



## Historical Perspective

## The emerging role of nanotechnology in skincare

Lucia Salvioni <sup>a</sup>, Lucia Morelli <sup>a</sup>, Evelyn Ochoa <sup>a</sup>, Massimo Labra <sup>a</sup>, Luisa Fiandra <sup>a</sup>, Luca Palugan <sup>b</sup>, Davide Prospero <sup>a</sup>, Miriam Colombo <sup>a,\*</sup>

<sup>a</sup> University of Milano-Bicocca, Department of Biotechnology and Bioscience, Piazza della Scienza 2, 20126 Milano, Italy

<sup>b</sup> University of Milano, Department of Pharmaceutical Science, Via Colombo, 71, 20133 Milano, Italy



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## ABSTRACT

The role of cosmetic products is rapidly evolving in our society, with their use increasingly seen as an essential contribution to personal wellness. This suggests the necessity of a detailed elucidation of the use of nanoparticles (NPs) in cosmetics. The aim of the present work is to offer a critical and comprehensive review discussing the impact of exploiting nanomaterials in advanced cosmetic formulations, emphasizing the beneficial effects of their extensive use in next-generation products despite a persisting prejudice around the application of nanotechnology in cosmetics. The discussion here includes an interpretation of the data underlying generic information reported on the product labels of formulations already available in the marketplace, information that often lacks details identifying specific components of the product, especially when nanomaterials are employed. The emphasis of this review is mainly focused on skincare because it is believed to be the cosmetics market sector in which the impact of nanotechnology is being seen most significantly. To date, nanotechnology has been demonstrated to improve the performance of cosmetics in a number of different ways: 1) increasing both the entrapment efficiency and dermal penetration of the active ingredient, 2) controlling drug release, 3) enhancing physical stability, 4) improving moisturizing power, and 5) providing better UV protection. Specific attention is paid to the effect of nanoparticles contained in semisolid formulations on skin penetration issues. In light of the emerging concerns about nanoparticle toxicity, an entire section has been devoted to listing detailed examples of nanocosmetic products for which safety has been investigated.

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\* Corresponding author.

E-mail address: [miriam.colombo@unimib.it](mailto:miriam.colombo@unimib.it) (M. Colombo).

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## 1. Introduction

Cosmetics include a wide range of products, mainly designed for external use and intended to cleanse, perfume, change the appearance of, correct odors emanating from, or more generally keep in good condition the areas of the body to which they are applied [1]. As a consequence of globalization, the role of these products is rapidly evolving and their use has been increasingly considered to be an essential part of personal wellness [2,3]. The improved life expectancy that has developed alongside the evolution of beauty standards has greatly changed consumer perceptions of routine daily care, which is no longer restricted to basic products (e.g., toothpaste, soap). Not surprisingly, the global beauty and personal care market value is predicted to exceed \$716 billion by 2025, with much of that value related to the development of innovative and/or redesigned products and technologies [4].

The rapid rise of the cosmetics industry has been characterized by a growing demand for innovative and personalized products designed on the basis of increasingly detailed scientific knowledge [5]. In addition, the recent COVID-19 pandemic and associated global events have suggested that market trends for cosmetics are strongly affected by customer perceptions and are thus ever-changing; indeed, after years in which the demand has been increasingly oriented towards the use of “clean” and natural products, the pandemic has highlighted the need for safer and transparent items [6,7].

Back in 1986, Lancôme and Dior simultaneously launched the first nanotechnology-based cosmetic products under the name of Niosomes® and Capture®, respectively [7,8]. The introduction of nanotechnology was pronounced to be a major scientific innovation and represented a major breakthrough towards the development of high-quality products; its use is now well-established in the cosmetics industry. Indeed, less demanding regulatory restrictions as compared to the development of new drugs, along with the localised action of these products, initially made the field extremely promising [9,10]. Nowadays, it is widely accepted that the use of nanoparticles (NPs) significantly improves the performance of cosmetics in diverse ways, performing both as an active ingredient and/or a carrier. For this reason, these technologies may be easily recognized as industry standards [11]. However, doubts about possible long-term [12] toxicity, together with concerns about the real advantages of nanomaterials in product performance, have often led to general mistrust [13,14]. Indeed, in late 2009 the European Union recast the individual directives associated with the use of cosmetics into a single platform collecting all of the relevant products. It was then proposed that the presence of nanomaterials in these products should necessitate additional restrictions before they are authorised for use as ingredients [15]. As a consequence, the cosmetics industry became wary of publicly promoting nanotechnology, often avoiding referring to ingredients as being composed of nanomaterials. Given this background, the present review aims to provide an update of the state of the art of the nanocosmetics field, exploring the beneficial effects of nanomaterials and offering a critical overview of toxicological issues. Among the various cosmetic product categories, our insights are mainly focused on

skincare, which more clearly highlights the reappraisal of exploiting nanotechnology in cosmetics.

## 2. Classification and purposes of skincare products

A cosmetic product can be defined as any substance or mixture of substances intended to be applied to the external surfaces of the human body (epidermis, hair, nails, lips, external genital organs), or to the teeth and mucous membranes of the mouth, for the purpose of cleaning, perfuming, or protecting them, modifying their appearance, keeping them in good condition or correcting odours emanating from them [16]. The products that are used on the epidermis are specifically denominated *skincare products*. The effectiveness of skincare products depends on the types of ingredients and the technology used to prepare them.

A cosmetic product is made up of an active ingredient and other substances (ingredients) that form the “base”, “vehicle” or presentation of the product, including products called creams, lotions and gels. The vehicle is formulated to 1) make the product suitable for efficiently transporting the active ingredient to the target site, and 2) ensure that the active ingredient remains in the site of action within the period of time necessary to achieve the desired effect [17]. Furthermore, the vehicle must also support the physical, chemical and microbiological stability of the active ingredient and of the entire formulation. However, it is not always easy to draw a sharp distinction between the bioactive agents and the other ingredients because the latter may have some properties that contribute to the overall effect of the final product. For example, lecithin is used as an emulsifier in cosmetic formulations, but it also exhibits a moisturizing effect. Moreover, it seems to increase the firmness of the dermis and therefore may have an anti-aging effect [18]. The main effects of cosmetic vehicles are shown in Table 1.

Cosmetics used on the epidermis are specifically denominated *skincare products*. Their effectiveness depends on the types of ingredients and the technology used to prepare them. Skincare products can be presented in different physical states: liquid (solutions or suspensions), solid (powders) or semisolid systems (gels and emulsions). Emulsions are the most frequently used and can be classified, depending on their consistency, as creams or lotions. Creams have a thicker or heavier consistency as compared with lotions. This difference is due to the higher water content of lotions.

**Table 1**  
Main effects of cosmetic vehicles on the skin.

Effect	Definition
Protective	Protects the skin from external harmful factors (dry air, pollution, UV light)
Cleansing	Eliminates dirt and microorganisms from the skin
Hydrating	Provides water in order to restore or maintain fluid balance
Moisturizing	Establishes an effective barrier that prevents water loss through the epidermis
Soothing	Provides a gently calming effect
Firming	Makes the skin more toned and smoother

The choice of the appropriate vehicle or presentation of a skin care product depends mainly on its purpose of use (Fig. 1). Other factors to consider when choosing the vehicle are the type of skin and the extension of the application area; in general, creams with a moisturizing effect are more recommended for dry skin, while for oily skin, gels or solutions are preferred. As regards to the application area, products are meant to be applied in large areas (e.g., body cream) must be much more spreadable than products that have to be used in a small area, like a blemish corrector, for example.

### 2.1. Emulsions

Emulsions are dispersed systems made up of two or more immiscible phases stabilized by one or more emulsifiers (surfactants). In cosmetics, one phase is “hydrophilic,” and its main component is often water; the other is “lipophilic” and may be made up of oils and/or waxes of vegetable or synthetic origin. The dispersed system is sometimes stabilized by one or more emulsifiers. The purpose of the emulsifying agents is to produce the emulsification of the immiscible phases and promote emulsion stability over time.

Depending on the phase ratio, the preparation technique and the type of emulsifying agent, emulsions can be either oil-in-water (O/W), where the oil is the internal phase, or water-in-oil (W/O), where the oil is the dispersing phase. O/W emulsions are easily spreadable and readily absorbed by the epidermis. They have a moisturizing effect and are particularly suited for normal, rather oily skin. Most day creams fall into this category [19]. W/O emulsions release an oily layer onto the skin. Because of their lipid-replenishing properties they can reduce water loss, and for this reason, they are recommended for dry and sensitive skin [19].

The effect and the overall stability of an emulsion can be improved by using multiple emulsions; these are complex dispersions made up of droplets of a similar nature as the continuous phase, dispersed in a second liquid, which is then dispersed in the final continuous phase. Multiple emulsions may be of the oil-in-water-in-oil (O/W/O) type or the reverse, water-in-oil-in-water (W/O/W). The first type of dispersion

is used to obtain a more prolonged moisturizing effect on the skin, to improve the process of formation of a protective lipid layer or to prolong the release of an active ingredient on the skin [20].

Emulsions can be categorized according to the dimension of the internal phase into coarse, micro- and nano-emulsions. The droplets of the internal phase of coarse emulsions have a diameter range from 0.1 to 10  $\mu\text{m}$  [21] and are thermodynamically metastable. The emulsions described above belong to this category. Micro- and nanoemulsions are mainly used as delivery systems for active ingredients and will be discussed later in this review.

### 2.2. Gels and emulgels

Gels are semisolid systems constituted by a network of colloidal particles that entrap large amounts of aqueous or hydroalcoholic solutions. Most of these particles are organic polymers of natural, semisynthetic or synthetic origin. Examples of substances used as gelling agents are hydroxypropyl-methylcellulose, sodium carboxymethylcellulose, acrylic acid polymers, polyoxyethylene-polyoxypropylene block copolymers and natural gums (xanthan gum, guar gum, locust bean gum) [22,23]. Due to their higher aqueous component, gels can easily dissolve large amounts of hydrophilic substances that may be released from the formulation when they are spread on the skin. Gels are the most suitable vehicle for the formulation of skin cleansers, because they are easily washed off the skin with water. They are also suitable as the vehicle of choice for some nanoparticulate systems which are incompatible with the surfactants present in the emulsions. The major limitation of gels is their inability to incorporate and deliver hydrophobic active ingredients. In order to overcome this limitation, emulgels have been developed.

Emulgels, consisting of an emulsion dispersed in a gel base, exhibit several favorable properties, including a pleasing appearance, easily spreadability and greaseless [24,25].

## 3. Nanomaterials in cosmetics

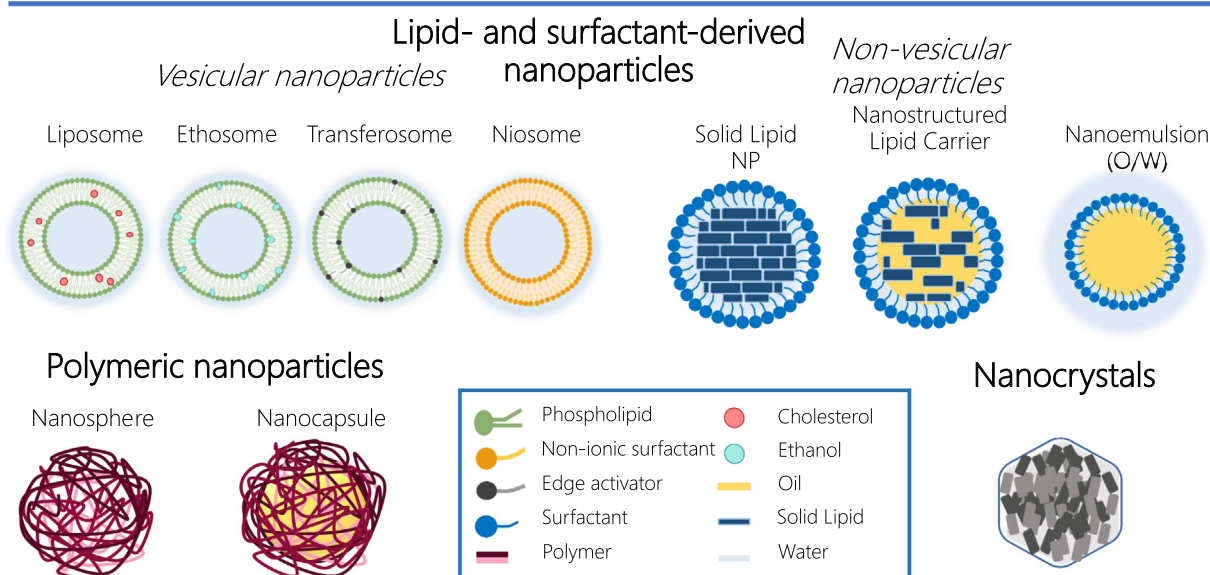
In a market where novelty is usually the driving force of business choices, it is not surprising that the cosmetics industry enthusiastically adopted nanotechnology, taking inspiration from its early involvement in biotechnology and bioscience. Since then, several nano-based products have been developed, exploiting a large variety of nanomaterials of different compositions, shapes and sizes. These were mainly chosen for their ability to overcome the common limitations of cosmetics by enhancing penetration, improving the stability of ingredients, controlling the release of active ingredients, and functioning themselves as active agents [11]. Moreover, the tiny dimensions together with the large surface-to-volume ratio exhibited by these objects were also able to enhance material dispersibility and improve the textural quality of the products [26].

