

Representative Inorganic Nanomaterials and Liposomes in Cosmetics

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Abstract. Nanomaterials are defined as materials ranging from 1nm to 100nm in at least one dimension or with internal nanostructures in bulk materials but showing distinct properties. Since the 20th century, when the feasibility of nanotechnology had been attested, nanomaterials' applications have radiated to various fields involving electronics, physics, chemistry, processing, biology, and measurement. Moreover, inspired by the physicochemical properties and targeted effects of nanomaterials in therapy and medicine, the anticipated applications in cosmetics are well-developed. Herein, the transparency and enhanced absorption of nano titanium dioxide/zinc oxide, the antibacterial property of nanosilver/nanogold, and the stability, increased penetration, and biocompatibility of liposomes in cosmetics are summarized. Besides, the existing problems such as security assessment, elevatable loading efficiency, and usage are classified. Particularly, the focus is on the mechanism of liposomes, preparation, routes of penetration, and liposome-cell interactions. This article intended better to understand the principles of nanomaterials behind cosmetic applications and get alerted to the inconclusive security.

Keywords: Nanomaterials, Cosmetics, Liposome, Penetration, Liposome-cell Interactions.

1. Introduction

Having size in the nanoscale (1 to 100nm) or unique nanostructures inside confers nanomaterials with unusual optical, electric, chemical, mechanical, and thermophysical properties. Moreover, the realization of these properties via advanced characterization and synthesis tools initiates today's multi-domain nano era (Figure 1), which contains non-scratch pigments, surface coatings, electronic devices, sensors, environmental governance, sports equipment, energy storage, cosmetics industries and so on [1].

Based on the excellent biocompatibility, penetration properties, or active chemical ability, nanomaterials with different roles and forms have been fabricated to broaden the boundaries of cosmetics applications and already have a mature manufacturing system for plenty of daily products like sunscreen, conditioner, shampoo, skin-brightening creams, etc [2]. Generally, nanomaterials in cosmetics can be divided into two types. First, as active substances, they behave efficiently in antiaging, moisturizing, and UV-filter in skin-care and hair-care products, which are related to their large specific surface area and increasing contact interfaces. Second, as stable carriers, an effective penetration scenario can reach the dermis layer rather than being blocked out by the stratum corneum while reducing the systemic absorption by the capillary infiltration in the subcutaneous layer, decreasing the potential toxicity to the human body [3]. However, their small size, high surface & interface energy, and deeper penetration also bring some unanswered problems. Recently, Scientific Committee on Consumer Safety proposed several suggestions for the safety of nanomaterials used in cosmetics under the authorization of the European Cosmetic Regulation (EU No1223/2009) [4]. In brief, the prominent opinions can be classified into three categories: 1) Safety issues arising from the physicochemical properties. The morphological/size features physically or the side effects generated between the chemical components and cells (toxic matters, allergenicity, decomposition). For instance, the powerful permeation that attacks healthy cells by releasing chemical matters in the blood vessels to induce a disorder of the immune system has not been concluded. What is more, take account

of the influences of modification; 2) Refinement of the instructions for use (frequency and dose); 3) Design of the validly matched methodology of characterization and assessment.

