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Review

Nano-systems for Cosmetic, and their Nanotoxicity and Regulatory Issues

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Abstract

Nano-systems can help penetrate or absorb cosmeceuticals actives within epidermal layers and/or in the dermis in a controlled way to achieve burst or/and sustain release of actives. A variety of nanomaterials have been developed and used in cosmetics. However, not all nano-systems are thermally, chemically or physically stable and/or safe to use on the skin. In principle, the actives should effectively reach either the epidermis or dermis depending on the skin indication but should not enter the blood stream and further affect vital organs. The global regulatory agencies are trying to work together to find suitable criteria to control the use of nano-systems in cosmetics and increase consumer awareness.

The present review discusses recent development in nanomaterials that can find potential applications in cosmetics, along with their toxicity and regulatory issues.

Introduction

Nano-systems (1-100 nanometer (nm)), developed using variety of production methods, exhibit size-dependent physiochemical, electromagnetic and optical properties and potential biomedical and cosmetic applications [1-12]. Due to its small size, nanoparticles exhibit high quantum size effects (particularly in metals such as gold and semiconductors such as ZnO) and increased surface area to volume ratio which enhances optoelectronic or sensory properties [1-12]. These enhanced size-dependent optoelectronic or sensory properties [1-12] make nanoparticles a promising and next generation materials for the use in cosmetics. Cosmetic companies are using both nanoparticles and nanosystems to achieve or enhance following properties of the cosmetic product development: (i) solubilise insoluble or partially soluble actives, (ii) provide stability to actives, (iii) provide better UV protection, (iv) controlled delivery of actives across the epidermis and/or dermis, (v) provide long-lasting sustainable effects (such as moisturisation, anti-aging, etc.), (vi) control color and fragrance, (vii) transparency, and (viii) a quality finish.

Nanoparticles exhibit different or better optoelectronic or sensory properties than large-scale particles [1-12] and that's why they are used in cosmetics. The top 10 claims made by nano-cosmetic products are given in **Table 1** [13]. These claims show that consumers need cosmetic products that can provide both instant and long-lasting, sustainable effects for skin indications (anti-aging and brightening) using nanotechnology and natural actives.

The human skin is a natural protective barrier against external mechanical, chemical, microbial and physical stimuli [14]. The large surface area of the skin with a diversified spatial microstructure provide different ways to achieve the transdermal cosmeceuticals delivery. The skin is composed of four distinguishable layers: Stratum corneum (SC),

Table 1: Top 10 claims made for nano-systems in cosmetic products

No.	Claims	AS A % OF TOTAL NANO LAUNCHES
1	Moisturising/Hydrating	46
2	Botanical/Herbal	45
3	Long Lasting	28
4	Vitamin/Mineral Fortified	28
5	Time/Speed	22
6	Antiaging	20
7	Antioxidant	20
8	Brightening/Illuminating	18
9	UV-Protection	17
10	No Additives/Preservatives	13

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epidermis, dermis and subcutaneous connective tissue. The SC, the outermost layer of the skin, is comprised of a 10-15 μm thick matrix of dehydrated and dead keratinocytes that are embedded in highly ordered lipid layers, and serve as a protective barrier against the entry of external entities [15]. The next skin layer, the epidermis, is approximately 100-150 μm thick and comprised of multiple layers of keratinocytes and other types of cells followed by the dermis layer, containing a network of blood capillaries, lymphatic vessels and nerve endings. The subcutaneous tissue (also known as hypodermis) resides below the dermis layer, is composed of loose textured, white, fibrous connective tissue with intermingled fat and elastic fibres [16].

Micro and macromolecules can penetrate the skin through three main pathways (showed by red colors in **Figure 1**): (1) The intercellular pathway - through the lipid matrix occupying the intercellular spaces of the keratinocytes, (2) the transcellular or intracellular pathway - through the keratinocytes, and (3) the transappendageal pathwayor follicular delivery-across hair follicles, sebaceous glands and sweat glands [17]. Actives smaller than 500 kDa, with sufficient oil solubility and high partition coefficients, can be absorbed into the skin. However, large molecules with a molecular weight of more than 500 kDa cannot pass the cutaneous skin barrier [17]. Chemical enhancers such as fatty acids, surfactants, esters, alcohols, polyalcohols, terpenes, and phospholipids are sometimes used to enhance the active's (mostly for more than 500KDa) transdermal delivery [16-19]. In addition to the size of actives, hydrophobicity of actives [20], and a melting point of less than 200°C can restrict the transdermal delivery [21]. The topical delivery of actives is used to treat local skin conditions whereas transdermal drug delivery helps the delivery of actives through the skin layers into systemic circulation. Topical or transdermal delivery [20] has several advantages over the oral and intravenous dosage forms, such as prevention of first pass metabolism, minimization of pain and controlled release of actives to avoid local toxicity of actives [21].

