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Investigations of NPs and Nano Carriers Properties for Dermatological Treatment

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ABSTRACT

Objective: *Nanotechnology (nano: One billionth) is a novel arena with promising applications in the field of medicine, especially pharmaceuticals for safe and targeted drug delivery. The skin is a phenomenal tool for investigation of nanocarriers for drug delivery for topical and dermatological application.* ***Method:*** *The physicochemical characteristics of the nanoparticles, such as rigidity, hydrophobicity, size and charge are crucial to the skin permeation mechanism. Even though different ways have been found to make therapeutics penetrate and permeate the skin better, they are often harsh and could cause permanent damage to the stratum corneum.* ***Results:*** *Nanosized carrier systems offer a novel methodology for contemporary technologies, causing negligible disruption to the skin's natural barrier function.* ***Novelty:*** *This Review discusses the use of Nano carriers to deliver drug molecules, genetic material, and vaccines into the skin, emphasizing nanotoxicology research and recent clinical advancement for market translation.*

INTRODUCTION

Nanotechnology can possibly trace its roots back to the 1950's when physicist Richard Feynman discussed the concept of machines making smaller replicas of themselves. Eventually it was demonstrated in fact that matter has unique behavior at the nanoscale. In addition to the size, the fact nanoparticles had been purposefully engineered contributed to the uniqueness that they penetrated the skin easier than their bulk counterparts [1], [2], [3].

People expect that nanotechnology will be the fastest moving arena for maintaining skin health as well as the diagnosis and management of skin disease. Skin disorders have genetic, metabolic, inflammatory, immune-system-related or malignant pathophysiological origins that occur in the upper dermal layers as, or manifest to deeper subcutaneous and systemic compartments. Though intact skin provides some advantages for topical therapy compared to other routes, the numerous detrimental alterations induced to the skin during disease renders topical therapy of these diseases harder and more troublesome [4], [5], [6].

In recent years, there has been growing interest in the use of inorganic nanoparticles for the treatment of skin diseases and cosmetic purposes (Table 2). The inorganic nature of nanoparticles renders them remarkably stable and can have beneficial

physical, chemical and biological properties including safety, versatility, good biocompatibility, targeted delivery and availability/functionality, to name a few.

Titanium dioxide and Zinc oxide nanoparticles are widely recognized inorganic nanoparticles commonly utilized in sunscreen for UVA and UVB protection. They have cosmetic advantages, including being transparent rather than the undesirable thick and opaque used in solutions for decades, and providing broad-range UV protection [8].These varying indications illustrate that nanoparticles within an evidence-based dermatological practice heralded a new era of skincare superiority over traditional dermatological practice. The precision and significance of nanoparticles coupled with the delivery allow for targeted treatment for specific skin concerns with an ineffability and significance reminiscent of Whorf's Sapir-Whorf hypothesis [7], [8], [9].

Nanoparticles, as an underlying mechanism for dermal penetration at the molecular level, enhance delivery of beneficial constituents to safe and efficacious levels. They also provide a lightweight, unencumbered, non-greasy substitute for cumbersome traditional formulations. Their versatility offers a range of active skincare ingredients that can be used with nanoparticles to customize each use. The prolonged benefits obtained with nanoparticle controlled release exceeds the temporary effects of many traditional skin care products. The use of nanoparticles in skin health is an impressive advancement, resulting in more effective, peaceful, and person-centered skin care. As technology continues to grow, nanoparticles in improving skin health standards offers hope for the future of skin health practices [10].

RESEARCH METHOD

Nanotechnology and dermatology

The skin is the largest organ of the human body, presenting a total area of approximately. Nanotechnology promises to transform the diagnosis and treatment of dermatological conditions because of its interaction at the sub atomic level with the skin tissue. The skin represents a marvelous vehicle through which these nanomaterials can be investigated for drug delivery, both with respect to active ingredient delivery and efficacy.

Being the most exposed part to the external environment, it is more prone to the ill effects of radiation and ultraviolet rays. Any pathology involving the skin is a matter of cosmetic concern. Since the systemic treatment for dermatological problems comes with its potential adverse effects, topical application is the preferred mode due to higher patient compliance and satisfaction.

The skin forms a barrier to the external environment and is impermeable to the drugs due to epidermal cell cohesion and stratum corneum lipids [Figure 1b]. There is a requirement for efficient drug delivery systems past this barrier. Nanotechnology can be used to modify the drug permeation/penetration by controlling the release of active substances and increasing the period of permanence on the skin, besides ensuring a direct contact with the stratum corneum and skin appendages and protecting the drug against chemical or physical instability. Further, the delivery of therapeutic agents without the need for chemical enhancers is desirable to maintain the normal skin barrier function.

treatment with chemical enhancers, such as surfactants and organic solvents, can cause not only a reduction in the barrier function of the skin, but also irritation and damage to the skin.

