

Nanotechnology in Cosmetics and Cosmeceuticals

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Nanomaterials (NM) arouse interest in various fields of science and industry due to their composition-tunable properties and the ease of modification. They appear currently as components of many consumer products such as sunscreen, dressings, sports clothes, surface-cleaning agents, computer devices, paints, as well as pharmaceutical and cosmetics formulations. The use of nanoparticles (NPs) in products for topical applications improves the permeation/penetration of the bioactive compounds into deeper layers of the skin, providing a depot effect with sustained drug release and specific cellular and subcellular targeting. Nanocarriers provide advances in dermatology and systemic treatments. Examples are a non-invasive method of vaccination, advanced diagnostic techniques, and transdermal drug delivery.

nanoparticles

agents

Au-NPs

1. Introduction

Nanoparticles (NPs) are defined as materials with dimensions smaller than 100 nm and presenting various shapes, i.e., spheres, rods, dendritic shapes, etc. ^[1]. This definition is accepted by the European Union (EU) Commission ^[2]. It should be noted, however, that there exists no uniform definition of nanomaterials ^[3]. The Environmental Protection Agency (EPA) emphasizes, in its opinion, the unique properties of NPs, which largely differentiate them from equivalent chemical compounds ^[4]. In turn, the US Food and Drug Administration (USFDA) clearly states that NPs should exhibit dimension-dependent phenomena ^[5]. The International Organization for Standardization (ISO), as the basic criterion, considers the nanoscale dimension of both the external dimension as well as the internal surface structure ^[6].

Naturally occurring nanostructures include allergens ^[7], microorganisms, i.e., viruses and bacteria ^{[8][9]}, but also NPs formed during volcanic eruptions ^[10]. In the human body, there are numerous nanostructures without which the normal functioning of the body is impossible, i.e., enzymes, proteins, antibodies, or DNA. Human bone, which is a multifaceted composite of hierarchical inorganic nanohydroxyapatite and organic collagen, can also be classified as a nanomaterial ^{[11][12]}. In the anthropogenic environment, one can find atmospheric NPs produced as a result of industrial activity, i.e., exhaust fumes, smoke, and dust ^{[13][14]}.

The history of synthetic nanomaterials (NMs) begins 4500 years ago in ancient Egypt ^[15]. Probably one of the first synthetic NMs was lead(II) sulfide NPs (5 nm) (PbS-NPs) used for dyeing or the so-called “Egyptian blue”, being a

mixture of cuprorivaite $\text{CaCuSi}_4\text{O}_{10}$ and silicon dioxide (SiO_2). The first scientific report describing the synthesis of gold NPs (Au-NPs) was made by Michael Faraday in 1857.

Generally, NMs are classified into four categories: carbon nanomaterials, inorganic, organic, and composite-based nanomaterials. Technologically produced nanotubes, fullerenes, quantum dots (QD), metals (silver Ag, gold Au), metal oxides (titanium dioxide TiO_2 , zinc oxide ZnO, iron (III) oxide Fe_2O_3 , SiO_2), and lipophilic NPs find more and more applications in cosmetics. This is due to the fact that NPs, thanks to their high surface-to-volume ratio [16], in addition to interesting physicochemical, electronic, optical, mechanical, catalytic, and thermal properties, also help in better penetration through the skin barrier [17].

Nanoparticles are ubiquitous in cosmetic products as antioxidants and anti-reflectants. Examples include TiO_2 -NPs added to creams as a white pigment or Ag-NPs as a component of shampoos and toothpaste [3]. In 1986, Christian Dior developed the first lysosomal anti-aging cream—Capture [18].

Many applications of nanoparticles have been described, not only in cosmetics but also in preparations for the treatment of skin diseases [19]. In nanomedicine, liposomal systems for transdermal drug delivery [20][21], contrast agents for diagnosing diseases, and gene therapies for cancer treatment have gained popularity [22][23][24][25][26].

