscosity product that was easily applied to the intended topical skin site which allowed for better performance of cosmetics and ease of use (25). In an example of a dendrimer-molecule conjugate system, coupling of amino butadiene with an amine-rich dendritic molecule provided advantageous of UV absorbing capabilities to the final product and ease in formulating a clear sunscreen composition without developing high-viscosity gels. Accordingly ease of application to the skin and nonpenetrate into the skin due to its high molecular weight would minimize the risk of irritation or sensitization reactions (49). In a patent, amine-terminated cationic dendrimers have been reported as mildness agents for personal care cleansing formulations which act interaction of cationic dendrimers with skin-irritating anionic surfactants for reducing the skin irritation potential of cosmetic formulations containing harsh anionic surfactants (50). Some of the selected dendrimers were found to have odor-absorbing properties and were claimed as deodorant active agents. These dendrimers could be formulated in water-based antiperspirant deodorant compositions to reduce underarm odors with appreciable amounts and were found to be nontoxic

or nonirritating (51). The amine-terminal group dendrimers in addition to a tanning agent was shown to have improved efficacy and self-tanning activity on application to skin. Dendrimer-containing compositions in this case were shown to increase the intensity and quality of skin coloration produced, as well as providing a shade that was closer to a natural tan (52).

Coenzyme Q 10, also known as ubiquinone, is a cosmetic substance that can protect the skin from early aging, wrinkle formation, and loss of cell. However topical bioavailability of highly lipophilic coenzyme Q 10 is very low. Recent developments reveal that encapsulation of coenzyme Q 10 in nanoemulsions results in a significantly enhanced bioavailability (27). In addition, multiple nanoemulsions prepared according to a patented process even allow the administration of several incompatible substances at the same time. Vitamin E and coenzyme Q 10, poorly water soluble compounds, form a dark complex when mixed together; its double nanoemulsion can be successfully prepared for the cosmetic purpose (1,29).

Nanocrystals for use in topical cosmetic formulations and method of production has been patented by Peterson (31) and reported that rutin nanocrystal formulation possesses 500 times higher bioactivity of SPF compared to water soluble rutin glycoside (31). Shegokar et al. reported that both rutin and hesperidin nanocrystals increased the SPF which proves that nanocrystals increase the penetration into the skin (30). Some flavonoids have antioxidant effect but their low water solubility limit their use in formulations. Such a flavonoid apigenin was preparaed as nanocrystals by Al Shaal et al (32) and it were reported that antioxidant capacity of apigenin nanocrystals were almost doubled compared to the original coarse suspension and UV skin protective potential can be significantly increased by decreasing the particle size from micrometer to the nanometer range The developed smartCrystals can be easily incorporated into gels, which makes apigenin nanocrystals available for dermal application as efficient antioxidant (32).

Both NLC and SLN have many advantages for dermal applications and they are colloidal carriers providing controlled release for many substances. Advantages obtained for chemical stability owing to incorporation into lipid nanocarriers was proven for many cosmetic actives, e.g. coenzyme Q10 (53-55,64,65), ascorbyl palmitate (56), tocopherol (vitamin E) (57) and retinol (vitamin A) (20,58,59). Study of Farboud et al. showed that in vitro release of coenzyme Q10 from SLN and SLN cream was biphasic

in comparison with simple cream. Additional in vivo skin hydration and elasticity studies on volunteers suggested good dermal penetration and useful activity of coenzyme Q10 on skin as a hydratant and antiwrinkle cream (54). Comparison of coenzyme Q10 loaded liposomes and SLNs as dermal antioxidant carriers was studied by Gokce et al and liposomes seem to have advantages over SLN in terms of effective delivery of Q10 to skin for antioxidant purposes (53). Film formation on the skin and subsequent occlusion effect was reported for lipid nanoparticles. In addition to their controlled release characteristics, it has been found that SLN have an occlusive effect. It was reported that the extent of the occlusive effect depends on various factors such as particle size, applied sample volume, lipid concentration, and crystallinity of the lipid matrix. Consequently it was found that the highest occlusion could be reached using low melting lipids, highly crystalline particles and very small particles (60). Nanoparticles have been found to be 15-folds more occlusive than microparticles (20,61). As colloidal carrier systems SLN and NLC besides their ability to provide controlled release for many substances, Souto et al., found a higher occlusive factor for SLN in comparison to NLC of the same lipid content (62). Due to the reduced water loss caused by occlusion, the skin hydration is increased after dermal application of SLN or NLC or lipid nanoparticles-containing formulations. Since skin hydration and viscoelasticity criteria are important for development of cosmetics, Wissing and Müller performed an in vivo study investigating the skin hydration effect after repetitive application of an o/w cream containing SLN and a conventional o/w cream for 28 days. The SLN containing o/w cream provide more skin hydration compared to conventional o/w cream and SLN represent a promising compound for hydrating new cosmetic formulations (63). Teeranachaideekul et al. compared the release profile of coenzyme Q10 loaded NLC and nanoemulsion. The coenzyme Q10 loaded NLC exhibit a biphasic release pattern and NLC provided a fast initial release followed by followed by a prolonged release dependent on the oil content while the nanoemulsion showed a constant release of coenzyme Q10 over the time (64). An increase of skin penetration was reported for coenzyme Q10 loaded SLN and NLC compared to nanoemulsion and liquid paraffin or isopropanol respectively, performing a tape stripping test (20,55,65). Prolonged release of perfume from nanostructured lipid carriers (NLC) by selecting a solid lipid that can enclose the perfume in its