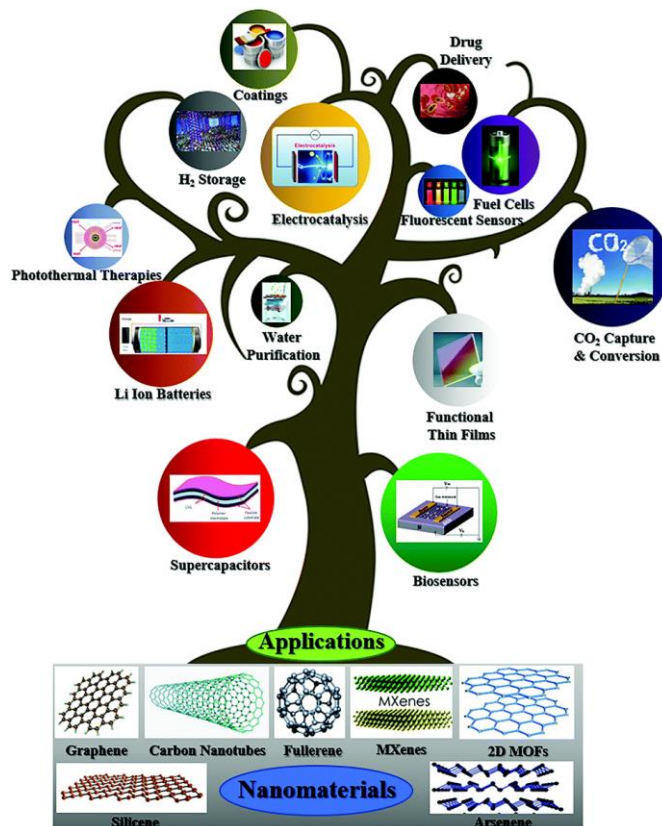


Figure 1. Nanomaterials and their applications. “Nanomaterials: A review of synthesis methods, properties, recent progress, and challenges.” by Nadeem Baig, Irshad Kammakam, and Wail Falath is licensed under CC BY 3.0 (ref [1])

In this essay, typical inorganic nanomaterials such as titanium dioxide/zinc oxide and organic nanomaterial liposome, which act as active substances and nanocarriers relatively, are elaborated on their basic applications and properties such as absorption, antibacterial, and penetration. Furthermore, concentrate on the preparation, the penetrations routes (intercellular, intracellular, and trans appendageal) of liposomes with their effect scenes and the critical role-playing processes—liposome-cell interactions (adsorption, fusion, endocytosis, and lipid exchange) with their sequence of occurrence. In addition, emphasize potential safety issues to be addressed. This essay aims to provide a complete awareness of the procedure of nanocosmetics logically spanning from applications, properties, principles, and drawbacks, on the other hand, to indicate the possible orientation of the improvement for the smooth growth of nanocosmetics.

2. Inorganic nanoparticles in cosmetics

Inorganic nanoparticles are the initial idea of nanomaterials to use in cosmetics, mainly including sunscreen and makeup products, which are ascribed to their adjustable size and size-dependent properties, thus the theoretical optimum physical property and chemical activity can be achieved by controlling the shape and particle size. Moreover, nanoparticles such as UV-filter and antibacterial substances are maturely developed in the cosmetic industry.

2.1. Titanium dioxide and zinc oxide

2.1.1 Properties and applications

Titanium dioxide and zinc oxide are used as UV filters in sunscreen at a size of less than 100nm. Apart from UVC (wavelength<290nm) that is blocked in the air atmosphere, TiO₂ have a UVB (290

to 320nm) protection while ZnO gives a broader UVA (320 to 400nm)-to-UVB shield. The arrived UV ray will be reflected and refracted partially. Scattering can be quantified by Rayleigh scattering when the particle size is an order of magnitude smaller than the wavelength of the incident light and Mie's scattering when the particle size is of the same order as the interacting UV wavelength. However, an improved absorption that is closely associated with their electron energy states is more critical. The band gaps of the rutile phase of TiO₂, anatase phase and ZnO are 3.06eV, 3.20eV, and 3.35eV respectively [5]. And the small size makes copious particles absorb a single photon simultaneously, upgrading absorption by preventing finite particles are saturated by a sustained UV light source. Furthermore, these metal inorganic nanoparticles eliminate the whitening and chalky appearance with better transparency on the skin, which is acceptable for dark-skin users.