In the next paragraphs, an overview of the most popular nanomaterials applied in cosmetics is provided, grouped into two broad classes—organic and inorganic NPs (Fig. 2 and 3). Notably, this overview does not provide an exhaustive list of the available nanomaterials in the field, but rather focuses on substances that have been investigated most thoroughly. This description also includes a few formulations that are not classified as nanomaterials by the regulatory agencies. Indeed, as made explicit by EU legislation, this term usually refers to any “insoluble or bio-persistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm” [27]. Accordingly, only preparations that do not change after applying them to skin should be considered to be nanomaterials; this excludes several widely employed organic systems, such as liposomes and nanoemulsions [12]. Since the purpose of this overview is to explore the benefits gained from nanotechnology in skincare, we group together all the formulations that exploit the “nano” dimension to improve in some way their cosmetic performance.



Fig. 1. Skincare product categories and relevant applications.

## ORGANIC NANOPARTICLES



## INORGANIC NANOPARTICLES

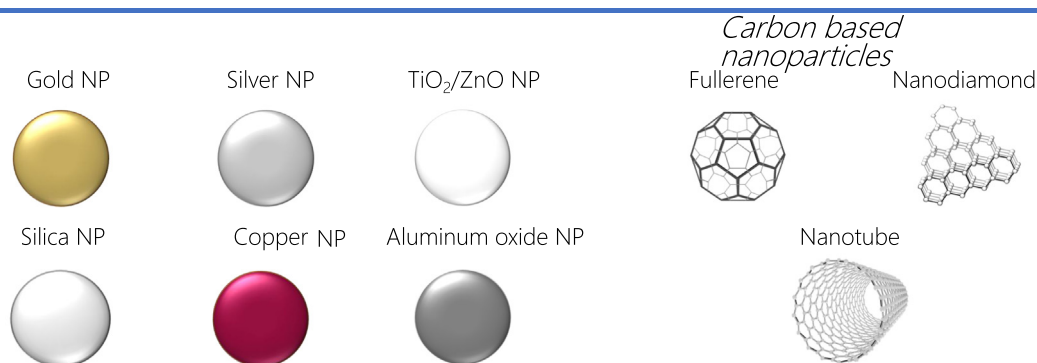


Fig. 2. Schematic representation of nanomaterials applied in skincare.

### 3.1. Organic NPs

This group comprises a wide range of nano-sized formulations made of natural or synthetic materials. As mentioned above, the poor intrinsic stability they demonstrate in some circumstances makes it uncertain whether to classify them as genuine colloidal NPs. This is one of the reasons why they are infrequently identified as nanomaterials in product labels [12,32]. Among the organic NPs, lipid-, surfactant- and polymer-based nanostructures are mainly used in the cosmetic industry as carriers of active molecules [33], while nanocrystals are solid particles produced with the aim of increasing substance solubility [34].

#### 3.1.1. Lipid- and surfactant-derived NPs

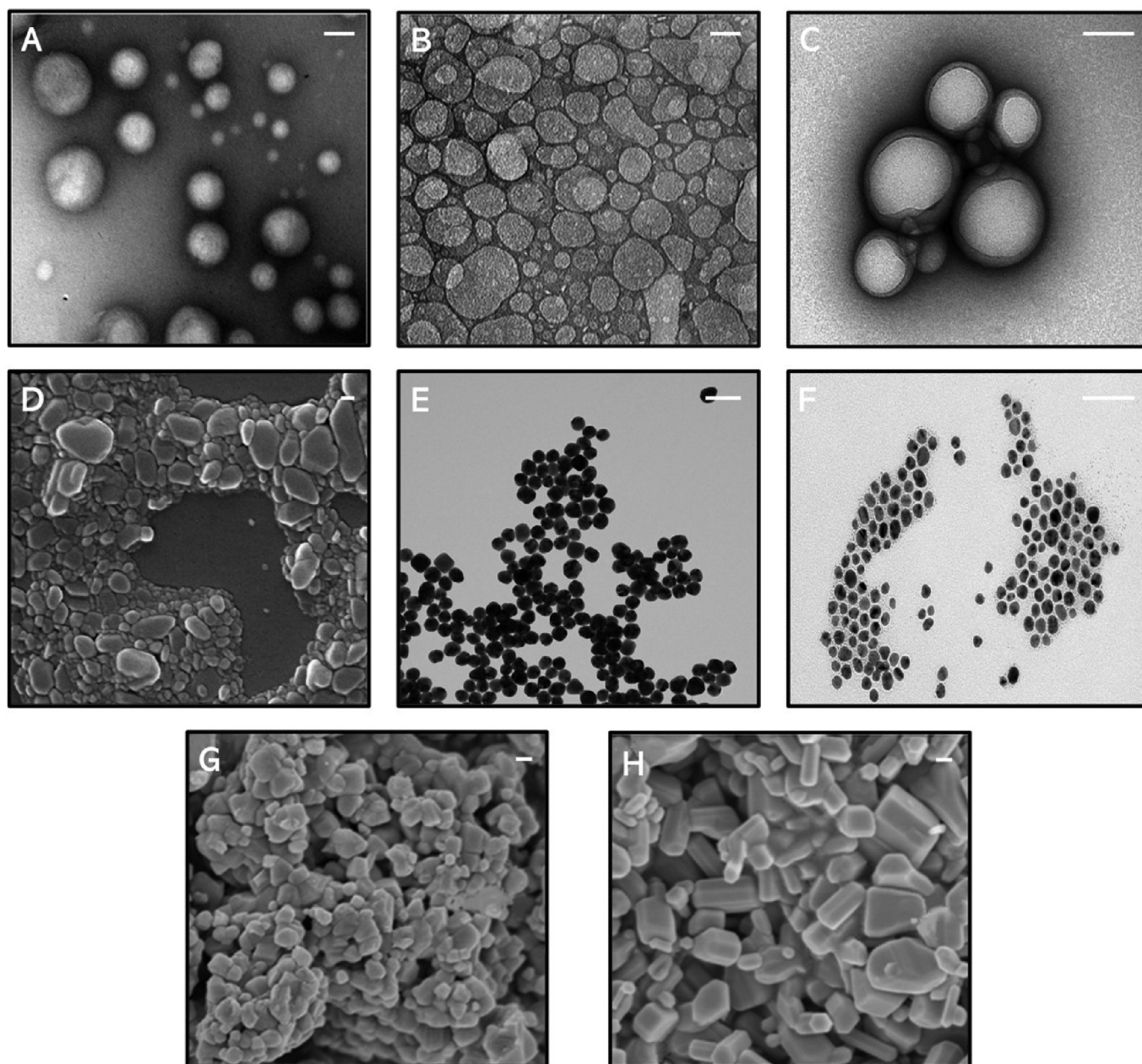
**3.1.1.1. Vesicular systems.** Vesicular NPs are generally classified according to their size and number of bilayers as multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs) and large unilamellar vesicles (LUVs) [32]. MLVs (0.5–10 μm) can be easily obtained upon dispersion of raw materials in aqueous phase, while SUVs (10–100 nm) and LUVs (100–500 nm) are produced from MLVs by various methods (e.g., extrusion, sonication, high-shear homogenization) [35]. In cosmetic science, the use of sub-micron nanocarriers is generally preferred [36,37]. In 1986, the resemblance of these systems to natural cellular

vesicles and membranes encouraged the cosmetics industry to introduce the use of such nanomaterials. As vesicles are in charge of molecular transport between cells, these nanoparticles were expected to enhance the penetration of and efficiently deliver the active ingredients into the deeper skin layer [38]. Thanks to their amphiphilic character, these engineered vesicles can accommodate both lipophilic and hydrophilic bioactive agents [36]. Moreover, the lipidic and surfactant main components of these vesicles are biocompatible and mostly biodegradable [38,39]. Not surprisingly, several products based on these technologies are still on the market and their formulation is constantly evolving.

Liposomes still represent by far the most investigated nanomaterial in cosmetics [33]. They are made of phospholipids (mainly phosphatidylcholine derivatives) and their bilayer composition strongly affects their delivery properties [38]. For instance, unsaturated phospholipids improve the nanocarrier permeability, whereas the use of saturated phospholipids with added cholesterol inclusions results in a more rigid bilayer structure [40]. Despite progress in their synthesis, several limitations remain with respect to liposome application, including poor chemical and physical stability, difficulty in large-scale production and suboptimal penetration [37].

Ethosomes (Fig. 3A) and transferosomes are ultra-deformable vesicles produced by including ethanol (20–45% w/w) or edge activators (i.e., softening surfactants) in the liposome formulation. It has been





**Fig. 3.** Transmission (A,B,C,E,F) and scanning (D,G,H) electron microscopy images of some nanomaterials applied in skincare; A) Ethosomes [28]; B) Solid Lipid NPs; [29] C) Polymeric NPs; D) Tinosorb®, BASF [30]; E) Silver NPs; F) Gold NPs; G) Titanium oxide NPs; [31] H) Zinc oxide NPs [31]. Scale bars: 100nm. All the images were adapted with the permission of the authors.

largely demonstrated that the improved flexibility of these nanocarriers results in a superior penetration through the skin barrier [41–43].

Niosomes are vesicles that are mainly composed of non-ionic surfactants (e.g., alkyl esters, including Spans and Tweens, and alkyl ethers such as Brijis) [44]. Niosomes were developed as an alternative to liposomes as their raw materials are cheaper and readily available. Besides overcoming high manufacturing costs, these delivery systems exhibit prolonged long-term stability compared to phospholipid-based vesicles [35,44].

**3.1.1.2. Non-vesicular systems.** This group comprises a number of different heterogeneous systems composed of dispersion of immiscible phases (i.e., lipophilic and aqueous) and stabilized by surfactants.

Solid lipid NPs (SLNs) and nanostructured lipid carriers (NLCs) have an inner lipid core which is solid at body temperature, and are commonly prepared by microemulsion and high-pressure homogenization

[45]. In SLNs (Fig. 3B), the lipid mixture is formed only by solid lipids (e.g., long-chain glycerides, fatty acids, waxes) [46], while in NLCs the hydrophobic matrix is made up of a combination of solid and liquid lipids (e.g., short-chain glycerides) in a ratio ranging between 70:30 and 99.9:0.1 [45,47]. This class of non-vesicular NPs is mainly investigated for their potential as carriers of chemically labile molecules and for their occlusive properties, which promote skin hydration and the penetration of bioactive agents [45,48]. NLCs are considered to be an upgrade from SLNs; indeed, the inclusion of oils in the lipid matrix decreases its crystallinity, improving the loading capacity and long-term encapsulation stability of the system [47].

Nanoemulsions are biphasic systems composed of oil, aqueous phase, and one or more emulsifying agents. The size of the droplets of dispersed phase are in the nanoscale range (20–400 nm) [49]. Even if W/O or multiple dispersions have been exploited for this purpose, most nanoemulsions used thus far have been of the O/W type [50].

Non-ionic surfactants as well as natural lecithin (i.e., a complex mixture that contains less than 80% w/w of phospholipids, mainly phosphatidylcholine) have been examined as non-irritating emulsifiers [51]. In general, these systems can be formed by both the low- and high-energy method, and show several advantages over traditional emulsions (coarse particle dispersion >500 nm): non-ionic surfactants are more stable against agglomeration and precipitation, and the large interfacial area displayed by their droplets makes the material transfer faster, enhancing delivery performance [50,52]. In addition, while traditional emulsions appear creamy with a semi-solid texture, nanoemulsions are fluid and transparent. Microemulsions share several features with nanoemulsions, including uniform particle dispersion, a droplet size around 100–200 nm and transparency [47]. An advantage of microemulsions over nanoemulsions relates to their high surfactant/oil ratio, which makes them thermodynamically stable and easy to prepare (i.e., they form spontaneously by simply mixing the constituents). However, the high proportion of surfactant can often lead to skin intolerance, thus limiting their applicability in cosmetics [49]. Besides the biphasic formulations, another non-vesicular system that has found wide application in the field are micelles. Micelles are formed when the surfactant amount is above the critical micellar concentration, and they find their main application in skin cleansing products [50].

### 3.1.2. Polymeric NPs

Polymeric NPs can be synthesized using either natural or synthetic polymers. Among the synthetic polymers, biodegradable aliphatic polyesters (e.g., polylactic acid (PLA), poly-lactic-co-glycolic acid (PLGA) (Fig. 3C) and poly-caprolactone (PCL)), biocompatible polyacrylates and cellulose derivatives are commonly employed, whereas extensively investigated natural polymers include chitosan, alginate and gelatin [53]. Despite the limitations of these latter substances, including an elevated manufacturing cost, a high degree of variability and the low purity of the products, the use of raw materials derived from natural sources is gaining increasing interest as they are considered safer and environmentally friendly.

Depending on the formulation components and preparation methods, two distinct systems may be obtained: nanocapsules and nanospheres. Nanocapsules are reservoirs consisting of a liquid core (generally oil-filled and stabilized by surfactant coating) surrounded by a polymeric shell. In most cases, the inner core accommodates the bioactive agent, while the polymeric counterpart controls its release. Nanospheres are composed of a polymeric matrix, in which numerous active ingredients can be entrapped or into which they can be adsorbed [54,55].

A large variety of hydrophilic and hydrophobic molecules can be loaded into these NPs, but they are mainly employed to improve the performance of chemically labile (e.g., antioxidants and retinoids), poorly water-soluble (e.g., organic filters) and volatile (e.g., fragrances) agents [56]. Moreover, these nanomaterials generally provide a sustained release of the loaded active molecules, prolonging their beneficial effects [57].

### 3.1.3. Nanocrystals

The presence of poorly water-soluble agents is a well-recognized issue in the cosmetic world. Indeed, several potent natural molecules and organic filters suffer from this limitation [34]. The production of nanocrystals is frequently proposed as a possible solution to this problem: the large surface area and poor crystallinity displayed by these particles produce a significant enhancement in compound solubility [34]. Nanocrystals, stabilized by surfactant/polymeric coating, can be obtained either by bottom-up or top-down approaches, although the latter (e.g., wet milling and high-pressure homogenization) are generally preferred [53].