solid matrix provide controlled perfume release (66). Furthermore, it was found that the release of perfume depends on the lipid matrix composition, the perfume load and the surfactant type (67). It was found by Wissing et al. that SLN can act as a physical UV blocker and are able to improve the UV protection in combination with organic sunscreens such as oxybenzone which allows a reduction of the concentration of the UV absorber. Results of in vitro and in vivo tests showed that in vitro-in vivo correlations could be made qualitatively and release rate of oxybenzone is strongly dependent upon its concentration and the formulation which could be decreased by using SLN and oxybenzone penetrated into human skin more quickly and to a greater extent from the emulsions. (68,69). These findings were confirmed by Song and Lui comparing UV absorption properties combination of chemical UV absorber and chitin formed 3,4,5-trimethoxybenzochitin-loaded SLN and SLN free system3,4,5-trimethoxybenzochitin-loaded SLN act both as physical sunscreens themselves and as carriers in order to enhance the effect of UVB protection which can been observed when tocopherol was added (70). Comparing SLN with a conventional emulsion, the amount of molecular sunscreen can be reduced by 50% in the SLN formulation maintaining the protective level of the conventional emulsion (71). Furthermore, a significant increase in SPF up to about 50 was reported after the encapsulation of titanium dioxide into NLC (72). It was reported that occlusive properties of SLNs make them ideal for day creams (73). Encapsulation of inorganic sunscreens into NLC is therefore a promising approach to obtain well tolerable sunscreens with high SPF. The evaluation of the occlusive factor of the NLC dispersion used in the final product and an o/w emulsion obtained by replacing the solid lipid by Miglyol 812, at the same concentration level as in the final product, showed a five-times higher occlusive factor for the NLC dispersion than for the o/w emulsion (65). Due to their good physical stability and compatibility with other ingredients, nanoparticles can be added to existing cosmetic formulations without any problem. Alpha lipoic acid, a novel antiaging substance, is chemically labile and degradation produces unpleasant odor. Therefore, the active was encapsulated in SLN to overcome this problem (74). It was possible to increase the occlusion of a day cream by using SLN without changing its light character, i.e. achieving higher occlusive properties without having the glossy skin appearance associated with the high occlusive night creams (20).

As a rigid type of nanoparticles, Ag nanoparticles suggested that they are a safe and stable preservative which are effective against a broad spectrum of microorganisms (20).

ZnO has property of broadly filtering the UV light spectrum is an active ingredient in sunscreens. UV irradiation-induced zinc dissociation from commercial zinc oxide sunscreen and its action in human epidermal keratinocytes was investigated by Martorano et al. (75) and it was found that UVB irradiation produces an increase in Zn^{2+} dissociation in ZnO sunscreen and, consequently, the accumulation of free or labile Zn^{2+} causes cytotoxicity and oxidative stress (75). The ZnO nanoparticles obtained from sol-gel zinc acetate dehydrate were nearly spherical-flower particles with a size about 50-100 nm and exhibited excellent UV shielding and transparency properties (76).

The effect of state of nano-sized TiO_2 on the sunscreen performance study examined by UV light attenuation, product stability, and potential damage to the skin barrier showed that both nano or micro scale TiO_2 included formulations were not decreased the barrier function of the skin and the best UV attenuation occurs when the TiO_2 particles are stabilized with a coating and evenly distributed such as with non-agglomerated coated nanoscale materials (77). Nano-sized TiO_2 is also widely using in toothpastes (78, 79).

A nanoemulsifing system for cosmetics has been developed by Fratter and Semenzato which describes developing and analytical characterization of this system containing melatonin (80). Visual aspects, richness and skin feel in a great variety of products such as lotions, transparent milks and crystal-clear gels can be changed and therefore nano-emulsions were evaluated by means of their size, electrophoretic mobility, viscosity, turbidity, crystallization and melting point in a study of nanoemulsions in cosmetic matrix enriched on omega-3. Results showed that the influence of formulation on the physico-chemical properties of each nano-emulsion obtained by the mixture design (81).

Since utilization of nanogold in cosmetics accepted safe, nanomaterials synthesis of gold (nanogold) was attempted using matrix as a barrier to the growth of gold clusters by Taufikurohmah et al. (82). The growth of gold clusters resulted as nano size increase and further aggregation becomes uncontrollable thus such conditions are evident from the occurrence of large-sized sediment from the synthesis results which far exceeds the nano size.

It was reported that such a basic constituent in a cosmetic cream, synthesis uses raw materials HAuCl4 1 mM, the reducing agent Sodium Citrate 1% and matrix mono glyceryl stearate 0.2% will be an alternative (82).