An example of the use of NPs in medicine is Fe_2O_3 -NPs used as a contrast in magnetic resonance imaging (MRI) [22]. Fe_2O_3 -NPs, similarly to other magnetic nanoparticles (MNPs), besides their use as MRI contrast agents, can be used as vehicles, combined with superconductors, in magnetic drug delivery systems (MDDS). Due to the possibility of precision-guiding MNPs by an external magnetic field to the required area, MDDS has become promising in cancer therapy. MNPs can not only effectively transport and deliver drugs with a high concentration in cancerous tissues, but also generate heat through the oscillation of their magnetic pulse (44–47 °C), enabling the process of thermoablation of cancer cells (magnetic hyperthermia) [23].

In view of the growing trend of applying NMs in medicine, there is also an intensified interest in their toxic side effects, especially of those NPs that are not biodegradable, i.e., NPs of metals and metal oxides (in contrast to biodegradable NPs prepared from a variety of materials such as lipids, proteins, polysaccharides, and synthetic biodegradable polymers such as starches, chitin/chitosan, or poly-(D,L-lactide-co-glycolide). Obtaining a therapeutic effect in the dermal or transdermal administration of drugs or cosmetic preparations chiefly depends on passing through the skin barrier [27]. NMs in biomedical applications are characterized by high bioactivity and bioavailability. Unfortunately, such features may prove to be a threat in the event of potential toxicity. Previous studies have shown that exposure to NPs contributes to the generation of reactive oxygen species (ROS) [28], as well as cytotoxicity and genotoxicity [29][30][31]. In vitro studies have shown that the cytotoxic effects of NPs may derive from many factors such as chemistry, dose and exposure time, particle size particle shape, aggregation, surface area, crystal structure, surface functionalization, and pre-exposure effects [29][32][33][34], which are crucial for optimizing potential applications. It should not be forgotten that the availability of pharmaceuticals, as regards topical administration, is rather limited to the organelles of the skin, i.e., hair follicles, sweat glands, and sebaceous glands. In this case, the systemic circulation is bypassed, which reduces adverse or toxic reactions.

It turns out, nevertheless, that the benefits of using NPs outweigh potential concerns related to the toxicity of NMs. The review article written by Gupta et al. [35] summarizes the regulatory guidelines and recommendations concerning the safe use of nanocosmeceutical products in India, Europe, and the USA. Since 2006, the FDA [36] and 2013, the EU [37] have been collecting data on the impact of NPs on humans and the environment. An example of such a study is the work of Lee et al. [38] describing the relationship between markers of oxidative stress, i.e., urinary 8-hydroxy-2'-deoxyguanosin (8-OHdG) concentration and the creatinine-adjusted concentration, and the exposure of cosmetics and clothing sellers potentially exposed to TiO₂-NPs and ZnO-NPs. It appeared that the co-exposure index was significantly positively associated with both markers, reflected by $\beta = 0.308$, 95% CI from 0.106 to 0.510, and $\beta = 0.486$, 95% CI from 0.017 to 0.954, respectively. Furthermore, participants with exposure to NPs had a statistically higher level of 8-OHdG in urine in comparison to the lower co-exposure group (5.82 vs. 2.85 ng/mL, $p < 0.001$). Other studies [39] also confirmed higher levels of 8-OHdG and inflammatory markers such as cytokines IL-6, IL-8, and TNF- α after exposure to NPs. There is no complete agreement on the penetration of TiO₂-NPs and ZnO-NPs through the epidermis into the bloodstream or whether this causes long-term toxicity [40].

2. Nanoparticles as Anti-Aging Agents

NPs in anti-aging products are used as a therapeutic agent to slow down aging and as a means of protecting the skin from external stresses such as radiation and pollution [41]. Both biodegradable and non-biodegradable NPs have been studied for anti-aging applications. Biodegradable NPs are useful for encapsulating active substances, which enables sustained release and thus an extended therapeutic effect. In turn, non-degradable NPs, i.e., TiO₂ and ZnO, act as protection against skin photoaging.