2.1.2 Problems

Actually, the anticipated risk of irritation to the skin owing to the aggregation of nanoparticles in the deep skin is not evident because of a lack of percutaneous penetration, while the real concern is the route of inhalation particularly related to the spray sunscreen product [6]. Regarding their health hazard, a study got the THP-1 cells (Human Acute Monocytic Leukemia Cells) exposed to TiO₂ and ZnO nanoparticles at the maximum molar concentration for 6 h and 24h, observing that the maximum cellular cytotoxicity is 15% approximately by detecting the RNA sequencing. Therefore, the potential damage to DNA is notable [7]. The potential influence on the environment is still under surveillance, which perhaps requires high concentrations and increasing usage to be monitored. On the other hand, considering the environmental influence, the size-dependent activity, the difficulty of dispersion, the optimal block property and transparency, suitable particle size needs more attention.

2.2. Nanogold and nanosilver

2.2.1 Properties

The antibacterial properties of nanosilver have been observed to inhibit the growth of dermatophytes, making them potential anti-infective agents active against infectious organisms such as *E. coli*, *Vibrio cholera*, *Pseudomonas aeruginosa*, *Staphylococcus epidermis*. One possible interpretation is the release of silver ions with their deactivation on proteins. Nanogold's unique ability to transport and unload medications and its ease of manufacture could be used in cosmetics. Because they are easily functionalized, typically via thiol linkages, and can be conjugated with cosmetic compounds to improve product quality [8].

2.2.2 Applications

Nanosilver has been employed as a preservative in various personal care products, including shampoos, conditioners, toothpaste, and skincare preparations, and additional research is being conducted for its vast product line. According to reports, nanogold has been utilized in toothpaste to give effective oral cleansing and is also used in other commercially available daily care goods [9], such as colorants, eye contour products, face masks, makeup removers, wrinkle treatment, and other cosmetic items [10].

2.2.3 Problems

The toxicity of Ag nanoparticles (AgNPs) in cosmetics poses a potential danger to human beings, and the studies of toxicologic mechanisms both on extracellular and intracellular are as follows. On the one hand, outside of the cell membrane, the Ag⁺ released by AgNPs that is adsorbed on the cell membranes causes protein denaturation, leading to the phagocytosis or autophagy of cells or the death of microorganisms. On the other hand, the damage of intact cell membranes due to the unstable expansion led by entered AgNPs and an increased endothelial monolayer permeability on account of adhered AgNPs occurs first. Ulteriorly, the enhanced penetration gives rise to three toxicity pathways:

- 1) Possibly vital disturbance of gene expression and transcriptional content to DNA;

2) Disordered autophagy behavior induced by ROS (Reactive Oxygen Species): the generated radicals such as $\cdot\text{O}^2$, H_2O_2 , and $\cdot\text{OH}$ will oxidate the active protein and deteriorate the autophagy effects, inducing the accumulation of dying organelles;

3) Inactivation of mitochondrion: AgNPs have negative influences on the mitochondrial membrane potential (MMP) and electron transport chain, enzyme activity, and metabolism, which is closely relevant to the production of ATP via respiration [11].

In general, toxicology is multifactor research, whether nanosilver or nanogold, which should ponder the electron potential, particle size, coating materials, physicochemical properties, shape, aggregation condition, and microscopic biology.

3. Liposome

3.1. Structure and properties

In the early stage, the conventional active particles cannot permeate the epidermis layer because the particle size is above the 50nm cellular gap in the stratum corneum, after reaching the nanoscale there is also confronting decomposition, instability and chemical irritation to the cell. Therefore, liposome becomes an effective nanocarrier for drug delivery, comprised of phospholipid one or bilayer membranes enclosing the aqueous medium [12]. According to the different vesicle structures, they can be classified into three categories (Table 1):

Table 1. Different types of liposomes

Category		Size
Giant Unilamellar Vesicles		>1000nm
Multilamellar Large Vesicle (MLV)		>500nm
Unilamellar Vesicle	Large Unilamellar Vesicle (LUV)	>100nm
	Small Unilamellar Vesicle (SUV)	20~100nm

In Table 1, “unilamellar” means the vesicles have only an individual phospholipid bilayer [13]. Since the first cosmetic product based on liposomes was fabricated, biocompatibility, stability, nontoxicity, and enhanced skin penetration properties were found in them. The hydrophilic and lipophilic active components can be encapsulated into the aqueous core and phospholipid layer, respectively, and such a cellular membrane-like assembly may interact with skin cells and sustainedly release the drugs deeper.