In cosmetics, saturated lecithin generally refers as main surfactants used to prepare liposomes, due to its stability, but it may be substituted with unsaturated lecithin, which has excellent skin affinity and penetration properties. In this respect the study of Kang et al., indicated that unsaturated lecithin is more suitable than saturated lecithin when preparing nano-liposomes (83).

In summary active ingredients like vitamins, sunscreens, fragrances, and essential oils have been widely used as nanoparticles. They provide improved stability of chemically unstable active ingredients, controlled release of active ingredients, achieved pigment effect, and improved skin hydration and protection through film formation on the skin. The preparations have low viscosity, are nongreasy, and have high bioavailability. As compared with liposomes, the payload of lipophilic substances by nanoparticles is much higher (1,84,85).

SAFETY CONCERN ABOUT NANOMATERIALS

Dermal exposure has raised concerns about safety and toxicity of nanomaterials which are present in many cosmetic products such as skin care products, hair products, sunscreens and make up products etc. (12) applied to skin. Although current discussions about nanoparticles toxicity are related to their dimension below 100 nm, hazardous effects may also occur after exposure to larger particles and agglomerates, where destabilization and disintegration can cause release of smaller fragments and toxic components (9,86). Nano engineered particles may also be concerned about contaminated solvents, side products, organics, endotoxins, etc. for toxicity (9). As a result of exposure, studies related the penetration depth of substances as nonaparticles or loaded on nanoparticles showed that nanoscale particles go in deeper than the bigger ones. For example a nanoparticle formulation of a fluorescent dye penetrated deeper than a particle-free formulation of the same dye only when the formulations were applied with a massage (87). Also size of the applied nanoparticles are indicative in the penetration depth and the selective targeting of certain compartments within the hair follicle (9,88).

The ratchet pump mechanism and some others could explain size-dependent penetration of particles on the nanometer scale (9). Although nanoparticles can penetrate into the superficial layers of the stratum corneum, they cannot penetrate the barrier of intact skin and reach the viable epidermis (9,89,90) and though nanomaterials can be deposited on the follicle orifice, they do not penetrate the skin via the follicle (91,92). In case of external effects such as UV radiation may weaken barrier function of skin which measured by transepidermal water loss, believed to be result of disorganization of the intercellular lipid lamellae (9,93) and the expression of tight junction related proteins was found to be perturbed following UVB exposure (9,94). In this respect suncreens become important and various nanomaterial preparations of zinc oxide or titanium oxide have been tested in vitro for percutaneous penetration, phototoxicity or photo-genotoxicity (12,95). Coating can be one of the arguments for safety. For example coating with dimethicone or silica of TiO_2 particles used in sunscreen formulations improve their stability and prevent possible photochemical reactions (96). In a number of in vivo toxicity tests, cytotoxicity, genotoxicity, photo-genotoxicity, general toxicity and carcinogenicity studies on TiO_2 and ZnO nanomaterials found no difference in the safety profile of micro- or nano-sized materials, all of which were found to be non-toxic (97) while the others were found to be toxic (6,98,99). It is indicated that until now there is little evidence for nanomaterials in cosmetics may penetrate to human skin and intake human systemic circulation. Thus available data suggest that risk from the dermal exposure to nanomaterials is low, but the published data needs extension and it is ethically suggested that five complementing actions; closing the gap, setup monitoring tools, continuing review, designing for safety, and regulative improvements need to take into consideration for sunscreens and for other nanomaterials (12, 100-102). However, the main concerns about nanomaterials in cosmetics are exemplified as the possible translocation to viable skin cells, its genotoxic, proinflammatory or sensitising activities and the influence of UV light on these parameters (103).

Another issue need to be considered is probability of change in physico-chemical characteristics of nanomaterials in the final product and coatings or impurities may be released cause to be the material more or less toxic. Moreover the properties of nanomaterials may change also during storage and handling (103).

The unusual properties of nanomaterials make them hard to predict their reactivity and risk. In order to support the research knowledge available in production, the European Commission has funded a project entitled 'Intelligent Testing Strategy for Engineered Nanomaterials - ITS-NANO'. This project aimed to identify the most effective research required to deliver an Intelligent Testing Strategy (ITS) for assessing exposure, hazard and the potential risks of engineered nanomaterials. The ITS, has launched in 2013 and will be a fluid document which can be adapted as new information emerges and the current knowledge gaps are filled, and will provide a direction for new research to meet the increasing demands for risk assessment of nanomaterials (104).

In case of developing new cosmetics technical, economic and sensory aspects should be taken into consideration while selecting an appropriate type of delivery system to enhance the safety, stability, extended efficacy and to enhance the aesthetic appeal of the final product (105).

CONCLUSION

Having importance in consumer aspects and economy, nanotechnology seems to be greater in cosmetics field. Due to their widely use in cosmetics the concerns about their risks for health and environment have gain much more importance. Consequently researches about their improvement, identification and safety will show an increase in the following years.

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