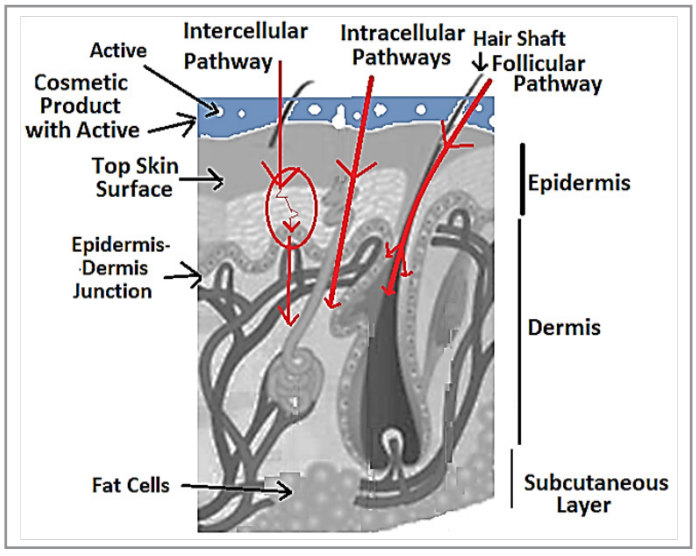

Figure 1

Alternatively, some of the devices such as microneedles, jet injectors, iontophoresis, ultrasound, electroporation, laser radiation and skin abrasions are used to enhance the skin penetration of actives that are above 500KDa in size [22]. However, some of these devices have their consumer compliance issues.

Nanocarriers may help solve some of the above-mentioned issues of devices by fluidizing the stratum corneum as a function of size, shape, surface charges, and hydrophilicity-hydrophobicity balance of nanoparticles while carrying actives across the skin layers [21].

Nano-Systems Used in Cosmetics

A list of some of the commonly used nano-systems [23-48] in cosmetic formulations is compiled in Table 2. Two main functions of these nano-systems are to encapsulate the actives and transport them across the skin barriers. Most of the nano-systems mentioned in **Table 2** provide control over shape and size of encapsulating core and chemical composition of the shell [23,24]. Most of these nano-systems provide a finite size nanocore to encapsulate mostly the hydrophobic actives and then disperse or solubilised them in aqueous formulations. These nano-systems can be used to encapsulate variety of cosmeceuticals (herbal extracts, nutraceuticals, etc.) and fragrances, stability of actives and their control release.

Figure 2 depicts schematics of (a) 2-dimensational (conventional) liposomes,(b) 3-dimensional (conventional) liposomes, (c) Transfersomes, (d) Cubosomes, (e) "Somes" characteristics, (f) W/O nanoemulsion and (g) Nanocapsule. Liposomes [23,24] have been further modified chemically to form transfersomes [25], ethosomes [26], niosomes [27,28], invasomes [29,30], and ufosomes [31] by researchers. With an addition of a surfactant, deformable vesicles are formed which can be helpful while penetrating through skin layers without breaking the vesicle and releasing the entrapped actives. Transfersomes can be used in many types of cosmetic products such as anti-acne to transfer photosensitive retinoids without affecting the stability of retinoids. Niosomes are made by adding non-ionic surfactants and cholesterol to achieve the lipidic delivery of hydrophobic (cosmetic) actives. Niosomes and Ufosomes (made form fatty acids) may be used in cosmetic products for the delivery of hydrophobic antioxidants such as vitamin E to the lipids to stabilise lipids. Both ethosomes and evasomes contain alcohol and can be used for dermal delivery of actives and may find potential applications in antibacterial (e.g. anti-acne) products and leave-off cosmetics such as cleansers. Bicelle [32], cubosomes [41,42], nanocapsules [36,37] and nanoemulsions [33-35] are mostly made from surfactant assemblies. These systems may find applications in the low viscous cosmetic products such as serums or toners for skin whitening, anti-aging, sunscreens, etc. Nanocapsules exhibit a thick polymer shell which can help protect actives from light or chemicals. Nanocrystals are made from aggregates of several hundred to tens of thousands of atoms and combine into a "cluster" of size between 10-400 nm. These can be used for concealers and scrubs because nanocrystals can