### 3.2. Inorganic NPs

Inorganic NPs are composed of metals or metal oxides and, differently from the organic polymeric nanoassemblies, they generally

behave like insoluble particles. Thus, these nanomaterials are not expected to disintegrate or substantially change after skin application [58]. Their reproducible synthesis, along with their tunable properties (i.e., size, morphology), make them suitable for large-scale fabrication and, thus, their application in the cosmetic industry has now become well-established [58]. Even if they are able to improve cosmetic performance by acting as a carrier or rheology modifier, they are mainly employed as active ingredients for antimicrobial and UV protection purposes [58].

The solid particles currently applied for skincare purposes are summarized below.

- 1) Gold nanoparticles (Au NPs) (Fig. 3E) are very versatile nanoparticles with a broad range of applications (e.g., colorant, anti-aging, preservative, carrier) due to their remarkable stability, high loading capacity and easy manipulability of morphological properties [59].
- 2) Silver nanoparticles (Ag NPs) (Fig. 3F) have been extensively explored for cosmetic purposes as broad-spectrum antimicrobial and antifungal agents and colored pigments [60].
- 3) Titanium oxide and zinc oxide nanoparticles (TiO<sub>2</sub> and ZnO NPs) (Fig. 3G and 3H) are prepared by the sol-gel technique and the precipitation method, respectively. Their ability to reflect and scatter UV-A and UV-B radiation makes them excellent UV inorganic filters [61].
- 4) Silica nanoparticles include a wide range of products (see the list of approved EU nanomaterials [62], which are mainly composed of amorphous silica). They are used both in rinse-off and leave-on products with the aim of improving the product texture and/or to provide a matte (i.e., opaque) finish in the location where the product is applied [63].
- 5) Given the central role of copper in the production of skin extracellular matrix and its biocidal activity, copper-based nanomaterials have been investigated for anti-aging and biocidal purposes [64]. Their role is still controversial and their use in skincare is not widespread.
- 6) Aluminum oxide nanoparticles are also included in the list of nanomaterials approved by the EU, but they are used in make-up products (e.g., concealers, foundations and mineral foundations) rather than in skincare [65].
- 7) Several carbon-based nanomaterials have been explored for cosmetic purposes such as nanodiamonds, fullerenes and nanotubes [66]. While the first two have been applied in skincare, the latter, together with other non-toxic and cheaper nanotubes (e.g., naturally-occurring halloysite), are largely employed in haircare as pigment carrier [67].

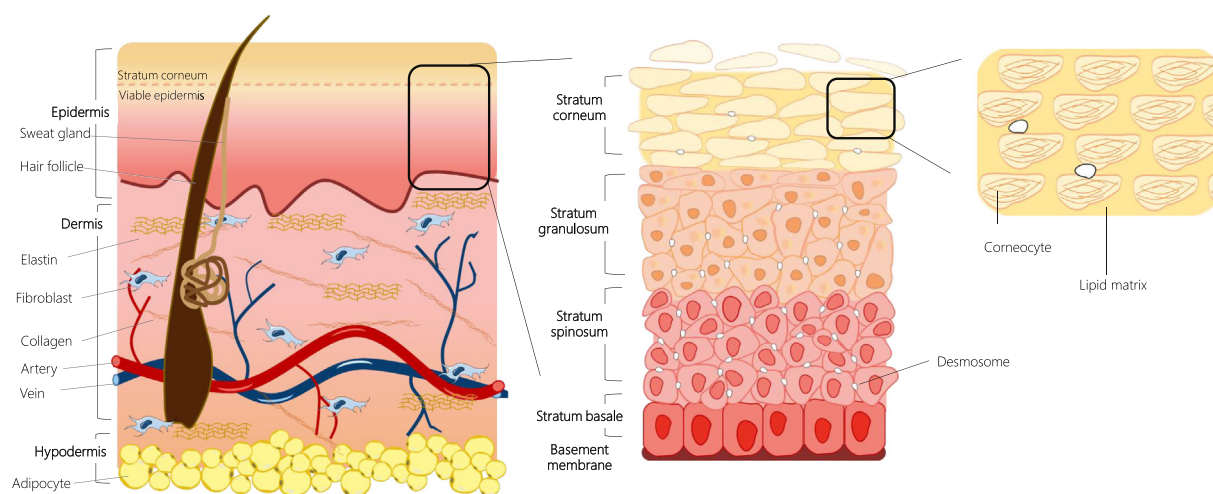
### 3.3. Role of NPs in overcoming the barrier properties of skin

#### 3.3.1. Skin barrier properties

Skin is a complex organ composed of multiple layers (i.e., epidermis, dermis and hypodermis) whose structure is schematically represented in Fig. 4A.

The epidermis, which is the most superficial layer, represents the main physical-chemical barrier to the permeation of bioactive agents, as it consists of a stratified, tight epithelium. Epidermis (Fig. 4B) consists of keratinocytes that are in a constant state of transition from the deeper layers to the shallower, connected to each other by desmosomes, adherent junctions and tight junctions, which limit the diffusion of substances into the underlying dermis. Different stages of keratin maturation determine the nature of the four epidermis layers, which, from the surface downward to the basement membrane (BM), include: the stratum corneum (SC), the stratum granulosum (SG), the stratum spinosum (SS) and the stratum basale (SB). SC (Fig. 4C) is composed of enucleated dead cells (corneocytes) surrounded by a lipidic matrix organized in a non-aligned “brick-and-mortar” structure and its surface presents numerous grooves of variable depths called skin furrows. While the majority of the epidermis’s defensive function is actuated by SC, which is considered a lipophilic stratum (15% water), all the other strata,





**Fig. 4.** A) Schematic representation of the skin. Epidermis and dermis have a thickness of 0.1–0.2 mm and 2.0–5.0 mm, respectively, while the thickness of the hypodermis varies greatly between individuals and depending on the anatomical site. B) Epidermis structure. Viable epidermis (50–150  $\mu\text{m}$ ) and the stratum corneum (10–20  $\mu\text{m}$ ) differ in hydrophilicity and pH, which ranges between 4.5 and 5.5 on mammalian SC surfaces and approaches neutrality at the SC-SG interface; C) Stratum corneum composition. This has been described as a “brick and mortar” structure laden with by desmosomes, in which non-aligned corneocytes (displacement 15–30%) are dispersed in a lipidic matrix.

grouped for simplicity into a single multilayer called viable epidermis (VE), exhibit a more hydrophilic character (75% water).

Dermis is mainly composed of fibroblasts and a reticulum of collagen and elastin fibers in a proteoglycan-based matrix, and, along with hypodermis, it provides trophic and mechanical support to the epidermis. Blood vessels and innervations are located in these deeper layers. Molecules can permeate across the epidermal layer by different routes according to their physical-chemical features, and a 500 Da threshold has been indicated as the molecular weight (MW) limit allowed for skin permeation of molecules [68]. Although the identification of the predominant pathway(s) is still under debate, it is generally believed that hydrophobic compounds preferentially penetrate via an intercellular route, whereas soluble molecules take advantage of a transcellular pathway [69]. Lipophilic compounds exploit the multiple lipid layers lying between the corneocytes, while the penetration of hydrophilic molecules takes place as the result of the aqueous pores delimited by the lipid head regions of the matrix and across the corneocytes. An alternative pathway that has been well described is the so-called appendageal route constituted by glands and hair follicles, whose absorption area represents only 0.1% of the total skin surface [68]. In general, passive skin permeation is typical of substances with low molecular volume and a moderate O/W partition coefficient. Indeed, lipophilic molecules penetrate more readily than hydrophilic ones into the SC, but it is difficult for them to exit this layer [70].

In addition to the physical-chemical properties of the molecules, skin penetration is also affected by other variables, including skin metabolism, location and tissue condition at the application site, how substances bind with the tissue structure (e.g., by a hydrogen bond with the heads of amphiphilic lipid components), and the extent of vehicle incorporation [70]. The latter is particularly relevant in cosmetic applications; indeed, the formulation can act by modifying the polarity and lipophilic/hydrophilic ratio of compounds [71] and by mechanisms that include hydration and/or modification of the epidermal barrier. In addition, phase behavior and viscosity seem to play a major role by impacting bioactive molecular partitioning [72].

Finally, it is worth mentioning that whether a bioactive agent must reach the systemic circulation (i.e., absorption) or the dermis (i.e., permeation) or must partially cross the epidermis, depends strictly on the ultimate target. For cosmetic purposes, the action is often restricted to the highest skin layers and, thus, the degree of penetration is very low; this means that the product does not need to satisfy the regulatory restrictions that are generally demanded of pharmaceutical preparations.

### 3.3.2. NP penetration across the skin barrier

NP penetration (Fig. 5) is a highly controversial topic among the scientific community for at least two main reasons: 1) the toxicological implications of nanotechnology, and 2) the need to disclose the role of nanomaterials as carriers for enhancing the penetration of the bioactive agent [12,73–75].

As mentioned above, the SC is the first and main barrier faced by any ingredient. NPs have been observed to penetrate skin through the same three pathways described for other substances (transcellular, intercellular and appendageal route) [76,77]. NP size plays a major role in this process. In principle, analysis of the SC structure suggests that penetration via aqueous pores (superficial diameter 0.4–36 nm) may occur for nanomaterials below 36 nm, while the chance that NPs will penetrate via the intercellular lipidic matrix increases when they are smaller than 5–7 nm [70]. Furthermore, the large follicular space (10–210  $\mu\text{m}$ ) allows for accumulation of nanoobjects that are able to be dispersed in sweat and sebum [78]. The skin surface's chemical-physical properties affect NPs' rate of penetration (e.g., negatively charged NPs cross the epidermis more easily than those with a positive charge) [79], or they may allow a longer availability of these systems in the SC (e.g., lipid coating enhances retention in the lipid-rich SC) [80].

Although NPs have a different ability to penetrate according to their size, composition, colloidal stability and vehicle properties, some general remarks can be made distinguishing insoluble and lipid/surfactant-based NPs [81]. The first group includes solid inorganic NPs and polymeric nanocomplexes that are bio-persistent after applying them to the skin. Several studies have been conducted to investigate the behavior of these nanomaterials. Among them, here we are focused on the results obtained with human skin, as this experimental setup is usually thought to be more reliable as compared to alternative models (e.g., rat and porcine skin) [82].

Given the tiny size required for penetration, reported data suggests that bio-persistent NPs mainly accumulate on the surface of intact skin and in the upper layers of the SC [12]. Topically applied ZnO, used most often in sunscreen, showed no significant penetration through normal skin [83] and thus zinc found in the deeper layers of the epidermis/dermis resulted from NP solubilization [84]. These results were also validated under occlusive conditions and on impaired skin [83]. Similarly, TiO<sub>2</sub> NPs, another effective mineral-based ingredient for sun protection, are not able to pass through the first layers of SC in the size range between 20 and 100 nm [85]. Although these NPs seem to

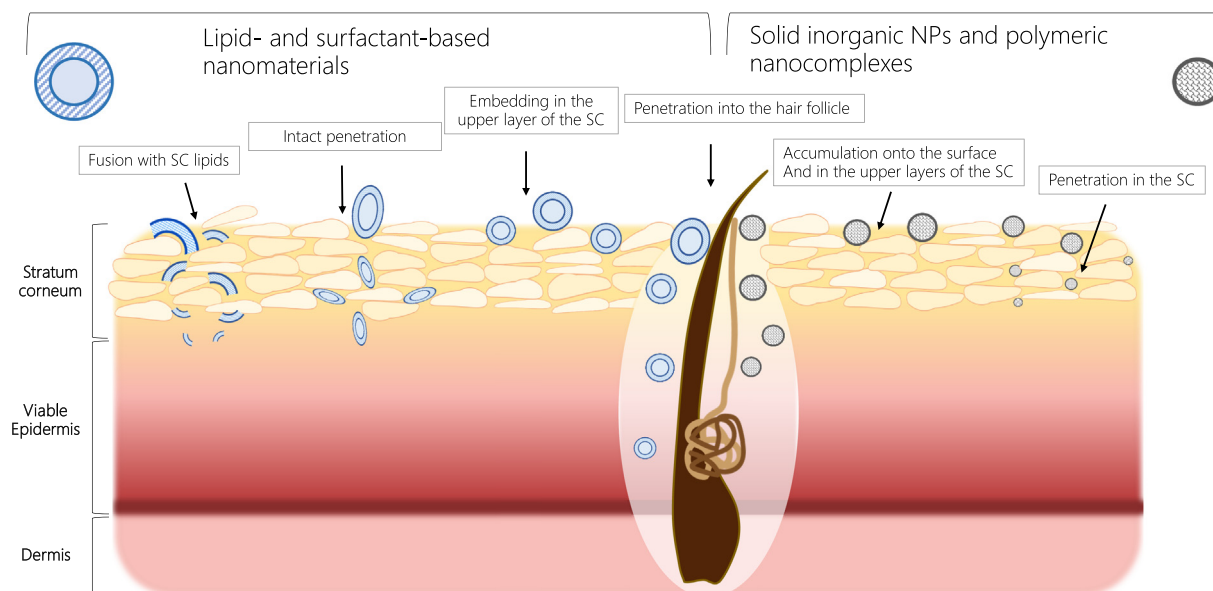


Fig. 5. Potential routes of the penetration of nanomaterials into the skin.

penetrate deeper into the follicular space, they do not diffuse into the surrounding tissues [86].