The inorganic NPs in these cosmetic products act primarily as effective sunscreens. For their synthesis, simple techniques can be used that allow obtaining NPs of very small sizes. It is also possible to modify the surface of the NPs, which extends the range of their applications. However, long-term use may raise concerns about toxicity [42] [43]. Currently, the cosmetics industry uses less toxic biocompatible NPs [44][45]. Commercially available are Ag-NPs [46], platinum–palladium (Pt-Pd) [47], and Au-NPs [48], which have anti-wrinkle, skin-whitening, or antioxidant properties owing to strong reducing agents such as rutin and *Panax ginseng* (*P. ginseng*), used for the surface modification. TiO₂-NPs and ZnO-NPs are used mainly as UV filters [49]. CeO₂-NPs, in addition, exhibit antioxidant and antiapoptotic properties [49]. In the case of ZnO-NPs coated by chitosan, besides UV protection, a skin-whitening effect was observed by Schneider and Lim [50]. In turn, Aditya et al. [51] reported anti-inflammatory activity of peptide-coated ZnO-NPs.

Organic NPs as nanocarriers not only increase the stability of the supplied antioxidants, vitamins, or peptides, but also ensure better penetration into the skin. No objections have been raised regarding their long-term use, thanks to their proven biocompatibility and biodegradation, which does not cause immunological reactions [52][53].

2.1. Lipid Nanoparticles

The composition of lipid NPs usually includes such lipids as phosphatidylcholine, cholesterol, and lecithin, found in skin tissues, which ensures excellent biocompatibility. The leading systems for the skin delivery of anti-aging active substances are various types of nanostructured lecithin gels [54], from classic liposomal hydrogel to modified forms (transferosomal, ethosomal, pro-liposomal, phytosomal), and vesicular phospholipid gel (VPG).

Lipid NPs can be in the form of micelles, SLNs, nanostructured lipid carriers (NSCs), and nanovesicles such as liposomes, niosomes, etosomes, transfersomes, and cubosomes. Lipid NPs possess the ability to carry both hydrophilic and hydrophobic bioactive molecules, providing them with high drug loading, stability, and excellent permeation through the skin layers. Several formulations have been described that are used in anti-aging products. Bi et al. [55] described liposomes (93 nm) that have been used to deliver vitamin D3. Liposomes enhanced the therapeutic effect of vitamin D3 and ensured the stability and protection of the skin against photoaging, increasing the production of new collagen fibers. The results indicate that liposome retention in the skin was 1.65 times greater compared to the vitamin D3 solution.

Coenzyme Q10 (CoQ10) is a powerful antioxidant used, for example, to protect against aging. Its lipophilicity and high molecular weight make it difficult to deliver it by topical application. The development of a liposomal (<200 nm) formulation of soy phosphatidylcholine (SPC) and alpha-tocopherol (vit. E) improved the local bioavailability of CoQ10 ($p < 0.05$) and doubled its accumulation in the skin [56]. Another proniosomal (PN) gel formulation of CoQ10 was prepared on the basis of soy lecithin and cholesterol [57]. In this case, the spherical vesicles formed from the hydration of proniosomal gel exceeded 1 μm . Despite this, CoQ10 PN showed better skin permeation, almost two-fold higher compared to conventional gel. The effectiveness of skin photoaging treatment was confirmed by measuring the level of antioxidant enzymes, i.e., superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH).

Both liposomes (LPs) and ethosomes (ETHs) improve penetration of drug molecules through the skin. In Yücel's study [58], ETHs were found to be more effective than LPs in the transdermal delivery of rosmarinic acid. The study was confirmed by measuring the antioxidant activity and the inhibitory effect of the preparations on collagenase and elastase enzymes. The measured size range of the etosomal formulation was 138 ± 1.11 nm.