Table 2 : Nano-systems and their characteristics

Nano-Systems	Characteristics	Reference
Liposome/Vesicles	Multi-walled systems with choice of encapsulating actives depending on the active's solubility. Different types: Transfersomes®, Ethosomes, Niosomes, and Bicelles.	23,24
Transfersomes®	Made up of phospholipids supplemented with single chain surfactant with a high radius of curvature which acts as edge activators to provide vesicle elasticity and deformability	25
Ethosomes	Contains phospholipids, ethanol and water. Soft and malleable novel lipid carriers.	26
Niosomes	Formed mostly by non-ionic surfactant (of the alkyl or dialkyl polyglycerol ether class) and cholesterol is incorporated as an excipient.	27,28
Invasomes	Composed of unsaturated phospholipids, small amounts of ethanol and terpenes, and water. More efficient in delivering highly lipophilic and hydrophobic drugs into the skin than other "somes".	29,30
Ufasomes	Fatty acid vesicles	31
Bicelles	Spherical micelles and discoidal micelles and two-dimensional network of branched flattened cylindrical micelles.	32
Nanoemulsions	Dispersions of nanoscale droplets of one liquid within another, metastable systems, smaller particle size provide higher stability and better suitability to carry active ingredients. Increases the shelf life of the product.	33,34,35
Nanocapsules	Made of a polymeric capsule surrounding an aqueous or oily core; decreases the penetration of UV filter octyl methoxycinnamate in pig skin when compared with conventional emulsions.	36,37
Nanocrystals	Aggregates of several hundred to tens of thousands of atoms and combine into a "cluster" of size between 10-400 nm.	38,39
Dendrimers	Star-shaped, multi-functional, unimolecular, monodisperse, micellar nanostructures, approximate 20 nm, a well-defined, regularly branched symmetrical structure and a high density of functional end groups at their periphery. Can load large amounts of drugs/actives covalently or ionically or by physical encapsulation in voids.	40
Cubosomes	Formed by the self-assembly of liquid crystalline particles of certain surfactants when mixed with water and a microstructure at a certain ratio. Discrete, sub-micron, nanostructured particles of bi-continuous cubic liquid crystalline phase. Offer a large surface area, low viscosity and can exist at almost any dilution level. They have high heat stability and can carry hydrophilic and hydrophobic molecules.	41,42
Bucky balls	Buckminster fullerene, C60, approximately 1 nm diameter. A potent scavenger of free radicals. Used as an active ingredient for wrinkle-care cosmetics.	43,44
Lipid nanoparticles: SLNs and NLCs	Oily droplets of lipids which are solid at body temperature and stabilized by surfactants. Used for the controlled delivery of cosmetic agents over a prolonged period of time and improve the penetration of actives into the stratum corneum. Efficient in skin hydration than a placebo. UV-resistant.	45,46
Nano-inorganic (titania, zinc oxide, etc.)	Zinc oxide and titania used as sun-block in sunscreen. Gold and silver nanoparticles have antibacterial properties.	47,48