For <15 nm NPs with a solid core, inconsistent results have been observed; for instance, Baroli et al. demonstrated that <10 nm iron oxide NPs were able to penetrate the hair follicle and SC, but only occasionally reached the VE [76], whereas in another publication, 13 nm Au NPs proved capable of permeating human skin mounted in a Franz diffusion cell [83]. Although the biological significance of penetration remains to be demonstrated and the experimental conditions are expected to strongly affect the results, the aforementioned data suggest that for very small nanomaterials the impact of their superficial properties substantially increases. Indeed, a comparative study conducted on a relevant selection of small AuNPs (6–15 nm) showed that hydrophobic nanoparticles are able to achieve skin penetration following the same penetration pathway of drugs through the lipidic intercellular route of the SC, even though with a lower rate of diffusion, consistent with theoretical predictions [87].

The fate of topically applied lipid- and surfactant-based nanomaterials has not been fully elucidated. Due to the similarity in their compositions, it is very difficult or even impossible to discriminate between these NPs and the skin constituents once they have been administered. Nevertheless, it is generally believed that these nanomaterials do not remain intact after crossing the epithelium and that flexible particles penetrate more deeply than rigid NPs [88,89]. Flexible NPs, such as liposomes composed of unsaturated phospholipids and emulsions, are inherently unstable upon administration as a result of interaction with skin components [82]. Different mechanisms of penetration have been proposed, including the induction of structural changes in the lipidic matrix, surface adsorption and fusion with the SC and accumulation in the appendageal space, with the prevalent mechanism being dependent on the nanoobject properties [32,90]. It is assumed that ultra-deformable vesicles (e.g., transferosomes and ethosomes) follow the same pathways previously described, although their ability to squeeze through the pores may increase the contribution of intact/partially intact particles in the penetration [91]. On the other hand, cutaneously administered rigid nanomaterials (e.g., SLNs, NLCs, liposomes composed of saturated phospholipids) are generally embedded in the upper layers of the SC, where they have an occlusive effect or support the skin barrier function [32].

## 4. NP formulations in cosmetics

### 4.1. Application of NPs in cosmetics

As already mentioned, nanomaterials are used for cosmetic purposes as active ingredients (Table 2), rheology modifiers and carriers for bio-active molecules. In this section, examples of each application are provided. It is worth noting that a general mistrust towards the use of NPs in cosmetics makes it difficult to identify and classify the nanomaterials contained in commercial formulations. Indeed, the role of nanoparticulates remains elusive because they are mentioned as ingredients on the product label only when they are intentionally synthesized and added to specific preparations. In general, few details about the manufacturing process of NPs are reported in the technical claims. Hence, the information collected in this paragraph pieces together the scientific literature from the most recent commercial perspective. Table 3 summarizes some relevant examples of commercially available nanocosmetics.

#### 4.1.1. NPs as active ingredients in cosmetics

**4.1.1.1. UV filters.** UV radiation constitutes ~10% of total light emission and is categorized as UVA ( $\lambda = 320\text{--}400$  nm), UVB ( $\lambda = 280\text{--}320$  nm) and UVC ( $\lambda = 100\text{--}280$  nm) [92]. Only radiation with the longest wavelengths (i.e., UVA and UVB) can significantly penetrate the atmosphere and, thus, represent a risk for human health. Photoprotection may be accomplished by means of UV filters, which are generally classified as either inorganic or organic [93]. In cosmetics, the reduction of UV-induced skin damage is of the utmost importance for preventing sunburn as well as long-exposure effects (e.g., skin aging, skin cancers), and the use of filters has now been established not only in sunscreens, but also in daily-use products [94]. Nowadays, filter-containing formulations are designed to give protection against both UVA and UVB. Although the latter exhibits higher energy associated with a substantial involvement in carcinogenesis, UVA penetrates deeper into the skin layers, inducing immune system inhibition and leading to precancerous mutations [95]. Moreover, UVA is primarily responsible for the loss of skin elasticity by upregulating the production of collagen- and elastin-degrading matrix metalloproteinases [96].



**Table 2**  
Use of nanomaterials as active ingredients in cosmetics.

Function	NP type	Attributes
UV filters	Inorganic NPs (TiO <sub>2</sub> NPs and ZnO NPs)	<ul style="list-style-type: none"> <li>TiO<sub>2</sub> NPs are UVB filters, while ZnO NPs have a broad spectrum of activity (against UVA and UVB)</li> <li>Optimal transparency</li> <li>Coatings (e.g., silica, alumina) are used to prevent the potential of long-term toxicity</li> </ul>
	Nanocrystals of organic filters	<ul style="list-style-type: none"> <li>Applied to broad-spectrum filters (e.g., MTTB and TBPT) to increase their water solubility</li> <li>Superior UV attenuation as compared to micronized powders</li> </ul>
	Nanodiamonds	<ul style="list-style-type: none"> <li>Excellent UVB filters</li> <li>Proposed to overcome toxicity concerns of common inorganic filters (no photocatalytic activity)</li> </ul>
	Ivy NPs	<ul style="list-style-type: none"> <li>Naturally occurring non-toxic nanomaterials</li> <li>Transparent UVA filters</li> </ul>
Antibacterial and antifungal agents	Silver NPs	<ul style="list-style-type: none"> <li>Broad-spectrum activity</li> <li>Superior antimicrobial power as compared to silver ions</li> <li>Used as preservative or main ingredient</li> <li>Able to interfere with biofilm formation</li> </ul>
	Gold NPs	<ul style="list-style-type: none"> <li>Broad-spectrum activity</li> <li>Safer and more colloidal stable than silver NPs</li> </ul>
Moisturizing and anti-aging nanomaterials	Liposomes made of unsaturated phospholipids	<ul style="list-style-type: none"> <li>Deep penetration into SC</li> <li>Strong hydration power mediated by their components and metabolites</li> </ul>
	Liposomes made of saturated phospholipids	<ul style="list-style-type: none"> <li>Stable upon application</li> <li>Skin protective function</li> </ul>
	SLNs and NLCs	<ul style="list-style-type: none"> <li>Rigid NPs able to adhere to the skin surface</li> <li>Occlusive effect</li> </ul>
	Gold NPs	<ul style="list-style-type: none"> <li>Multiple and not fully elucidated anti-aging actions (e.g., antioxidant effect and prevention of ECM protein modifications)</li> </ul>
	Copper NPs	<ul style="list-style-type: none"> <li>Physiologically involved in dermal regeneration</li> <li>Mainly used in beauty devices</li> </ul>
Cleansing agents	Fullerenes	<ul style="list-style-type: none"> <li>Powerful antioxidant agent</li> <li>Reduction of UV damages (e.g., hyperpigmentation, wrinkles)</li> </ul>
	Micellas and Nanoemulsions	<ul style="list-style-type: none"> <li>Alternatives to conventional detergents</li> <li>Efficient removal of skin soil while preserving barrier integrity</li> </ul>
Bioactive molecules	Nanocrystals	<ul style="list-style-type: none"> <li>Increased dissolution rate</li> <li>Improved product texture, appearance and skin penetration</li> </ul>
Other uses	Silica NPs	<ul style="list-style-type: none"> <li>Chemically inert nanomaterials</li> <li>Widely used as thickeners and to achieve a matte finish</li> </ul>

Among the inorganic filters, insoluble titanium oxide and zinc oxide particles are broadly employed, especially in their nanometric form (30–150 nm) [61]. In comparison with micron-sized particles, the use of TiO<sub>2</sub> and ZnO NPs better meets consumer needs, as they reflect a small portion of the incident light particles, resulting in a transparent effect [61]. Furthermore, they are photostable, safer and more environmentally friendly as compared to organic filters [93]. Although it was believed that mineral filters act primarily by scattering and reflecting incident UV radiation and thus were denoted as physical filters, it is now accepted that they provide UV protection mostly by light absorption [97].

TiO<sub>2</sub> NPs primarily absorb light in the UVB region, a capability that is strongly dependent on particle size. Notably, particle size reduction is to

some extent responsible for increasing UVB attenuation but also for decreasing the attenuation of visible light, and 40–60 nm has been mentioned as the optimal size range to achieve acceptable UV protection with good transparency [98]. ZnO NPs are more efficient as UVA filters, although they have a broad absorption spectrum across both UVA and UVB [99]. NPs below 200 nm are visually transparent upon application [100]. There is a debate around the potential long-term toxicity of these NPs (cfr section 5 below) because they are able to generate reactive oxygen species (ROS) upon UV exposure [101]. In order to limit their photocatalytic activity without affecting UV attenuation, coatings such as silica, aluminum oxide, aluminum hydroxide, methicone, and polymethylacrylic acid are commonly applied [102]. These coatings can act by minimizing interactions with the surrounding medium or by ROS capture. Alternatively, Zaccariello et al. developed a novel inorganic filter by growing bismuth titanate in mesoporous silica NPs, which not only suppress photocatalytic activity, but also enlarge the absorption window [103]. Alternatively, other inorganic nanomaterials have been explored as UV blockers: for instance, carbon-based nanodiamonds demonstrated to act as UV-B protectant with excellent biocompatibility [104,105].

The use of nanotechnology also improves the performance of some organic filters. Indeed, most of them are oil-soluble or oil-miscible and, thus, dispersed in the hydrophobic phase of the sunscreen formulation. Since the oily phase amount is generally limited and some filters are either poorly soluble in oils, the production of nanocrystals has been proposed in order to substantially increase the loading capacity of such organic filters into the water phase [106]. Nanocrystals of tris-biphenyl triazine (TBPT) (Fig. 3D) and methylene bis-benzotriazolyl tetramethylbutylphenol (MBBT) are broad-spectrum UV filters authorized in Europe [62]. These organic pigments have shown superior performance because they combine absorption (90%) with scattering (10%) capabilities and the UV attenuation is higher than in the micronized compound [107]. Moreover, the absorption spectrum of water nanosuspension can be significantly different from that obtained with organic solutions, broadening the filter applicability; for instance, in an MBBT nanosuspension, a maximum shift at longer wavelengths accompanied by the appearance of new spectral bands was detected [106].

Besides the synthetic compounds, the use of organic “green” material has always been attractive in cosmetics and, in this context, naturally occurring ivy NPs secreted from the adventitious roots of *Hedera helix* (English ivy) have been proposed as an alternative to conventional inorganic filters that may pose issues of possible long-term toxicity [108,109]. These protein-based nanocomplexes are indeed biodegradable, transparent, potent against UVA radiation and able to maintain their protective capability over a wide range of temperatures and pH levels [108]. Despite the results, to our knowledge there is no commercial sunscreen containing these NPs, meaning that their use would need to be validated.

**4.1.1.2. Antibacterial and antifungal agents.** Commonly used antimicrobial agents suffer from several limitations, including modest potency and efficacy due to the development of resistant strains and toxicity [110]. Hence, various metal-based NPs such as Ag NPs, Au NPs, ZnO NPs, TiO<sub>2</sub> NPs and copper-based nanomaterials, have been investigated for their antibacterial and antifungal activity for a wide range of applications (e.g., the textile, food and cosmetics industries) [111].

In cosmetics, antimicrobial agents may be included in the final formulation as an active ingredient to prevent and treat skin infections: indeed, bacterial and fungal settings were found to be a common cause of several cutaneous manifestations, and the imbalance of skin microbiota have been implicated in various disorders, including acne and atopic dermatitis [112,113]. Alternatively, they can be used as preservatives with the aim of preventing microbial contamination of the product during the manufacturing process and customer use [114].

Among all of these, Ag NPs are probably the most popular nanomaterials used for antimicrobial purposes. The use of silver derivatives has recently garnered a lot of interest; indeed, it exhibits a broad-spectrum activity

**Table 3**  
List of some commercially available nanocosmetics.<sup>†</sup>

Commercial Name	Company	Nanotechnology	Cosmetic Action
Eucerin Sun Lotion for Dry Skin SPF 50+	Beiersdorf AG	TiO <sub>2</sub> NPs	Sun protection
Daylong Baby Cream SPF 30	Galderma Laboratory GmbH	ZnO and TiO <sub>2</sub> NPs	Sun protection
Moisture Liposome Face Cream	Dercortè	Liposomes	Hydrating
Moisture Liposome Eye Cream	Decortè	Liposomes	Hydrating
Sparkling Glacier Complexion Mist	Aubrey Organics	Liposomes	Hydrating
C-Vit Liposomal Serum	Sesderma	Liposomes encapsulating Vitamin C and Ginkgo Biloba extracts	Anti-aging
Resveraderm ANTIOX	Sesderma	Liposomes encapsulating a blend of antioxidants (Resveratrol, Epigallocatechin gallate, idebenone)	Anti-aging
Rehydrating Liposome Day Crème	Kerstin Florian Skincare	Liposomes delivering active anti-inflammatory and antioxidant botanicals	Hydrating and reduction of redness, unevenness and cuperose skin
Lumessence Eye Cream	Aubrey Organics	Liposomes	Anti-wrinkle and firming
Natural Progesterone Liposomal Skin Cream	Now	Liposomal skin cream containing progesterone	External use
Longevity-C Serum	Setarè	Liposomal Vitamin C	Anti-aging
Proteos Liposome	Martiderm	Liposomal Vitamin C and E	Hydrating and antioxidant action
Serum Night Repair	Estée Lauder	Liposomes	Skin repair
Active Anti-Aging Face Cream	Perris Swiss Laboratory	Liposomal Tocotrienol	Anti-aging
Body Strategist Cream Gel Revive	Comfort Zone Du Cosmetics	Liposomal delivery Vegetable Collagen and Witch Hazel extracts encapsulated in retard liposomes	Anti-cellulite Firming
Niosome Day Cream	Blossom	Niosomes containing cannabidiol	Hydrating and firming
Antiage Response Cream	Nouvelle-HSA Cosmetics	Niosomes encapsulating pomegranate seed oil, concentrated yeast extract and a mix of monophosphate ribonucleosides	Anti-aging
Eusu Niosome Makam Pom Whitening Facial Cream	Eusu	Niosomal delivery	Skin whitening
Anti-Fatigue Eye Contour Roll-On	Möller for Man	Niosome elastic complex	Moisturizing
Nio-Cell Body Cream	Bellezza Italiana	Niosomes encapsulating forskolin, caffeine and aescin	Anti-cellulite
Renewal Jelly Aquarysta	Astalift	Nano-Ceramide, Nano-Astaxanthin, Nano-Lycopene	Anti-aging
Bruma De Leite	Natura	Nanoemulsion	Body Hydration
Skin Caviar	La Prairie	Nanoemulsion	Anti-aging
Bepanthol Facial Cream Ultra Protect	Bayer Healthcare	Nanoemulsion	Hydrating
Coco Mademoiselle Fresh Moisture Mist	Chanel	Nanoemulsion	Body Hydration
Nanovital VITANICS Crystal Moisture Cream	Vitacos Cosmetics	Nanoemulsion	Moisturizing, firming and lightening
Dragon's Blood Hyaluronic Night Cream	Rodial	Retinol-loaded Lipodisq	Anti-aging
Multi-Targeted Elixir	Re:Erth	Lipodisq-based delivery	Skin-refining
Allure Body Cream	Chanel	SLNs	Body moisturizer
Cream Nanorepair Q10	Dr. Rimpler GmbH	Coenzyme Q10-loaded NCLs	Anti-aging
Filler Intense Cream	Cellact	Nanospheres containing Dimethylsilanol Hyaluronate	Anti-aging and hydrating
24K Nano Ultra Silk Serum	Orogold Cosmetics	Gold NPs	Anti-wrinkle
Nano Gold Energizing Eye Serum	Chantecaille	Gold NPs	Moisturizing
Cor Silver Soap	Cor	Silver NPs	Cleanser
The Silver Anytime Moisturizer	Cor	Silver NPs	Hydrating
Micro Silk White Lotus Intensive Lotion Mask	Joyona	Silver NPs	Skin balancing and hydration