In turn, dispersions of alpha-lipoic acid (ALA) cubosomes, obtained using poloxamer gel (P407) as a carrier, have shown efficacy in the treatment of aging skin [59]. The product was tested on volunteers, resulting in a reduction in facial wrinkles in the area of the eye socket and upper lip, as well as an overall improvement in skin texture and color.

Cosmetic preparations containing extracts of rice (*Oryza sativa* L.) bran trapped in niosomes by supercritical carbon dioxide proved to be very effective. The use of preparations by volunteers in a monthly treatment improved the state of hydration, brightening, thickness, and elasticity of the skin [60]. It should be noted that rice bran extracts are a rich source of antioxidant compounds, including ferulic acid, γ -oryzanol, and phytic acid.

Thanks to the nanosize, better bioavailability of the active substance is obtained, and thus the effectiveness of the anti-aging effect. For the transdermal delivery of antioxidant enzymes, i.e., Cu,Zn-SOD, and CAT, carriers composed of various mixtures of soybean phosphatidylcholine (SPC/NaChol), mainly in the form of lipid bilayers, have been developed [61].

2.2. Nanoemulsions

Nanoemulsions are kinetically stable colloidal systems. In the case of nanoemulsions, droplet sizes range from 20 to 500 nm. The encapsulation of nanoemulsions of bioactive compounds ensures ease of application and increases their solubility, controlled release, and penetration through the skin. Topical formulations are usually O/W emulsions prepared using emulsion inversion point or through high-pressure homogenization [62]. These types of oil-based nanoemulsions are used in anti-aging products. Oil phases are usually of natural origin, such as sunflower oil, tea tree oil, soya lecithin [63][64], olive oil, or cosmetic oils such as Eutanol G. According to Gupta [62] the amount of API in the oil phase is 80–100 mg/g, while the oil phase is typically about 15–20 wt. of the entire formulation. Nanoemulsions also include surfactants, usually non-ionic surfactants such as Tween 20, Tween 80, polyvinyl alcohol, or natural products like sucrose esters and cyclodextrins [65]. A common addition to facilitate application to the skin is the addition of a cross-linking agent to convert the formulation into a gel, such as carbopol 940 [66], glycerol, or PEG.

An anti-wrinkle nanoemulsion containing the hydrophilic molecule acetyl hexapeptide-8 (AH-8) was developed by Hoppel et al. [67]. Another example of a tea-tree-oil-based nanoemulsion is a preparation for transdermal delivery of fish protein hydrolysates (FPH) [68].

Nanoemulsions based on Compritol ATO containing an additional two-component mixture of surfactants were used as carriers for applying resveratrol to the skin [69]. A high drug load was achieved, which ensured the effectiveness of (i) antioxidant activity confirmed by the study of the activity of antioxidant enzymes (CAT, GSH, SOD), (ii) anti-inflammatory activity, confirmed by the study of anti-inflammatory markers interleukin 6 (IL-6), interleukin 8 (IL-8), and rat nuclear factor kappa B (NF- κ B), and (iii) the anti-wrinkle test (matrix metalloproteinase (MMP-1) and granulocyte macrophage colony stimulating factor (GM-CSF)) after UVB irradiation.

2.3. Nanoparticles of Precious Metals, i.e., Pd, Pt, and Au

Noble metal nanoparticles are characterized by strong catalytic activity in many chemical reactions, such as hydrogenation, hydration, and oxidation. This property results from the large surface area and high proportion of atoms on the surface of NPs [70]. In addition, noble metal NPs are believed to be powerful antioxidants [71][72]. Pd is known to prevent the oxidative degradation of Pt. Already in 1915, Hideyo Noguchi and Saburo developed a solution of Pd and Pt NPs used as a medicine against many chronic skin diseases, i.e., burns, frostbite, and urticaria, as well as other diseases such as pneumonia, acute gastritis, chronic gastritis, and rheumatoid arthritis [73]. Many years later, the therapy was recreated by Dr. Ishizuka, who developed PAPANAL, a mixture of Pd and Pt NPs [74]. PAPANAL was patented as an antioxidant against superoxide anions and hydroxyl radicals [75] in the