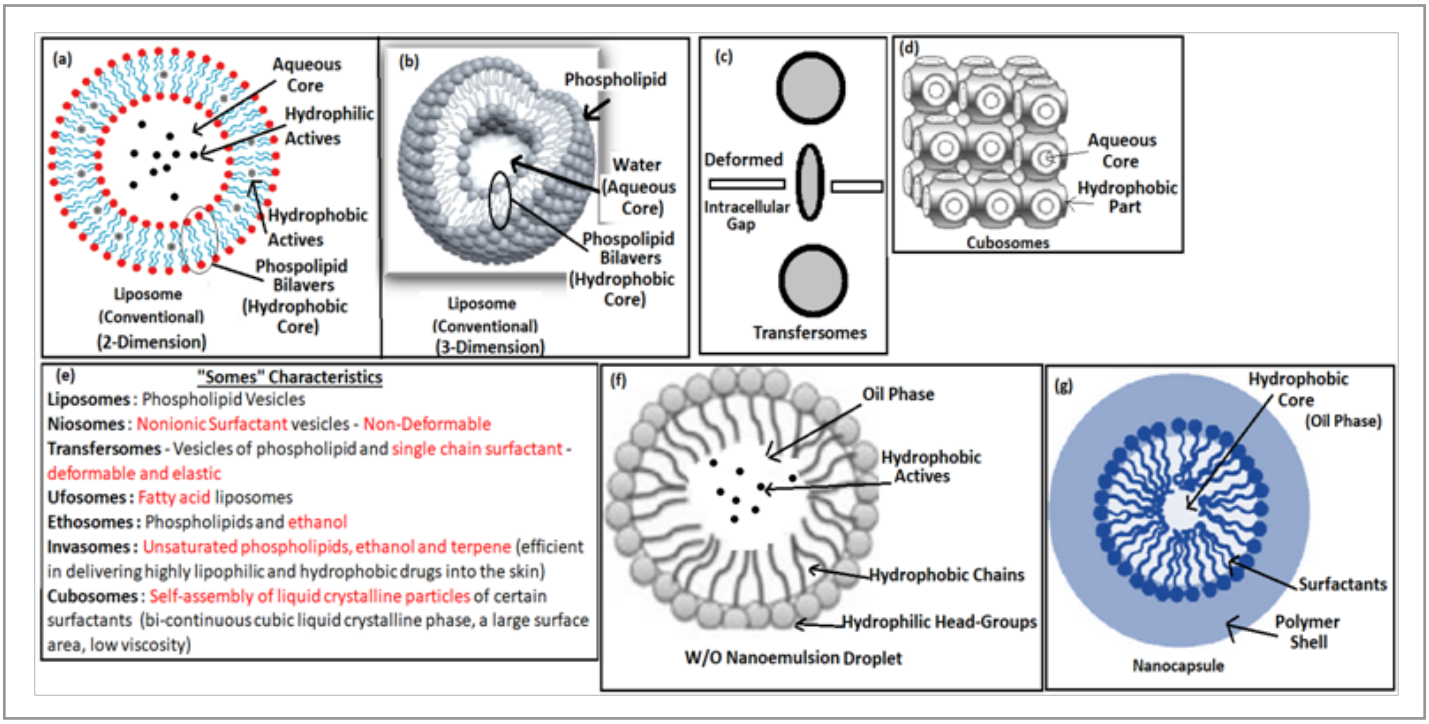

Figure 2

provide good abrasions and incorporate actives within clusters which can be released upon smearing or spreading of cosmetic products on the skin.

As seen above, with control over the chemistry the shell can be made flexible or hard. The soft and elastic structure will help flexibility while entering through the skin microstructure [25,26,31,32,38,39]. Some of the structures are formed by self-assembly [38,39,41,42] which may spread upon the application of cosmetic products on the skin. Some of these structures can encapsulate hydrophilic and hydrophobic actives [31,32,38,39] and encapsulate chemical enhancers such as ethanol and terpene [29,30] to enhance efficient delivery of actives through the skin. Furthermore, some structure like solid lipid nanoparticles (SLNs) and nanostructure lipid carriers (NLCs) can provide prolonged delivery of actives [45,46] to the skin. SLNs and NLCs can be used in multiple cosmetic products including sunscreens. However, their thermal stability may be an issue.

Star-shaped dendrimers [40a,b] are multi-functional, unimolecular, monodisperse, micellar nanostructures, and approximately 20 nm in size. Additionally, they exhibit a well-defined architecture, regularly branched symmetrical structure and high density functional end groups at their periphery, and can load large amounts of drugs/actives covalently, ionically or by physical encapsulation in voids. **Figure 3** shows the dendrimer with its different active-loading modalities [40b]. Figure 3 depicts G0-G4 as dendrimers generations and drug (actives) traps within voids and chemically bonded at the periphery. Dendrimers can find potential applications in the development of antiwrinkle and skin-whitening cosmetic products. Inorganic nanomaterials such as TiO_2 and ZnO [77b] act as UV blockers and antimicrobial agent [77c]. In addition to sunscreens, inorganic nanomaterials may find potential applications anti-acne products where metal nanoparticles may kill bacteria to treat acne.