<sup>†</sup> The products of these companies were selected because they explicitly list nanomaterials in the label.

and the multiple mechanisms of action displayed by this metal (e.g., cell membrane leakage, DNA damage, protein denaturation) hinder the development of resistant strains [115]. As was also demonstrated by our group, Ag NPs frequently show superior antimicrobial power as compared to silver ions, an effect that is likely due to unique microbial-nanomaterial interactions attendant to the sustained release of silver [60,116,117]. Moreover, it has been demonstrated that Ag NPs interfere with biofilm formation, which is often responsible for infection relapse [118,119]. Ag NPs can be synthesized by conventional or “green” (i.e., silver reduction operated by microorganisms/using nontoxic reducing agents) chemistry: while the former is low-cost and high-performance, several examples of the latter have been reported in recent literature, indicating an increasing interest in

eco-friendly processes and bio-manufactured products [120]. Ag NPs can be included in semisolid formulations such as gels and creams [114,121], and owing to their activity against bacterial and fungal infections, Ag NPs have found applications in many cosmetic and personal care products, including facial cleanser, creams, masks, foot balms, deodorants, shower gels and shampoos—performing as well or even better than conventional antimicrobials. A recent example is a randomized trial comparing the activity of Ag NPs with clindamycin in the treatment of acne vulgaris: Ag NP-based gel proved to be as effective as a gel containing an antibiotic, showing good tolerability and receiving a better satisfaction score [122].

Au NPs exhibit antimicrobial properties as well and are often proposed as alternatives to Ag NPs—they are inert, biocompatible and

exhibit a superior safety profile as compared to silver-based materials [120]. Moreover, a recent publication claims that Au NPs are more colloidally stable than Ag NPs when included in a semisolid formulation [123]. However, at present Ag NPs remain the primary choice in cosmetics and the potential for alternative nanomaterials needs further examination.

**4.1.1.3. Moisturizing and anti-aging nanomaterials.** Although they are not predominantly used with this aim, a number of nanomaterials have the intrinsic ability to improve skin wellness, further increasing the value of nanocosmetic products.

Liposomes composed of unsaturated phospholipids tend to come apart after being applied to the skin, and for this reason their components are able to deeply penetrate into the SC, where they exert a moisturizing effect. This is both a consequence of the inner hygroscopicity of these phospholipids as well as their metabolism [32]. Notably, the action of the skin phospholipases leads to the production of osmolytes (e.g., betaine) that prevent water loss [124] by preserving the volume of keratinocytes and increasing the tight junction expression [125,126].

On the other hand, preparations made up of saturated phospholipids possess a skin protective function; in fact, these lamellar structures remain stable upon application and resemble the lipidic matrix [32]. Since the disruption of matrix architecture is a common cause of dry skin and classical surfactants are able to extract and wash out SC lipids, formulations containing such ingredients are used in irritated, sensitive dry skin as an alternative to conventional emulsions [127–129].

Among the lipid-/surfactant-based NPs, SLNs and NLCs may also regulate the skin water content when topically applied. Due to their nanometric size and rigidity, SLNs and NLCs are able to adhere to the skin surface, forming an invisible occlusive film that prevents water loss, contributes to reinforcing the skin barrier, and protects it from environmental contamination [130,131].

The usefulness of gold for beautifying purposes has been known since ancient times—it was part of Cleopatra's beauty routine. Beyond the myths surrounding it, this noble metal possesses several beneficial qualities, and many anti-aging cosmetic products incorporate Au NPs. However, it is not well-understood exactly how this nanomaterial works. It likely has multiple actions; for example, it has been shown that Au NPs possess antioxidant properties targeting UVA-induced ROS generation [132] and that they can compete against carbohydrates in binding with extracellular matrix proteins to inhibit the formation of advanced glycation end-products, whose accumulation decreases skin elasticity [133].

The physiological role of copper in dermal regeneration (e.g., the stimulation of collagen and elastin production and the induction of fibroblast proliferation) has spurred investigation into copper-based nanomaterials in the treatment of skin aging [64]. However, very few skincare products containing these NPs are available; in fact, the only well-documented example of copper NPs with anti-aging properties is an NP-impregnated pillow that reduces facial wrinkles [134].

Even if in Europe it is only approved for haircare purposes, several reports investigated the use of fullerenes in skincare. Indeed, their distinctive antioxidant power make them suitable for minimizing the sign of aging induced by UV exposure [135].

**4.1.1.4. Cleansing agents.** The skin is coated by a hydrolipidic layer composed of secretions from sebaceous and sweat glands, in which endogenous (e.g., decomposition products, cellular debris) and exogenous (e.g., pollutants, pathogens) contaminants accumulate. Hence, cleansing, with the aim of removing impurities and controlling odors and skin microbiota, is fundamental to preserving skin health.

The removal of dirt on the skin is mainly accomplished by using surfactants that are able to bind lipophilic substances not eliminated by simple washing with water. However, surfactants may also impair the skin barrier function by solubilizing a number of skin components and/or accumulating in the SC matrix [136]. Thus, novel formulations have been

developed as alternatives to conventional soap bars and detergents, especially for facial cleaning. Micellar systems and nanoemulsions have especially found application in this area [137,138]. A widely used product that exploits the first is so-called micellar water—it contains water and small amounts of mild surfactant and is able to efficiently remove dirt from skin without foaming and/or disrupting the skin barrier [139].

Another effect of skin cleansing is the elimination of dangerous microbes and, as mentioned above, a number of metal-based NPs are used as disinfectants and decontaminants. Thus, Ag NPs are integrated into products like soap bars and fluid detergents. These products also take advantage of the anti-inflammatory properties of silver and claim to efficiently treat acne and sun-damaged skin [140].

**4.1.1.5. Improved active agents resulting from nanonization.** In addition to their use as UV filters, it has been proposed that nanocrystals may improve the performance of a number of bioactive agents used in cosmetics. Consumers typically have a positive perception of creamy, smooth and silky products; however, several molecules and extracts that offer beneficial effects for skin health are colored and poorly soluble, which hampers their usefulness. Besides giving the product an unpleasant appearance, the poor solubility of an active ingredient may compromise the product's homogeneity and limit its absorption [34].

Nanonization of bioactive agents has been proposed as a strategy to overcome these issues; indeed, the large surface area of nanocrystals increases dissolution rates and skin adhesion capacity, and promotes penetration [34,141].

Several publications have reported on the use of nanocrystals for cosmetic applications. Most of the bioactive ingredients investigated are fat-soluble antioxidant agents (e.g., flavonoids, ubiquinone, lutein, resveratrol) [34,142]. For instance, Romero et al. reported on the production of large amounts of hesperidin nanocrystals by smartCrystal® technology (wet-bead milling followed by high-pressure homogenization); the obtained concentrated nanosuspension proved to be stable after 1.5 years and more permeable when incorporated into hydrogels [143]. Interestingly, the same group showed the superior performance of the antioxidant activity of a formulation containing rutin nanocrystals as compared to other commercial rutin-based products [144].

Although early products and the first group of patents entered the marketplace in 2007, the use of nanocrystals is still in its infancy in cosmetics [143,145]. However, this technology could be useful because it allows the development of formulations containing novel and poorly soluble active ingredients without the mediation of a delivery system.

**4.1.1.6. Rheology modifiers and other uses to improve the properties of formulations.** Rheology modifiers, often referred to as thickeners, are included in the formulations of cosmetics to increase their viscosity, improve their sensory characteristics and give the consumer the perception of quality. The use of nanomaterials, mainly clay and silica NPs, as rheology modifiers has become very popular. Notably, the chemical inertness of silica NPs makes them optimal for cosmetic purposes, to such an extent that important cosmetics companies—e.g., L'Oreal—report their systematic use [63]. The thickness effect is likely due to the transient aggregation of NPs into a percolating network that does not compromise the product's spreadability as it falls apart under mechanical pressure [146]. Besides acting as thickeners, silica NPs give the product an opaque finish and have been investigated as skin protectors for their ability to absorb and neutralize hazardous compounds [147].

#### 4.1.2. Nanoparticles as delivery vehicles

The use of nanomaterials as delivery systems is intended to improve the performance of the active ingredients in diverse ways. In cosmetics, nanocarriers are generally exploited to solve issues related to the bioactive agents, such as their poor stability, low solubility or penetration ability, or the need to control their release. A number of active ingredients are inherently unstable under conditions of environmental stress (e.g., antioxidants and retinoids are sensitive to UV light, oxygen and



heat), but nanoencapsulation may protect them from degradation, enhancing their shelf-life and *in vivo* efficacy [37,148]. By apparently increasing the solubility of certain active ingredients, nanocarriers may also make the formulation of poorly soluble molecules practical and thus lead to the development of new or redesigned products [33,149]. On the other hand, the enhancement of bioactive agent penetration may also be achieved by a different mechanism that is strictly related to the properties of nanocarriers. Especially when bio-persistent and relatively large, nanomaterials tend to adhere to the SC surface and/or accumulate in the skin furrows and follicles, which act as depots for bio-active agents and increase their concentration gradient [150]. As mentioned above (2.3.2), some nanomaterials, intact or not, are also able to directly promote penetration into the SC [82]. In addition, SLNs and NLCs exert an occlusive effect that may contribute to an increase in the diffusion of the active ingredient, whereas nanomaterials composed of surfactants, phospholipids and other amphiphilic molecules may act as penetration enhancers by affecting the organization of the skin lipidic matrix [45,150,151]. Penetration enhancement is crucial for many active ingredients because, as highlighted in paragraph 3.3.1, the skin is a very selective organ—the physical-chemical properties required for penetrating the SC are very stringent and the diffusion of relatively large as well as strongly lipophilic and hydrophilic molecules is hampered [152]. Lastly, the nanoencapsulation of active ingredients may modify their release kinetics as compared to conventional formulations: 1) numerous nanocarriers, including several polymeric and lipidic NPs, provide a sustained release; 2) few groups/companies are investigating the use of stimuli-responsive materials as well as active targeting approaches to selectively tune delivery. The stimuli can be both internal (pH, enzymes) or external (UV), while the active targeting can be directed towards keratinocytes and other skin cells [153–157].

Overall, one concrete benefit of nanotechnology derives from the versatility of the materials that compose the carrier, which could in particular preparations result in one or more of the aforementioned effects and in general increase the efficacy of the product [82]. After this general overview of the advantages of nanomaterial-mediated delivery, the next paragraph subsections provide several examples of nanotechnology applications in the formulation of active ingredients in cosmetics, grouped according to their function and structural similarities.