3.2. Penetration and mechanism

The widely accepted methods of skin penetration of intact nanosystems include three routes: transcellular, intracellular, and transappendageal (Figure 2). However, the particle size can also influence this. The transcellular and intracellular have a rigorous constraint although they have relatively weaker resistance in transport, which can only be allowed when the molecular weight is less than 200 Da due to the partition mechanism. Whereas the transappendageal is not limited to the nanometer size, it is limited in that it can only take place in the specific locations (less than 1% of the total skin area) that stretch the end of the hair follicle and sweat gland [14]. And the corneocytes constructed in the stratum corneum aggregate into clusters and are separated by inter-cluster “canyons” that offer more channels to contort the intracellular route.

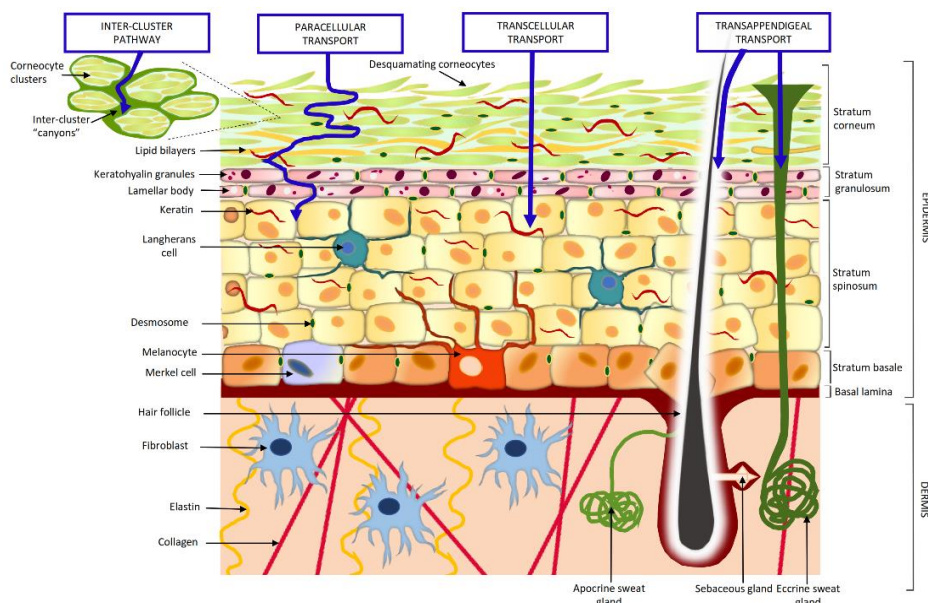


Figure 2. Penetration pathways through the skin. “Nanosystems in Cosmetic Products: A Brief Overview of Functional, Market, Regulatory and Safety Concerns” by Chiara Ferraris et al. is licensed under CC BY 4.0 (ref [14])

During the penetration, the interactions between liposomes and cells are paramount for the results *in vivo* after administration (Figure 3). Liposomes first adsorb to the cell membrane (by combination with specific components of the cell membrane, electrostatic attraction, or non-specific weak hydrophobic bonds [13]) then most of them are engulfed into phagocytes where the lysosomal enzymes destroy liposomes and phospholipids are hydrolyzed into fatty acids, while the rest undergo fusion, inter-membrane transfer or contact-release with the cells that do not have specificity. In contact-release and inter-membrane transfer, the enclosed entities can be exchanged without destroying the intact structure of liposomes [15].