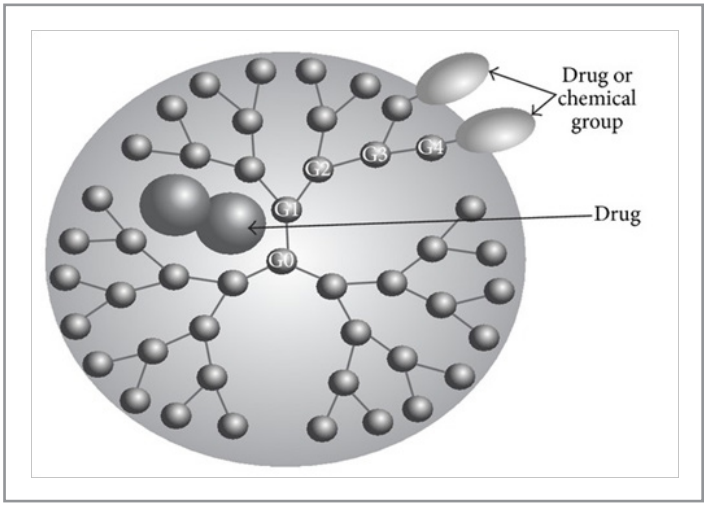

Figure 3

Fullerene (1nm) are a potent scavenger of free radicals and are used as an active ingredient for wrinkle-care in antiaging cosmetics [43,44].

Nano-systems can also be made multi-functional to impart more than one function of delivering actives to the skin. In addition to delivering actives across the skin barrier, nano-systems can provide moisturisation, improving skin elasticity or decrease the wrinkle depth and reduce toxicity. A few such examples are described below.

Manjula *et al.* [49] have evaluated the efficacy of new topical nanoparticles of low molecular nano-hyaluronic acid (50 kDa HA) to treat wrinkles, skin hydration, and skin elasticity in humans. Authors found an improvement of the wrinkles depth (reduction of up to 40%), and skin hydration (increased up to 96%) and skin firmness and elasticity (improved by up to 55%) at the end of the eight-week trial. Recently Xia *et al.* [50] and Huang *et al.* [51] have demonstrated that nanoparticles from English Ivy can be a natural alternative to the metal oxides for UV protection, and may reduce the nanotoxicity of metal oxides. Kirilov *et al.* [52] have developed organogel nanoparticles with encapsulated UV-Bblocking agent to protect the UV-B agent, and develop a water-resistant sunscreen. Felippi *et al.* [53] have encapsulated actives, coenzyme Q10, retinyl palmitate, tocopheryl acetate, grape seed oil and linseed oil in 140nm particles, and developed a multifunctional nanoparticle suspension that is safe (not irritant, sensitizing and comedogenic and photo-toxic) to use in cosmetics for increasing hydration and reducing wrinkles.

In addition to structures and chemistry of nanoparticles, the size, shape and charge on nanoparticles can be used for the delivery of actives through the skin. However, the size, shape and charge, and structure and chemical composition can also lead to toxicity issues [21,56b].

Nano-Toxicity

A growing number of scientific publications have demonstrated that nanomaterials currently used in sunscreens, cosmetics and personal care products may cause serious toxicity risks for human health [54-56a,b]. Recently Fu *et al*. have suggested that that despite the unique properties of nanomaterials have been extensively exploited in products, but their cytotoxic and genotoxic data is not fully studied so far [56b].

Some Mechanisms of Nanotoxicity

Adenosine triphosphate is synthesized in the mitochondria of cells by reduction of molecular O_2 to water through a sequence of coupled proton and electron transfer reactions. However, a small percentage of the O_2 is not reduced completely, form superoxide anion radicals and other oxygen-containing radicals. ROS are by-products of cellular oxidative metabolism which mostly occurs in the mitochondria [56b]. In addition to cellular oxidative stress, transition metals such as copper and iron can also participate in one-electron oxidation-reduction or redox reactions to form ROS [56b]. Additionally, some of nano-metal oxides can enhance ROS through Fenton reaction, Fenton-like reactions, or the Haber-Weiss cycle reaction and yield hydroxyl radicals (●OH) from H_2O_2, and superoxide anion radicals ($\bullet O^-_2$). The ●OH exhibits the highest one-electron reduction potential of all the physiologically relevant ROS, and is extremely reactive with almost every type of biomolecule, including proteins and nucleic acids [56b]. Both nano-metal oxides and nano-metals can further induce oxidative stress, DNA damage, and unregulated cell signaling, and cell motility [56b]. Hydroxyl radicals cannot be blocked by antioxidant enzymes such as superoxide dismutases (SODs), peroxidases, and catalases and can damage DNA quickly [56b].