**4.1.2.1. Retinoids.** Vitamin A (retinol) and its derivatives (retinoids) are among the most commonly used active ingredients in skincare. They are able to promote the growth, differentiation and maintenance of epidermal cells, regulate the sebum and enhance extracellular matrix production, reducing skin wrinkles and acne. Moreover, because of their ability to stimulate cellular turnover, inhibit melanogenesis and block the transport of melanin to epidermal cells, they are utilized to treat pigmentation and photoaging disorders [158]. However, their chemical structure exposes these compounds to photoisomerization, photopolymerization, photooxidation and photodegradation and some of them induce skin irritation and sensitization, which limits their usefulness [159]. These drawbacks may be overcome by means of nanotechnological approaches. The performance of tretinoin (*all-trans* retinoic acid) and its precursor (retinal) are improved by conjugating them into polymers that are able to self-assemble into NPs. Castelberry et al. proposed the conjugation of tretinoin into a hydrophilic synthetic polymer (polyvinyl alcohol), while Limcharoen et al. produced retinal-grafted chitosan. Both of these biodegradable NPs exhibited increased photostability and acted as prodrugs, providing a sustained release of retinoids that significantly reduced the undesirable effects associated with their overloading into the skin [160,161]. Alternatively, the nanoencapsulation of retinoids has been exploited in order to ameliorate their activity. For instance, both liposomes and caprolactone-based nanocapsules loaded with tretinoin demonstrated protection of the active ingredients from photodegradation [162,163]. Retinol, popular for its anti-aging and anti-acne effects, has been recently encapsulated into biocompatible silicon particles. This process has

demonstrated a high encapsulation efficiency, and the resulting NPs enable a slow release of the active ingredient over time and offer enhanced photoprotection in comparison with an industrial standard [164]. Adapalene is a third-generation retinoid used in the treatment of acne, and recent reports have focused attention on the ability of nanocarriers to provide a follicular delivery of this active ingredient. Two groups reported adapalene encapsulation into SLNs that were subsequently incorporated into Carbopol gels; in both cases, this formulation possessed suitable viscosity and spreadability, allowed sustained release and local accumulation of the active ingredient and reduced irritation [165,166]. Moreover, Harde et al. showed follicular accumulation of SLNs and improved *in vivo* anti-acne potential as compared to conventional formulations [166]. An alternative delivery system (oil-free and alcohol-free) has recently been described: by means of tyrosine-derived nanospheres, optimized for the encapsulation of hydrophobic compounds, the authors were able to deliver sufficient amounts of adapalene to hair follicles and epidermis even at a decreased dosage as compared to the marketed product [166].

**4.1.2.2. Antioxidants.** Antioxidants (AOs) protect against DNA damage caused by the presence of ROS generated after various internal or external stimuli [152]. AOs accomplish this task by neutralizing ROS, inhibiting ROS-producing enzymes or chelating transition metal ions. In skin, exposure to UV radiation causes an excessive production of ROS, which is responsible for aging (wrinkles and hyperpigmentation) and cancer. These negative effects can be tackled by the local administration of AOs, which can be classified as enzymatic (e.g., catalase, superoxide dismutase, glutathione reductase) or non-enzymatic (coenzyme Q10, vitamin C, vitamin E, polyphenols). Besides being incorporated into anti-aging products, the use of AOs has been proposed as a strategy to enhance the photoprotective power of sunscreens [167]. Despite their efficacy, AOs contained in topical preparations suffer from limited stability; a number of nanocarriers have been investigated to overcome this drawback [53]. The optimal delivery system is, in general, selected depending on the polarity of the bioactive molecule. The most established nanocarriers in cosmetics are liposomes and hence they are often the primary choice in commercial skincare products (Table 3) [37], but liposomes lack stability. Several approaches have been reported for ameliorating this problem, including the use of biocompatible polymer coating or encapsulation of liposomes in stimuli-responsive hydrogels or double emulsions [168–170]. A detailed overview of the challenges in using liposomes for the delivery of AOs was recently provided by Van Tran et al. [37]. Beyond liposomes, other delivery systems have been exploited to improve the activity of AOs.

Coenzyme Q10 (CoQ10, ubiquinone) is an endogenous AO contained in a number of anti-aging products. When enzymatically converted in its reduced form, CoQ10 acts as a radical scavenger, protecting lipid membranes and DNA from oxidative damage. However, this active ingredient is characterized by a high lipophilic profile; for this reason, several studies reported CoQ10 encapsulation in lipid-/surfactant-based nanomaterials. SLNs containing CoQ10 were developed by Farbound et al. and then incorporated into a semisolid emulsion. This formulation showed a sustained release of the bioactive agent *in vitro* and, after two months of application on healthy volunteers, led to a substantial increase in skin elasticity and hydration as compared with a conventional cream [171]. In a study aimed at optimizing a nanoemulsion formulation designed to increase CoQ10 solubility, the selected preparation was tested in rats, and showed a significant anti-wrinkle effect after 30 days of treatment [172]. Lohan et al. developed so-called ultra-small NLCs (~80 nm) and compared the *in vitro* activity of the new formulation with standard NLCs and nanoemulsions using the same ingredients. This novel system showed promising results *in vitro*, but before they can be safely applied in cosmetics, the behavior of nanocarriers after incorporation into semisolid formulations and possibly *in vivo* validation should be further investigated [173]. The group of Olivera and Cruz focused their investigation on the use of CoQ10 and Vitamin

E-loaded caprolactone nanocapsules subsequently incorporated into hydrogels. The purpose of this formulation was to improve the active ingredient's stability, facilitate cutaneous application and reduce the effects of UVB radiation on skin. The latter was evaluated in mice and the group found a significant decrease in edema and inflammatory cell recruitment after the administration of treatment [174].

Another fat-soluble AO that may benefit from nanoformulation to improve its solubility and stability is alpha-tocopherol (vitamin E). This potent AO could be used as a main active ingredient as well as a stabilizer for other compounds [175]. In addition to its antioxidant properties, this vitamin has largely been investigated for its wound healing abilities. Due to its lipophilic nature, the nanocarriers investigated for vitamin E encapsulation and delivery are similar to those already in use for CoQ10 [174,176]. As part of an alternative delivery system, Caddeo et al. synthesized vitamin-loaded transferosomes composed of phosphatidylcholine and Tween 80, which afforded high active encapsulation efficiency and stability and demonstrated a protective effect against oxidative damage in vitro, as well as wound healing potential [177].

Ascorbic acid (AA, vitamin C) is a hydrophilic compound that, even though it possesses a variety of dermatological functions—including UV protection, free radical neutralization and an essential role for collagen biosynthesis—is very unstable; indeed, it is unavoidably inactivated in the presence of oxygen as well as under light and in alkaline conditions. The use of derivatives and/or carriers has been proposed to manage its poor stability and its poor penetration capability [178]. The pronounced water solubility of this compound makes liposomes optimal for vitamin C encapsulation. The studies available in the literature used conventional liposomes (i.e., those composed of phosphatidylcholine/lecithin, already on the market; see Table 3) or advanced vesicles [179]. An example of the latter is the inclusion of charged phospholipids in the nanocarrier formulation; notably, according to Maione-Silva et al., negatively charged liposomes loaded with AA showed a significant improvement in bioactive agent penetration as compared to positive or neutral vesicles [180]. Zhou et al. demonstrated that coating the formulation with negatively charged pectin enhanced its stability and, similarly to the previous example, improved skin permeation, while the Wang group proposed the inclusion of photo-responsive lipid to control AA release [153,181]. Exploiting the amphiphilic nature of ascorbic palmitate, Aboul-Einien et al. have recently developed a novel liposomal system that they have termed “aspasomes” for treating melasma. After optimizing the nanocarrier composition, they incorporated aspasomes containing an AA derivative into two different semisolid formulations (gel and cream), selected the best one after in vivo animal testing and demonstrated the product's efficacy on melasma-affected patients [182]. Another promising delivery system, based on completely different materials and normally applied in oral care, are nanocomposites made of hydroxyapatite. Indeed, hydroxyapatite is widely accepted in cosmetic and biomedical applications because it closely resembles the constituents of bone. Sliem et al. explored this strategy by synthesizing AA-loaded nanocomposites stabilized by carboxymethyl cellulose, and was successful in demonstrating the stability of the nanoassembly [183].

Given the interest around the use of naturally derived compounds, including production waste, it is not surprising that polyphenols have been widely investigated for cosmetic applications. Among them, flavonoids are bioactive molecules broadly found in fruits, vegetables, and herbs, that feature a wide range of biological activities [184]. Indeed, in addition to their antioxidant action, the anti-inflammatory and blood vessel protection functions of flavonoids are interesting for cosmetic applications. Nanocosmetic products based on flavonoids may contain either single compounds or complex extracts; examples of the second type are nanoemulsions and vesicular and polymeric NPs [185–187]. However, probably due to poor material availability, the nanoformulation of complex extracts is less frequently studied; our discussion here is thus focused on single-compound products. Quercetin

is the most widespread flavonoid in nature, but in addition to possessing limited stability, it suffers from poor solubility and low permeability. Bose and Michniak-Kohn optimized SLN and NLC preparations for improving the topical delivery of quercetin. When tested in vivo on healthy volunteers, both NPs significantly promoted the accumulation of quercetin in skin, but the highest reproducibility was obtained with NLCs, probably because of their enhanced stability [188]. In a recent publication, Hatahet et al. compared various delivery strategies, including quercetin-loaded liposomes, lipid nanocapsules and quercetin nanocrystals. Given the low loading efficiency found in liposomes (more than 20 times lower than the other two preparations), this formulation was considered not optimal for cosmetic purposes and was therefore excluded from in vivo testing. On the other hand, penetration studies conducted on healthy volunteers indicated that the selected lipid nanocapsules improved the penetration of quercetin in the deeper layers of the SC/VE because of their tiny size (~27 nm), whereas nanocrystals accumulated mainly in the upper layers of the SC. Hence, the author suggested different possible applications for these two nanoformulations: it would be preferable to utilize nanocapsules for psoriasis/anti-aging purposes, while nanocrystals could be applied in photoprotection [189]. Another delivery system alternative to liposomes is phytosomes. These nanomaterials consist in vesicular NPs composed of phospholipids complexed into a single botanical derivative [190]. The effect of a cream containing quercetin-phytosomes was recently evaluated in a single-blind study conducted with 30 volunteers. After inducing controlled and reversible skin stress in four different regions of the back, the subjects were treated, and different formulations compared for their ability to reduce skin inflammation. In summary, phytosome-based cream had a protective effect against a variety of insults (UV radiation, histamine stimulation and contact with irritating chemical agents) and was effective as a commercial formulation containing antihistamine [191]. Resveratrol is another potent AO found in grapeskins, peanuts, berries, and even chocolate [192]. Since this polyphenol has multiple beneficial effects, several groups are investigating delivery systems for the purpose of overcoming its limitations. According to a recent review, the most popular resveratrol nanocarriers for topical administration are lipid nanoparticles and liposomes [193]. However, a few examples of dermal applications have been reported and, given its increasing use in cosmetics and dermatology, alternative strategies could be explored [194–196]. For instance, Abbas and Kamel developed and characterized resveratrol-encapsulating ultradeformable niosomes (Spanlastics) composed of Span surfactants and edge activators. Once optimized, the selected formulation was tested in mice with damaged skin, and its superior protection against UV radiation was confirmed by means of visual examination and molecular markers [197].

Overall, the reported studies suggest that nanoformulation may actually improve AO activity, even when incorporated into semisolid formulations. Since many commercial products incorporate more than one AOs, future investigations could be directed towards the development of more complex nanocarriers containing multiple AOs.

**4.1.2.3. Enzymes.** The use of enzymes in cosmetics is relatively recent and at present only a limited number of products are available. If on the one hand they are attractive because they have demonstrated superior performance as compared to traditional active ingredients, on the other, they are difficult to deliver in a cosmetic preparation. Their activity is in fact strongly affected by several common ingredients that destabilize their native structure. In addition, their skin penetration is limited by their high molecular weight. Various enzymes have been proposed for skincare purposes, including the aforementioned enzymatic AOs, DNA-repairing enzymes (photolyase and *micrococcus luteus* endonuclease), lipases, hyaluronidases and exfoliating enzymes (bromelain, papain, actinidin) [198]. The latter group is particularly interesting because these enzymes can be extracted from natural sources (e.g., pineapple, papaya) and are considered to be a milder alternative to

irritant beta and alpha hydroxy acids in the treatment of sensitive skin [199]. Although the nanoformulation of enzymes is expected to improve their usefulness, only a few examples can be found in the literature so far, likely because their use is still uncommon [198,200]. For instance, the liposomal formulation of *m. luteus* endonuclease and photolyase, referred to as ultrasomes and photosomes, respectively, has been described, and their incorporation into sunscreens has been proposed to reduce the incidence of skin cancer [201,202].

**4.1.2.4. Peptides.** Another important group of biomolecules widely used in cosmetics are short peptides consisting of 2–7 aminoacids. Mostly applied in anti-aging products, this class of cosmetics comprises many compounds having various cell functions. They are categorized as signal peptides, carrier peptides, neurotransmitter inhibitor peptides and enzyme inhibitor peptides [203]. Even if their use in cosmetics is now established, very little *in vivo* efficacy data is available and their inclusion in a commercial product is generally justified by the need to improve skin appearance [204]. Topical peptides may benefit from nanoformulation as it may protect them from degradation and enhance their permeability. For instance, Puig et al. demonstrated that the use of liposome-loaded tripeptide-10 citrulline, selected for its ability to interact with collagen fibers (in a decorin-like activity), improved skin elasticity [205]. More recently Suter et al. took advantage of the use of SLNs to deliver a heptapeptide using shea butter as the dispersant phase and lecithin as a stabilizer [206]. The Infinitec company has developed a delivery technology for peptides based on the use of NPs comprised of noble metals or precious stones [207].

Nevertheless, in the few reported attempts to optimize peptide delivery, none demonstrated the superiority of nanoformulation over conventional formulations. This result is likely attributable to the fact that the peptides useful for cosmetic applications were generally selected to penetrate the SC (MW < 500 Da and moderate log of partition coefficient) without using a delivery system. Hence, the potential of this approach remains mostly unexplored.