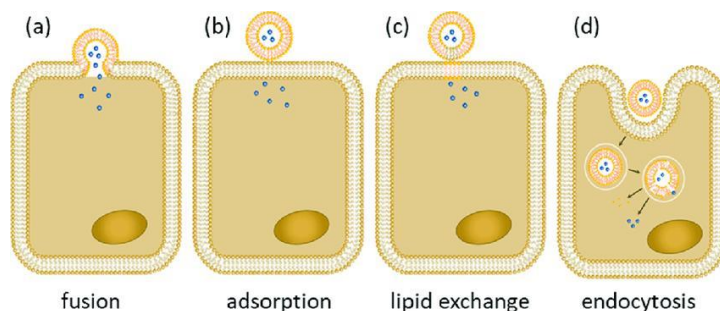


Figure 3. Liposome-cell interactions. Reprinted with permission from Alhariri, M., Azghani, A., and Omri, A. (2013) Liposomal antibiotics for the treatment of infectious diseases. *Expert Opin. Drug Delivery* 10, 1515 (ref [16]). Copyright 2013 American Chemical Society.

3.3. Preparation

In this regard, numerous methods are used for encapsulating the liposome's hydrophilic or water-insoluble actives. However, the six basic procedures are contained in all of them:

- 1) Dissolving the phospholipids into organic solvents;
- 2) Drying of lipid solutions formed in an organic solvent;
- 3) Dispersion of the dried lipid into an aqueous medium (ultrasonic, stirring, or other physical dispersion methods);
- 4) Dimensional reduction (remove the layers of multilamellar structure);
- 5) Post-processing (purification, sterilization);
- 6) Characterization of the manufactured products.

The film hydration method is the simplest and original method to prepare the liposome (Figure 4), the lipophilic drugs can be dissolved in the phospholipids before the evaporation, and the hydrophilic drugs are presented in the aqueous phase before the hydration. The drawbacks of this method are the difficulty to evaporate the organic solvent, low encapsulation efficiency, and small-scale production.

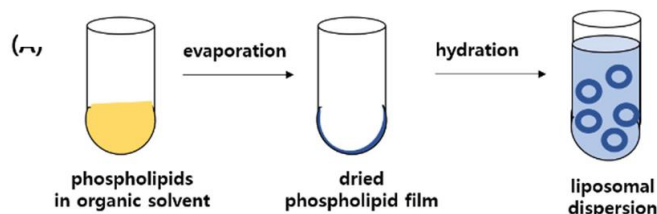


Figure 4. The film hydration method “Liposomes for Enhanced Bioavailability of Water-Insoluble Drugs: In Vivo Evidence and Recent Approaches” by Mi-Kyung Lee is licensed by CC BY 4.0 (ref [17])

In the dispersion process, the sonication technique seems to be a common way to fabricate the SUV, which includes probe sonication and bath sonication. Another method is Freeze-thawed liposomes, which have a unilamellar structure owing to the increased mutual ionic strength by operation of rapidly frozen and slowly thawed, and the loading efficiency can reach 20% to 30%. Regarding the solvent dispersion method, ether injection and ethanol injection can get sizes of 70 to 200nm and 30 to 110nm. At the same time, the reverse phase evaporation method gained the relative optimal encapsulation capacity for hydrophilic substances (above 80%) with a high water-to-lipid ratio (Figure 5), where the lipids are dissolved in an organic solvent to form the initial inverted micelles. An aqueous medium with buffer (phosphate saline) is added to the solution. After stirring or mechanical vibrations, the inverted micelles are reconstructed into the water-in-oil microemulsion, and finally, the organic solvent is evaporated to prepare the LUVs [18].