Japanese Patent Office (Patent No. 3411195, 2003). Recently, Elhousseiny and Hassan confirmed the anticancer and antimicrobial activity of the complex of Pd-NPs and Pt-NPs [73]. The anti-aging effect of the PAPANAL complex (Pd:Pt; 2.7:1) applied transdermally in a mouse model was demonstrated by Shibuyai et al. [47]. Au-NPs, unlike Au in the bulk state, can absorb light and convert it to heat, acting as miniature thermal scalpels to remove, for example, cancer cells [76].

In the Cao et al [77] study, percutaneous permeation of Au from Au nanosheets as well as a cream containing Au nanosheets was systematically investigated using guinea pigs. Au from both preparations was demonstrated to be able to permeate into the skin in a time-dependent manner, but could not enter the systemic circulation. The main permeation route of Au nanosheets was through hair follicles. It was revealed by synchrotron radiation X-ray fluorescence (SRXRF) imaging. Unfortunately, both the extracted Au nanosheets as well as the Au nanosheets embedded in cosmetic creams inhibited the growth of hair. It has been observed that the expressions of hair growth marker proteins (CD34, ALP, and KRT19) were downregulated after exposure to the cosmetics containing Au nanosheets. The extracted Au nanosheets, in contrast to the cosmetic cream, were nontoxic to keratinocytes and skin fibroblasts.

Unfortunately, metallic NPs synthesized by chemical methods require the use of toxic-reducing and stabilizing substances (hydrazine hydrate, sodium borohydride, DMF, and ethylene glycol), which are adsorbed on the NPs. The above phenomena reduce the biocompatibility of nanomaterials and limit their use in medicine and cosmetology [78]. Therefore, natural methods of synthesis are gaining more and more popularity. This is the so-called green synthesis or biogenic or phytochemical synthesis using extracts from plants, yeasts, fungi, and bacteria. NPs obtained in this way are stable and less toxic compared to chemical synthesis products. Importantly, the bioactive components of the reducing extract, e.g., vitamins, alkaloids, carotenoids, polyphenols, fats, carbohydrates, and proteins, are adsorbed as stabilizing factors in the formation of NPs [79]. Ag-NPs (468.7 nm) loaded with phytochemicals have so far been used in anti-aging applications. Radwan et al. [46] showed that Ag-NPs stabilized with ethanolic *Eucalyptus camaldulensis* bark extract, the main component of which is rutin, reduced cell senescence and apoptosis in a human melanocyte cell line (HFB-4). The authors also confirmed a significant decrease in the activity of elastase, collagenase, and tyrosinase enzymes. Another example is the synthesis of Ag-NPs (87.46 nm) using *Symphytum officinale* leaf extract [11]. The anti-aging effect of S-AgNPs was studied using HaCaT keratinocyte cells treated by Ag-NPs after UVB irradiation. The authors emphasized photoprotective properties of Ag-NPs as indicated by the inhibition of matrix-degrading enzymes metalloproteinase-1 and pro-inflammatory cytokines IL-6 and increasing the expression of procollagen type 1 in keratinocytes.

Jimenez et al. [45] obtained Au-NPs in a green synthesis process using *P. ginseng* berry extract. Non-toxic to human skin fibroblasts, Au-NPs have a high potential for cosmetic applications, thanks to the ability to retain moisture and mitigate damage caused by oxidative stress. In addition, Au-NPs significantly reduced melanin content and suppressed tyrosinase activity in α -MSH-stimulated B16BL6 cells.