**4.1.2.5. Ceramides.** Moisturizing agents are used to increase skin hydration. Conventional moisturizing strategies rely on the use of occlusive agents or humectants: occlusive agents (e.g., petrolatum, beeswax, fatty acids) create a film that impairs water evaporation, while humectants (e.g., glycerol, panthenol, pyrrolidone carboxylic acid) bind and retain water in the skin [208]. Although efficient, these compounds are not physiologically involved in skin moisturization and, hence, exhibit only a transient hydration power. As constituents of the lipidic matrix, ceramides have been proposed as novel moisturizing agents to restore the functionality of the skin barrier. Given the low solubility of these compounds, a number of nanocarriers have been proposed to improve their penetration as well as to enhance formulation properties [209]. Among these potential nanocarriers, microemulsions and nanoemulsions have been shown to encapsulate ceramides with high efficiency [210]. Yilmaz and Borchert investigated the use of positively charged nanoemulsions stabilized by biocompatible phytosphingosine and then incorporated into a semisolid formulation, demonstrating improved activity as compared to negatively charged nanoemulsions [211]. In another study, Tessema et al. evaluated the *ex-vivo* delivery of microemulsion-containing gel compared to a starch-based NP formulation: the former was able to increase the degree of penetration into the deeper layers of the skin [212]. According to a recent review, microemulsions exhibit the best performance; this is likely because, in addition to the nanosized droplets, this formulation contains large amounts of surfactant, which may act as a penetration enhancer [209]. Alternative carriers are ceramide-based liposomes, nanodispersions and polymeric nanoparticles [213,214]. An interesting example of the latter is the stimuli-responsive system developed by Jung et al. for the treatment of atopic dermatitis. Briefly, PLGA NPs encapsulating ceramides were coated with chitosan, exploiting the latter's adhesiveness and solubility at an acidic pH in order to obtain a sustained release

of the active ingredient. Data suggested that treatment with this formulation was able to promote skin regeneration in an *in vivo* atopic dermatitis model more effectively than the commercial product [214].

**4.1.2.6. Hyaluronic acid.** Hyaluronic acid (HA) is an endogenous glycosaminoglycan that is abundant in younger skin, but its presence unavoidably decreases with aging. Due to its capability of retaining water molecules, HA is widely employed as a moisturizing agent [215]. Moreover, as a physiological constituent of the skin's extracellular matrix, HA could be used for anti-wrinkle purposes [216]. Despite these beneficial effects, HA's large MW (>500 kDa), along with its high hydrophilicity, results in poor penetration that strongly limits its potential [217]. HA can be incorporated into a number of cosmetic products for topical application as well as used as a soft-tissue filler. In this case, the poor permeability of HA is overcome by means of intradermal microinjection [216]. Although HA microinjection is quite common, accounting for 80% of filler treatments in the US, and allows for maximal accumulation down to the dermal layer [218], several non-invasive strategies have been proposed to improve HA performance, some of them exploiting the use of nanotechnology. For instance, Jegasothy et al. assumed that a superior penetration of HA can be achieved by reducing its MW and formulating the polymer in the form of NPs (nano-HA, 5 nm). A treatment based on the use of several formulations (lotion, serum and cream) containing nano-HA was tested on thirty-three women and an improvement in skin hydration and elasticity, together with a decrease in skin roughness, were detected after 57 days [219,220]. Although the effectiveness of the nano-HA-based products was demonstrated, this study did not compare its results to non-nanosized HA treatments. In addition to the size reduction, HA nanoformulation has been explored as an alternative strategy for increasing penetration. Tokudome et al. synthesized a 100 nm complex comprised of HA (1200 kDa) and cationic protamine and compared *ex-vivo* penetration of free HA and HA NPs in full-thickness mouse skin. Interestingly, the improvement in skin accumulation was observed only when the nanocomplex was included in a diisopropyl adipate-based emulsion. Moreover, the quantification of HA using HPLC analysis of homogenates suggested that the nanocomplex disaggregates while crossing the skin and releases free HA into the deeper layers [221]. More recently, the same authors investigated the penetration pathway of similar nanocomplexes (based on polylysine instead of protamine) and confirmed the intercellular transit by fluorescent microscopy [222].

A different approach was followed by Chen et al., who harnessed skin-penetrating peptide (SPACE) conjugation to improve the performance of HA-loaded ethosomes. The efficacy of formulation was tested both *ex vivo*, using porcine and human skin, and *in vivo* (in hairless mice), and an enhanced HA penetration was observed with the conjugated ethosomes as compared with free-HA and non-conjugated NPs [223]. Likewise, Martins et al. designed a nanodispersion using lipid materials to circumvent limitations on transporting hydrophilic macromolecules across skin layers. The authors used a solid-in-oil (S/O) technology, in which the complex between surfactant and protein mixed with HA was lyophilized and dispersed in isopropyl myristate by ultrasonication, forming an S/O nanodispersion. An NP formulation loaded with 30kDa HA was tested *in vitro* on abdominal pig skin, and showed successful permeation across the SC layer. Results suggested that the diffusion of HA down to the dermis was consequent to the nanocomplex's dissociation [224].

**4.1.2.7. Organic UV filters.** Organic UV filters are classified as either UVA, UVB or broad-spectrum absorbers, and their chemical structure typically involves a chromophore conjugated into aromatic rings substituted for by electron-donating groups [93,225]. Originally conceived as additives to products designed for sun protection, these compounds are now included in daily-use cosmetics to enhance their value in the prevention of long-term UV-induced damage. So that they can provide sufficient protection (i.e., broad-spectrum activity with high



absorption capacity), they are often used in combination [93]. A common concern about their use is percutaneous accumulation and absorption, which could trigger the generation of toxic metabolites and ROS responsible for several adverse effects [226,227]. Given the ability to finely optimize the properties of carriers, nanoencapsulation has been proposed as a strategy for increasing the retention of the active ingredient in the uppermost layers of the skin, avoiding permeation [228]. Moreover, as has been previously reported for other bioactive agents, common drawbacks, including high lipophilicity and limited photostability, may be positively impacted by the use of nanocarriers. Among the nanomaterials suggested for organic filter entrapment, SLNs and NLCs have been seriously investigated. Indeed, the solid core of these NPs may act as a UV blocker, having a synergistic effect with the active ingredient and potentially decreasing the amount of the filter that is loaded into the formulation [227,229,230]. In addition to the aforementioned nanomaterials, polymeric nanocapsules as well as silica NPs have been investigated for their potential to deliver organic filters [231–233]. Recent studies on this topic have focused their attention on the encapsulation of multiple filters and on the search for delivery systems with superior performance. Here we report only a few representative examples; a more comprehensive overview of nano- and microencapsulation of UV filters is given elsewhere [228].

In a study conducted by Hayden et al., three organic filters (i.e., octinoxate, oxybenzone, avobenzone) were encapsulated together with vitamin E in ethylcellulose nanospheres. These biocompatible NPs could be incorporated into various sunscreen formulations (e.g., emulsions, oil), while vitamin E was used as photostabilizer. Such nanoencapsulation limited ROS generation, displayed a broad UV blocking activity and formed flexible films [234]. Another study exploited AO lipids (i.e., rice bran and raspberry seed oils) to synthesize vegetable-based NLCs loaded with two organic filters, namely octacrylene and butyl-methoxydibenzoylmethane. The formulation obtained after NP incorporation into a cream showed minimal release of the active ingredients and actually blocked UVA and UVB radiation. It is noteworthy that this effective broad-spectrum photoprotection was achieved with filter concentrations significantly lower than the allowed dosage [235]. The use of bioadhesive materials has been also investigated for improving sunscreen safety and preventing nanocarrier accumulation in hair follicles. Saltzman and Girardi's group achieved this goal by oxidizing NPs based on biodegradable PLA- hyperbranched polyglycerol: notably, the polyglycerol coating was converted into an aldehyde-rich corona able to bind the amines exposed by skin proteins. After encapsulation of a UVB filter, the authors demonstrated *in vivo* that these NPs were water resistant, easily removable by active towel drying, did not penetrate the skin and were as effective as a commercial formulation [236]. The same group co-encapsulated avobenzone/octocrylene filters into the same nanomaterials to provide a broad-spectrum activity. A pilot study was conducted on volunteers and showed protection against UV radiation comparable to that of the standard for an FDA-approved sunscreen [237].

#### 4.2. Formulation and characterization of cosmetic products containing NPs

The formulation and characterization of NPs in skin care products is a very extensive topic. However, in this session, a brief summary of the most relevant aspects concerning this topic are presented. Once the NPs have been synthesized it becomes necessary to include them in a vehicle suitable for cosmetic use, in fact, aqueous dispersions of NPs are seldom applied directly on the skin, and it is therefore necessary to formulate them in an appropriate vehicle. In a skincare product, the physical and chemical stability of NPs not only depends on the composition of the medium in which they are dispersed, but also on the formulation used to deliver them. The ideal formulation confers physical, chemical and microbiological stability and determines the efficacy and safety of the final product. Moreover, the vehicle choice also depends

on the purpose of a cosmetic product—i.e., day or night cream, body lotion, concentrated serum, etc.

The physical stability of a cosmetic formulation containing NPs depends on the nature and tightness of the interactions among particles, dispersant, emulsifiers and thickeners. Buffers, AOs and chelating agents are used to confer chemical stability to the formulation. Preservatives prevent the growth of microorganisms. Dyes and fragrances can improve the organoleptic characteristics of the product and make it more attractive to the consumer.

The main advantage of NPs is that they release the active ingredient in the outermost skin layers in order to ensure the introduction of large amounts of this ingredient into the epidermis. Cosmetics containing liposomes have a good substantivity, which prevents them from being easily washed off. Liposomes can in particular increase the content of lipids in the SC and thus increase moisturization and reduce skin dryness [238,239].

Liposomes are mostly prepared in aqueous systems, and for this reason they can be incorporated into gels [240–242] or O/W emulsions with low surfactant content. High concentrations of surfactants can cause damage of liposome structure [238,243]. Polymers derived from cellulose (methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose and carboxymethyl cellulose) were among the most used colloids. Better results in terms of stability and consistency were achieved by using acrylic acid polymers (Carbopol®). Later, the use of polymeric emulsifiers such as Pemulen® (copolymers of acrylic acid and C10-C30 alkyl acrylate crosslinked with allyl pentaerythritol) allowed the preparation of stable surfactant-free emulsions [243,244]. More recently, innovations in liposome formulation were introduced by using a blend of surfactants derived from vegetable sources [245,246].

Like liposomes, preparations containing niosomes are usually aqueous dispersions with low viscosity that are therefore not suitable for spreading on the skin because they can easily leak from the application site. To overcome this drawback, gelling polymers are usually added to these dispersions in concentrations that allow an appropriate spreadability; furthermore, the gel produces an occlusion effect on the application site that prevents the evaporation of water. In this way, skin hydration increases and the active ingredient's penetration through the SC is promoted [44].

As reported for other types of dispersions, SLNs can aggregate if an appropriate stabilizer agent is not used. A review of SLN and NLC formulations concludes that hydrogels are promising vehicles for the cutaneous application of these NPs. The authors suggested that O/W creams may show a synergistic hydration from the lipids present in both systems [45]. When SLNs were added to a cream, they increased the cream's occlusive character without changing its consistency, which is advantageous from a marketing viewpoint. Another important feature of SLNs is that highly concentrated particle dispersions exhibit good physical stability during storage, whereas dispersions with low concentrations often aggregate. The authors explain this unexpected behavior as being the result of particle movement inside the emulsion. In less concentrated dispersions, NPs can move more freely, leading to particle collision and aggregation; in contrast, NPs in more concentrated dispersions exhibit reduced mobility in the network, thus preventing aggregation. In any case, concentrated NLC or SLN dispersions exhibit a consistency that is suitable for skin application. For this reason, the addition of thickeners or creams to the dispersion is no longer necessary to achieve the final product, resulting in strategic cost savings [247].

The selection of an appropriate formulation as a vehicle for nanoemulsions depends on the type of emulsion being employed. Most cosmetic nanoemulsions are of the O/W type, the consistency of which can be improved by either increasing the oil content (in some cases up to 25%) [248] or by adding hydrocolloids, such as Carbopol, cellulose derivatives, xanthan gum, etc. In this case, the final product is termed a "nanoemulgel" [249]. On the other hand, W/O nanoemulsions

can be formulated as oleogels or incorporated into an O/W cream by means of the emulsion inversion point method [250].

The production of nanocrystals for cosmetic purposes involves the use of appropriate solutions in which the nanosized active ingredient is dispersed. Usually, only low volumes of nanosuspension are required to prepare the final product because of the higher efficacy of small nanocrystals as compared to larger particles. Nanosuspensions can be added directly by mixing them into a gel or cream to obtain the final product. However, some precautions should be observed: it is necessary to avoid high temperatures when the nanosuspension is added to a cream to prevent the particle from growing and aggregating during storage (Ostwald ripening). It is also necessary to avoid the use of ionized additives like electrolytes to prevent nanocrystal agglomeration [251].

The use of inorganic NPs like titanium dioxide and zinc oxide has improved consumer satisfaction with sunscreen formulations. However, their physical stability has been a great challenge. Inorganic NPs should be dispersed into a suitable vehicle before being added to the final preparation, whether it be a lotion, cream or gel. Polymeric surfactants are mostly used to achieve colloidal stabilization. Some precautions are necessary for obtaining good dispersion stability; in particular, the hydrophilic chain of the polymer is designed to favor its anchorage onto the NP surface, while the hydrophobic chain should be highly soluble in the dispersant medium and strongly solvated by its molecules. Most sunscreen formulations are O/W emulsions. In this case, the particles can be in the continuous phase or the internal phase or both. In W/O emulsions, the non-aqueous dispersion remains in the oily phase [252].

Before the incorporation in a cosmetic formulation, the NPs are usually characterized in terms of morphology, size distribution, zeta potential, encapsulation and/or loading efficiency. On the other hand, it is necessary to carefully assess the entire cosmetic product in order to confirm its compliance with required quality parameters. This evaluation should begin in the pre-formulation phase with the choice of compatible ingredients and the appropriate manufacturing technique, followed by carrying out stability studies [253]. A product's final evaluation includes physical, chemical and microbiological analysis. Physical analysis takes into account organoleptic properties, including colour, odour and presence of phase separation, but also pH and viscosity. If the product contains active ingredients, it is useful to evaluate their content and their release rate from the formulation by means of dedicated analytical tests. In sunscreen formulations, sun protection factor (SPF) and determination of water resistance are required to assess product quality. Also, microbiological stability must be evaluated to warrant compliance with product quality standards during the preparation of the product, as well as during the period in which it will be stored and utilized by the consumer.