Size, shape and crystal forms also influence the toxicity to the human skin cell. Toxicity increases as the particle size decreases. 25 nm TiO_2 particles induced more photocytotoxicity to human keratinocytes than high size (50 - 325nm) TiO_2 particles and, induced greater cell damage. Additionally, the anatase form of nano-TiO_2 has induced higher photocytotoxicity than the rutile form [56c].

Carbon nanomaterials such as Fullerenes become phototoxic upon exposure to visible or UV light irradiations which excite the fullerene surface. The excited triplet-state fullerenes transfer energy to molecular oxygen to form singlet oxygen, and then transferan electron to induce superoxide anion radicals. Superoxide anion radicals induce lipid peroxidation, leading to cytotoxicity [56d]. However, the modification of the fullerene surface by attaching one or more malonyl groups can yields derivatives of fullerenes possessing antioxidant activity [56d].

Nanoparticle Induced Toxicity

Nanomaterials can penetrate the skin [57-58] and induce cellular oxidative stress, inflammatory cytokine production, DNA mutation and even cell death [54]. They can easily penetrate the human bodyor cross biological membranes, [59] enter the blood stream, and then into vital organs such as the heart, kidney, liver and spleen [54]. Further, nanomaterials can be transported within cells and be taken up by mitochondria [60-61] and the cell nucleus [62a], where they can cause major structural damage. Moreover, Dechsakulthorn *et al*. have showed that both ZnO and TiO_2 nanoparticles (50 nm - 70 nm) are sensitive to human skin fibroblast [62b]. The small size of nanoparticles results in a large surface area per unit volume of particles which in-turn can enhance chemical reactivity and increase the production of reactive oxygen species (ROS) [63]. Both metal oxide nanoparticles [64-68] used in sunscreens and cosmetics, and carbon fullerenes [69] used in face creams and moisturisers can induce ROS. ROS and free radical production is one of the primary mechanisms of nanotoxicity which can lead to oxidative stress, inflammation, and damage to proteins, membranes and DNA [70]. Titanium dioxide nanoparticles as compared to large particles that are used in sunscreens, cosmetics and personal care products can cause far greater cell damage. Subcutaneously injected 2-5 nm TiO_2 have resulted in a moderate inflammatory response in rats [71]. 500nm TiO_2 particles can break DNA strands where as 20nm TiO_2 can destroy super coiled DNA completely, even at low doses

in the absence of UV [72]. Additionally, TiO_2 nanoparticles can produce ROS in human brain cells [73]. Moreover, TiO_2 nanoparticles can cause cell death in cultured neurons at low concentrations (>20ppm) after 24 hours of exposure [74]. In addition to the ROS production, both TiO_2 nanoparticles and nanoparticles of zero-valent Fe can influence adenosine triphosphate levels and mitochondrial depolarization [75]. Photo-activated TiO_2 nanoparticles and zinc oxide have caused oxidative damage to DNA in cultured human fibroblasts [88]. Similarly, photo activated TiO_2 nanoparticles have caused oxidative stress mediated toxicity in in-vitro skin fibroblasts and nucleic acids [89] and in human colon carcinoma cells [90]. Therefore, TiO_2or ZnO nanoparticles from cosmetic products should not enter the blood circulation with potential of reaching vital organs.

Silver nanoparticles are known to be highly toxic to pathogens and bacteria [76] and are widely used in toothpaste, soaps and face creams, antimicrobial formulations and wound dressings [77a]. However, silver nanoparticles are highly toxic to mammalian cells in-vitro, even in the absence of photo-activation. The exposure of low concentrations of silver nanoparticles to rat neuronal cells [78], mouse germline stem cells [79a], rat liver cells (all in-vitro) [80] has resulted in the reduction of the cells size and shape, mitochondrial dysfunction and increased oxidative stress. Additionally, gold nanoparticles (40 nm and 80 nm) with different surface coatings (branched polyethyleneimine, lipoic acid and polyethylene glycol) showed that the surface chemistry (particularly polyethyleneimine) can affect the cellular uptake of gold nanoparticles, and induce the modulating expression of genes involved in DNA damage and repair, heat shock response, mitochondrial energy metabolism, oxidative stress and antioxidant response, and endoplasmic reticulum stress and unfolded protein response cascades [79b].