2.4. Cerium Oxide Nanoparticles (CeO₂-NPs)

UVA radiation is particularly dangerous for the photoaging of human skin. The reason for this phenomenon is the formation of ROS in the epidermis and dermis. CeO₂-NPs have been shown to have a protective effect against skin photoaging due to their ability to scavenge free radicals [80]. The antioxidant activity of CeO₂-NPs is similar to that of the antioxidant enzymes SOD and CAT. Li et al. [49] studied the effect of CeO₂-NPs on human skin fibroblasts (HSF) irradiated with UVA. The authors confirmed that CeO₂-NPs may reduce the production of pro-inflammatory cytokines, intracellular ROS, β-galactosidase activity, and phosphorylation of c-Jun N-terminal kinases (JNKs) after exposure to UVA radiation.

2.5. Anti-Aging Polymeric Nanoparticles

Many polymer compounds are used for the production of NPs, i.e., PLA, PGA, PLGA, polyvinyl alcohol (PVA), and PCL. Polymer NPs serve as drug delivery vehicles and are rarely used in anti-aging cosmetic products [81]. In cosmetic products, polymeric NPs play a photoprotective role. Among the few examples that report the use of polymeric NPs in anti-aging products is curcumin encapsulated in silk NPs (700 nm) (silk/curNPs). Curcumin is a natural antioxidant isolated from turmeric (*Curcuma longa*), thus it is functional for anti-aging. Yang et al. [82] showed that synthesized silk/cur NPs had an effect on markers of aging (P53, P16, HSP70 gene expression, and β-Galactosidase activity). In the study, the percentage of β-galactosidase in rat bone marrow mesenchymal stem cells (rBMSCs) decreased from 36% to 25.7% after treatment with silk/cur NPs.

Nanocarriers present in cosmetic products along with active substances are listed in **Table 1**, which was developed on the basis of review articles [83][84][85][86].

Table 1. Types of commercial skin care nanoformulations with their active ingredients.

The Active Ingredients	Nanoformulations
vit.E, panthenol	nanocapsules
coenzyme Q10, vitamins (A, C and E), natural extracts (<i>Symphytum officinale</i> , <i>Camellia sinensis</i> , <i>Ginkgo biloba</i> , <i>Chondrus crispus</i> , <i>Rosa damascena</i> , <i>Aloe barbadensis</i>), natural oils (<i>Helianthus</i> , <i>Prunus Armeniaca</i> , <i>Symphytum officinale</i>), hyaluronic acid, SOD	liposomes
plant extracts (<i>Canadian Willow</i> , <i>Camellia sinensis</i>), olive oil, vit.E, hyaluronic acid, soy firming agent, UVA/UVB filters	nanospheres
gold powder (24 k), silk, plant extracts (<i>Coffee arabica</i> , <i>Aloe barbadensis</i> , <i>Cucurbita pepo</i>), vitamins (A, C and E), hyaluronic acid, plant extracts, plant stem cell extracts	Au-NPs
coenzyme Q10, natural oils (hemp, macadamia nut), plant extracts (<i>Leontopodium nivale</i>)	NLCs, SNLs
ZnO-NPs, Fe ₂ O ₃ -NPs, TiO ₂ -NPs, plant extracts, vitamins	nanocomplexes
vitamins (E, B3, provitamin B5), UVA/UVB filters, bepanthol	nanoemulsions

The Active Ingredients	Nanoformulations
plant extracts (<i>Gingko biloba</i>), oils (almond, lavender), natural compounds (caffeine, amino acids, polyphenols)	nanosomes ↓;
<p>Porritt, J.; Ryan, J.; et al. Nanoscience and Nanotechnologies: Opportunities and Uncertainties; The Royal Society & The Royal Academy of Engineering: London, UK, 2004; Volume 44, pp. 7–10. Available online: http://sscottgraham.com/314/redesign4.pdf (accessed on 24 December 2021).</p>	
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