## 5. Toxicological impact of cosmetic NPs on the skin

The subject of the toxicological impact of nanoformulated "cosmeceuticals" on the skin barrier concerns their permeation into this organ, which is mainly associated with NP solubility, but also with their dimensions, surface chemical-physical properties and ability to undergo degradation. This implies that it is not possible to fully generalize about the toxicological behavior of the different nanomaterial classes, and each nanoformulation has to be considered specifically. However, it is well accepted that NPs permeability through the SC and their ability to reach the viable tissues play a key role on dermatological safety and some general remarks can be drawn distinguishing their biopersistent and non-biopersistent character. Although insoluble nanoparticles are characterized by lower diffusion coefficient compared to soluble nanomaterials, and thus they are expected to be less toxic, their use has always risen more concerns because the latter are generally composed by ingredients broadly accepted in cosmetics (i.e. lipids and surfactants).

### 5.1. Metal oxide NPs

The safety of TiO<sub>2</sub> and ZnO NPs is of great importance to the development of zinc oxide- and titanium dioxide-based sunscreens. The US-based NGO the Environmental Working Group, which peer reviewed more than 400 documents and 16 studies on skin absorption, concluded that almost no absorption of small-scale zinc and titanium sunscreen ingredients occurs through intact skin, making these formulations among the safest and most effective sunscreens in the marketplace [254]. Nevertheless, exposure of the skin to these NPs leads to the accumulation of TiO<sub>2</sub> and ZnO NPs into the deepest layers of the SC. The photocatalytic activity of these NPs is mainly responsible for their (photo)cytotoxicity and genotoxicity, even if adverse effects have also been observed in the absence of light [102]. The mechanisms responsible for TiO<sub>2</sub> and ZnO NPs toxicity seem to involve the release of ROS. Both in the deepest SC and in the keratinocytes, a higher impact was observed with partially soluble ZnO NPs as compared to the insoluble TiO<sub>2</sub> NPs [255]. In 2013, Yu et al. demonstrated that ZnO NPs lead to cell death through ROS-induced autophagic vacuole accumulation and mitochondria damage [256].

It is clear that some of the toxicity of ZnO NPs would be related to released zinc ions, which are able to penetrate VE down to the lower layers. Indeed, it has been demonstrated that dissolution of ZnO NPs results in a deep penetration of solubilized zinc ions into intact human skin [84], and Zn<sup>2+</sup> absorption by skin is mainly mediated by Zn transporters (e.g., Zrt-/Irt-like protein (ZIP) and zinc transporters (ZnT)) [257]. The cytotoxicity profile of ZnO NPs is strictly dependent on the zinc species released—whether Zn<sup>2+</sup> ions or ZnO nanocrystal fragments.

It is well known that also copper- as well as zinc-based nanomaterials, can be an irritant for skin, especially when converted to ions under the effect of exudates (sweat and sebum) [258]. Indeed, released metal ions can easily interact with SC proteins, leading to the formation of deposits that are useful reservoirs for the homeostatic control of these elements, but that can also be responsible for the toxic effect of these ions on the underlying epidermal layers [258].

In a recent work, the toxicity of antimicrobial CuO and ZnO NP-coated textiles was assessed in an *in vitro*, reconstructed 3D model of epidermis. The results confirmed that Cu<sup>2+</sup> and Zn<sup>2+</sup> ions released by NPs in acid sweat, and not intact NPs, were responsible for inducing adverse effects on this tissue. Moreover, these ions permeated across the epidermis and exerted their cytotoxicity on the underlying dermal cells [259].

### 5.2. Gold and silver NPs

The toxicity of Au NPs on skin has also been widely investigated, but the cytotoxicity of these nanomaterials on epidermal cells has not been fully elucidated. Indeed, exposure to spherical Au NPs is reported to be safe for keratinocytes, whereas gold nanorods are toxic due to the coating materials commonly used to synthesize and stabilize them in solution (e.g., cetyl trimethylammonium bromide, CTAB) [260]. The *in vitro* safety of Au NPs on keratinocytes was confirmed by Huang et al., who demonstrated a dose-dependent, yet not significant, effect of these NPs up to a concentration of 200 μM [261].

Dermal fibroblasts are also a target of Au NPs, which are known to cross the epidermis in reaching the dermal layer. Au NPs are internalized by fibroblasts into large vacuoles, inducing a size-, dose- and time-dependent reversible effect on proliferation rates, cytoskeleton morphology and extracellular protein expression [262].

Ag NPs are nontoxic for keratinocytes, but a certain cytotoxicity can be attributable to the residual contaminants in Ag NPs solutions [263]. In addition, a transient alteration of the skin microbiota could not be ruled out due to the well-documented toxicity of Ag NPs and Ag ions for bacteria and microorganisms [60]. A recent study compared the response of 2D keratinocyte cultures and 3D epidermal models to

24-hours exposure to Ag NPs. It was demonstrated that only the monoculture was subjected to oxidative damage and inflammation-related cytotoxicity, while the 3D model, exposed to the same amount of NPs, did not show any toxicological response. This is likely due to the barrier properties of this structure, more similar to those of the real tissue, which impairs Ag NPs penetration [264]. This result opens important questions about the reliability of 2D assays for the application of colloidal NPs to cosmetics.

Topical applications of 10–50 nm NPs on rabbits or pigs confirmed the contact safety of these NPs. They were not an irritant for skin when topically applied in a higher amount (16 mg silver/cm<sup>2</sup>) for a few hours in rabbits [265], or at very low doses (~0.06 and 6 µg silver/cm<sup>2</sup>) for several days in pigs [263].

### 5.3. Silica NPs

In 2013, Park et al. performed an in vitro evaluation of the toxicity of negatively charged silica NPs (20 nm and 100 nm) in keratinocyte monocultures and reconstituted epidermal 3D models (EpiDerm) [266]. A cell viability reduction was observed only with a high dose of 20 nm silica NPs, and this effect was associated with ROS generation, a common response to cell exposure to silica NPs [267–269]. No cytotoxicity occurred using 100 nm anionic NPs or with the same NPs modified to expose a less negative surface charge. The lack of any adverse effect was also recorded on EpiDerm, which resembles an actual physiological setting [266].

An official report of the Scientific Committee on Consumer Safety (SCCS) in 2016 related to the use of silica and silica-derived nanoformulations in cosmetic products suggested that a general conclusion about the safety of these compounds is still not possible from the available data. Indeed, appropriately designed studies taking into account the exposure route, concentration, stability and surface properties of these synthetic amorphous silica materials in their final vehicle, are necessary to exclude the possibility of their toxicity [270].

### 5.4. Lipid- and surfactant-based NPs

Given the poor persistence of lipid- and surfactant-based NPs in biologic environment, the toxicity of these nanomaterials is similar to the one displayed by their constituents. Notably, while the lipids are generally well tolerated, the use of surfactants may impair the skin barrier function by washing out the SC lipids or modifying the lipidic matrix permeability [136,271]. Surfactants can be included either as major component or stabilizers and the possible negative effects of the nanoformulations containing them (i.e., niosomes, SLNs, NLCs, micro and nanoemulsions) are strictly correlated with their physicochemical properties and their relative amount [271]. However, given the large variability among the formulations, the empirical knowledge shall prevail in defining their risks.

Niosomes are composed by biocompatible non-ionic surfactants, that are generally recognized to be less irritant than their anionic and cationic counterparts [271,272]. An investigation around the skin toxicity of surfactants used in niosomal formulation was conducted demonstrating a major impact of the bond type (ether- or ester-) compared to hydrocarbon and polyoxethylene chain lengths. Notably, the lower toxicological impact on human keratinocytes exposed to niosomes made of ester-type surfactants is probably due to their higher biodegradability [273].

Among non-vesicular NPs, SLNs and NLCs are generally considered safe nanocarriers for topical application: indeed, they do not require organic solvents for their scaling up and no large amounts of surfactants are demanded for stabilizing their structure [274]. Several surfactants have been successfully tested for dermatological uses including polysorbates, poloxamers phospholipids, sodium lauryl sulfate and recent studies confirmed that NPs stabilized either by Pluronic F-68 or Tween 20

and 80 mixture are totally safe on foreskin fibroblast and keratinocytes [275,276].

The choice of the surfactant to be used is a critical aspect also for micro- and nanoemulsions development. A single/mixture of surfactants can be used to make stable and homogeneous dispersions and, as previously reported (paragraph 3.1.1), for microemulsions higher concentrations are needed [51]. Like in SLNs and NLCs preparation, non-ionic surfactants such as polysorbates, poloxamers and lecithin, are generally preferred [277] even if the search for safer and environmentally friendly solutions is still in progress [278]. Moreover, beside the type and the relative amount of surfactants, the internal structure of the formulations also correlates to their toxicity. For instance, microemulsion with the same qualitative composition (isopropyl myristate/Tween 40/Imwitor 308/water), but in which varies the oil/water content, were tested in their ability to induce skin irritation, phototoxicity and cytotoxicity on keratinocytes and 3D epiderm models and gel-like microemulsions with a lamellar structure revealed to be the more toxic than droplet-like ones [279].

## 6. Conclusions

Three hot topics are motivating R&D tasks in the rapidly evolving field of cosmetics. *Innovation* is incontrovertibly the driving force of the rapid changes in the marketplace, causing the development of ever-new solutions to unresolved issues. Following in this spirit, the use of NPs and nanoemulsions is providing a renewed spur to conventional research approaches [280]. *Sustainability* is a second hot topic, especially as it relates to the environmental impact of cosmetic products, while a third key issue concerns the *health status* of consumers. This latter concern is pushing the cosmetic sector to develop products that have not only an aesthetic purpose but are also able to provide curative and preventive support to counteract adverse health factors such as aging, stress and skin alteration. Thus, in this era of sustainable "cosmeceuticals", cosmetics could be synergistically combined with other research fields, including the development of food supplements and good nutrition habits. Given the analytical technologies that are presently available to us, it is possible to integrate all of these research areas and evaluate the real efficacy of new cosmetic products on human models. Thus far, nanotechnology has proved that it is able to ameliorate the performance of cosmetics in diverse ways, in particular: 1) increasing entrapment efficiency and dermal penetration of the active ingredient; 2) controlling the release of the active ingredient; 3) enhancing physical stability; 4) improving moisturizing power; and 5) providing better UV protection [11]. The cosmetics industry has recently shown great interest in nanotechnology applications, and the superior properties of nanomaterials is encouraging research and development into innovative products [149]. Furthermore, the regulatory requirements in the field of cosmetics are much less demanding than in the pharma sector, a fact that opens up numerous opportunities for nanocosmetics.

## 7. Future outlook

The production of cosmetics is now harnessed to nanotechnology, but the future of the industry will be greatly affected by the technological advances offered by omics sciences, which, in combination with big data analysis and machine learning approaches, will allow us to better evaluate the biological responses to specific cosmetic formulations and bioactive compounds at the cellular and tissue levels. This scenario is well-integrated into the concept of "cosmeceutics," with the idea that a cosmetic item has a scientifically obvious preventive or curative effect. This claim is becoming increasingly popular thanks to social media dissemination and has a direct impact on consumers and on market demand. Consumers are now advocating for the incorporation of new bioactive or functional ingredients into cosmetic products to promote cellular revitalization through the introduction



of anti-aging and antioxidant properties [281]. Biodiversity is the new (or even old) source of these natural and sustainable compounds. As a matter of fact, significant research efforts are currently dedicated to bioprospecting and the evaluation of natural ingredients in terms of their mechanisms of action on skin.

Plants, algae and many microorganisms are rich in bioactive compounds and secondary metabolites belonging to the classes of flavonoids, phenolic acids, tannins, glycosides, terpenes and alkaloids. Bioactive compounds of natural origin have thus been extensively investigated, and some of them have been used in innovative cosmetic formulations [282]. Also, vitamins, proteins/peptides and sugars may play an important role in promoting human health, including by up-regulating specific aging-associated pathways or protecting cells from stress factors. However, most of these bioactive compounds are not easily absorbed by the skin, and additionally, numerous bioactive molecules derived from plants can be toxic or allergenic [283]. It is therefore necessary to carefully consider both the positive effects of as well as any problems related to the use of specific plant extracts or their single metabolites prior to commercialization. An important challenge is to identify sustainable and specialized extraction strategies that are capable of avoiding the shortcomings of conventional techniques like a chemical alteration risk, long extraction time and the requirement of a high energy input, and are, at the same time, able to obtain specific bioactive metabolite fractions that do not contain toxic contaminants [284].

In a context of sustainable and healthy cosmetics, nanotechnology can play a fundamental role for two main reasons. First, nanotechnology may be able to develop biomimetic particles that are able to translocate natural metabolites to the cellular target of interest that is fundamental to promoting the expected benefits. In addition, NP structural features, such as size, shape, composition and surface charge, and their formulation, can be tuned to allow control over the efficiency of transcutaneous penetration through the diverse epidermal and dermal layers [74,285,286]. A second role played by biotechnology is directed to the biosynthesis of the excipients of cosmetic formulations. Specifically, with the growing demand for natural and organic ingredients in new cosmetic items, there is also a request for preservative-free products, dyes and plastic derivatives (e.g., silicones). Biotechnological innovations are also involved in the development of biodegradable materials such as bioplastics [287] to replace synthetic counterparts, thus placing major attention on the sustainability of processes.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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