Fullerenes are used in some face creams and moisturisers and their toxicity is still not completely understood. However, carbon fullerenes (buckyballs) have been found to cause brain damage in fish [81], kill water fleas and have bactericidal properties [82]. Additionally, low levels of water soluble fullerenes are toxic to human liver cells, carcinoma cells and dermal fibroblasts in-vitro [83]. Fullerene-based amino acid nanoparticles can reduce the viability of human epidermal keratinocytes and induce a pro-inflammatory response [84]. Toxicity of fullerene is found to be a function of surface structure [85] and the degree of aggregation (due to different solvents or emulsion bases) [86]. Photo-activation of fullerenes C60 and C70 in the presence of biological reducing agents (e.g. reduced form of nicotinamide adenine dinucleotide, NADH) resulted in cleavage of super coiled DNA in-vitro and induced ROS [87]. Thus, almost all types of nanomaterials used in sunscreens and cosmetics can be harmful as they may produce ROS and free radicals upon UV light exposure [54].

The broken skin is acompromised protective barrier and particles of up to 7,000nm can penetrate through the skin layers to reach the living tissues [54]. Skin conditions like acne, eczema or shaving wounds are likely to enable the uptake of nanoparticles.Therefore, further research is required to establish the relationship of the damaged skin conditions, including sun burn and the uptake of nanomaterials, from sunscreens and cosmetics [91].

The choice of vehicles (serums, gels, cream, penetration enhancers, etc.) can also influence the penetration of nanomaterials through the skin. This may be the reason that there are conflicting results about the penetration of metal oxides and fullerenes in the skin (when used in sunscreens) and their toxicity profiles [92-101].

Regulatory Issues with Nanomaterials

There are concerns about some of the nanomaterials that can cause potential ill-effects to humans and environmental health and safety risks. Some efforts have been undertaken internationally to harmonize approaches to address definitional issues and safety concerns related to the use of nano-systems in cosmetic products [102].

Australia, USA, and European union [103-105] are assessing the safety of cosmetic products utilising nanomaterials. New Zealand is setting up rules related with specific mention of nanomaterials, and labelling requirements in cosmetic products containing nanoparticles [106].

The organisation, Friends of the Earth Australia, has found foundations and concealers containing nanoparticles being sold by 10 top name brands [107]. Some of the concealers, foundations and mineral foundations sold by leading brands contained 100nm particles. Some cosmetic products also contained penetration enhancers which may help the penetration of nanoparticles into the skin which can help nanoparticles to enter the blood-streams and reach vital organs. Some of mineral foundations pose greater inhalation risks due to their powdered form. Only one brand indicated the presence of nano-particles on the product label. Such labelling should be made compulsory so that consumers can make an informed choice before buying cosmetic products containing nanoparticles. There are some concerns about long term health risks of nano-cosmetics because the long-term health risks of nanoparticles remain poorly understood. The likely exposure in 'real life' conditions is also unknown. But early studies have suggested that if exposure is high enough, nanoparticles now used by the cosmetics industry could cause lung damage, cell toxicity, damage DNA, and possibly even harm unborn children. In 2004, the United Kingdom's Royal Society, recommended that nanoparticles should be treated as new chemicals and be subject to new safety assessments before being allowed to be used in consumer products. Australian nano-cosmetics still largely remain unlabelled and effectively unregulated. The Australian laws neither ask companies to test the product safety before using nanoparticles, nor enforce labelling of nano-ingredients [108]. Europe has passed new laws that will require most nano-ingredients in sunscreens and cosmetics to require safety testing and compulsory labelling. However, a lot of research and regulations are needed to make safe and efficacious cosmetic products containing nano-systems for consumers.

Conclusion

Nano-systems offer a wide variety of delivery systems to develop cosmetic products. This is to deliver cosmeceuticals actives across the skin by various mechanisms and impart a wide variety of functions including moisturisation, sun protection, wrinkle reduction, etc. However, toxicity remains an issue to solve within many nano-systems. Regulatory agencies in many countries are trying to establish some guidelines to control the safety of cosmetics that utilises nano-systems, to protect consumers. More international collaborative efforts between researchers as well as between global regulatory agencies are needed to develop standard rules and regulations of using nano-systems in cosmetics and labelling for cosmetic companies. Then cosmetic companies can develop safe and efficacious nano-systems and use them in cosmetic products for the benefits of consumers, and educate consumers about the potential dangers of nano-systems.

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