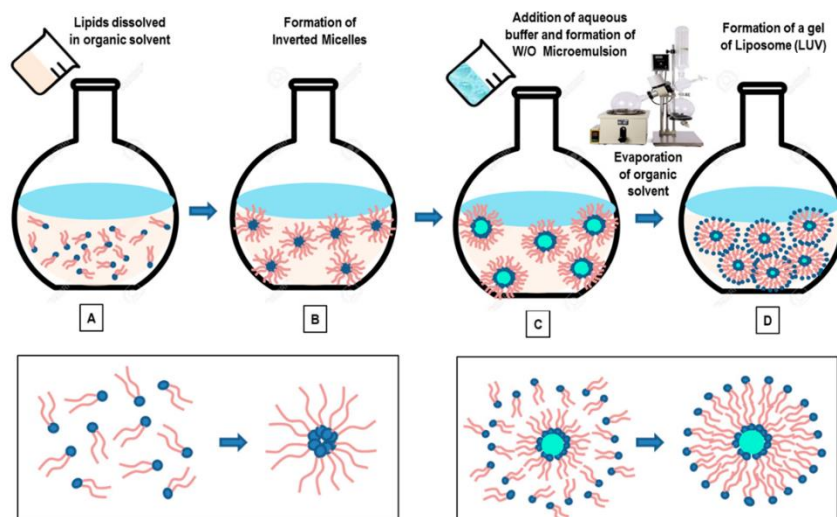


Figure 5. The reverse phase evaporation method “Methods of Liposomes Preparation: Formation and Control Factors of Versatile Nanocarriers for Biomedical and Nanomedicine Application” by Mikhail A. Kiselev and Domenico Lombardo is licensed by CC BY 4.0 (ref [18])

3.4. Problems and constraints

The liposomes have benefits in transport, improved penetration, and protection of drugs theoretically, but there still are essential problems to be solved. Moreover, they can be classified into four dimensions: preparation, structure & components, property, and performance (Figure 6). The high cost limits the industrialization of the production of liposomes, and other problems urgently need to be addressed are enhancing the loading efficiency of water-insoluble substances and maintaining

the stability of the structure in the meantime, which are subject to the finite space of phospholipid layers and thermodynamically unstable properties of phospholipids.

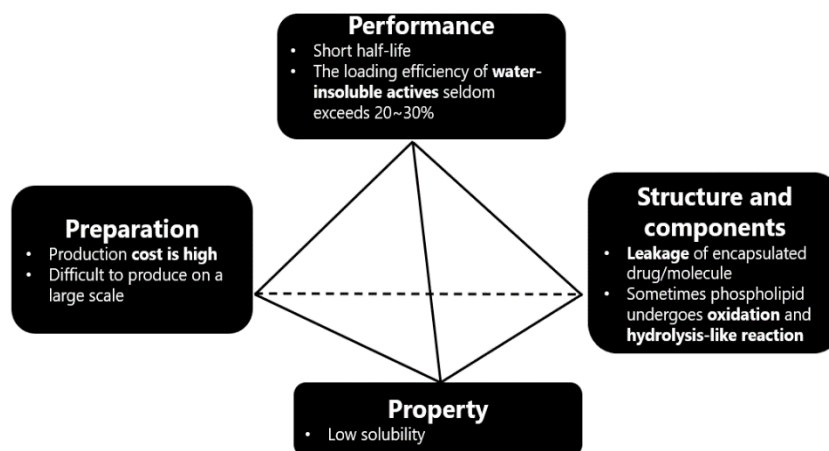


Figure 6. Constraints of liposomes in diverse dimensions

4. Conclusion

Overall, both the inorganic nanoparticles that have UV-filter and antibacterial properties, and the liposomes that have stability, increased permeation and biocompatibility have impelled the trend of the nanocosmetics industry in the last few decades. However, there are also significant challenges ahead. The first is figuring out the intrinsic toxicity of material and overcoming the restrictions of materials themselves. The second is rigorous instructions for nano-based cosmetic products. Furthermore, the third challenge is scientific and detailed monitoring mechanisms and coordinating regulatory guidelines in different organizations. Therefore, innovation in the preparation, structure of nanomaterials, and modifications are deemed feasible solutions to break the barrier. Meanwhile, conducting deeper and more fundamental mechanistic research with more effective analytical tools to assess the safety of nano components is also imperative. In short, with enough time and a clear direction, the comprehensive understanding of their properties with the intersection of multiple disciplines and the invention of new preparation techniques will take the usage of nanocosmetics to new heights.

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