RESULTS AND DISCUSSION

Nano carriers

Nanostructured carriers have emerged as an alternative system for drug delivery in recent years due to their unique advantages compared to traditional formulations. This class of carriers comprises colloidal particulate systems, with dimensions ranging between 10 nm and 1000 nm, and have demonstrated unique advantages: they can enable targeted drug delivery, sustain release, conceal labile groups from degradation, and have a low toxicity and have drug adhesion to the skin. Various formulations and drug release nanocarriers have been developed, including liposomes, micelles, polymeric and solid lipid nanoparticles, and inorganic nanoparticles as well as sub micron emulsions.

Nanocarriers offer a unique opportunity to overcome limited diffusion of free molecules in the skin. Designing nanocarriers to interact with skin components can improve skin penetration and expands the clinical use. Properties of the nanocarrier such as size, shape, rigidity, and surface charge will all affect skin penetration and interaction with other biological constituents. The nanocarrier design lends itself to multi-functionality. Therefore, one may design nanocarriers for drug molecule delivery, genetic material delivery, and even large antibody formats for delivery. Various aspects of Nano carriers are presented in Figure 1 and table 1

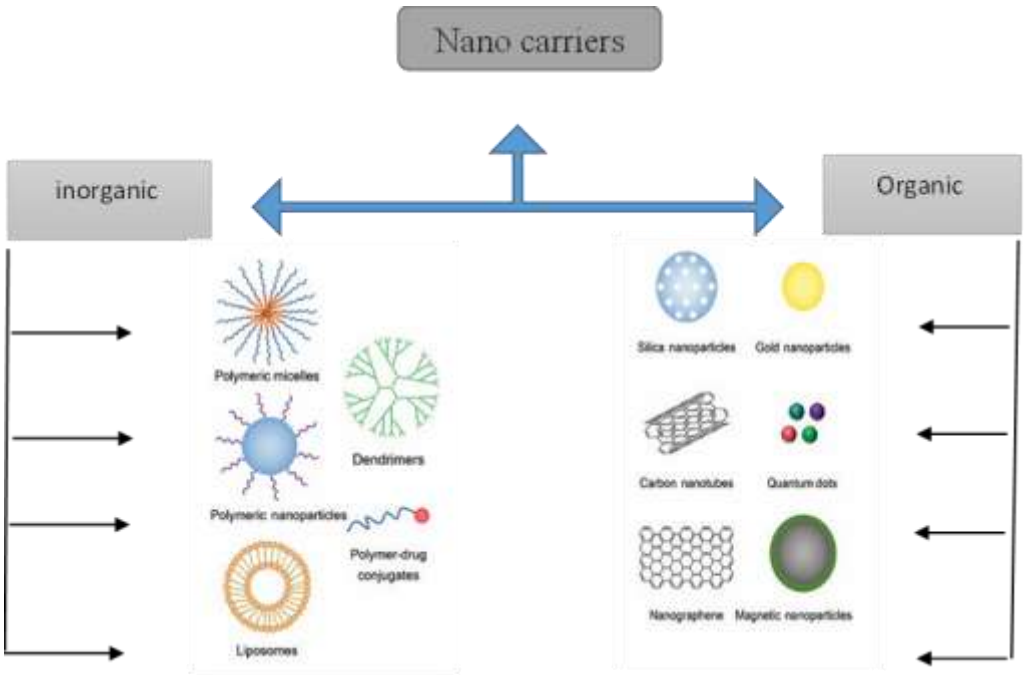


Figure 1. Types of nanocarriers including Inorganic and organic

Table 1. Types of nanocarriers including Inorganic and organic

Inorganic nanocarriers	*Organic nanocarriers*
Carbon nanotubes: are lightweight, cylindrical carbon structures with high surface area and mechanical strength, making them effective nanocarriers for drugs and proteins. They are increasingly applied in cosmetics, such as hair color products, with several related patents filed.	**Liposome:** Liposomes are versatile carriers that improve the delivery of vitamins, antioxidants, and active compounds in cosmetics. Their biodegradable and non-toxic nature makes them valuable in creams, sunscreens, anti-aging products, and hair treatments.
Gold and silver nanoparticles :are biocompatible nanocarriers with high drug-loading capacity, antimicrobial properties, and the ability to penetrate targeted cells. They are widely used in cosmetics—such as creams, masks, lotions, and perfumes—for antibacterial, antifungal, and skin-tightening effects.	**Dendrimer as a nanocarrier:** are nanosized, branched polymeric structures built around a core that enhance drug penetration through the skin. They are widely applied in cosmetics such as shampoos, sunscreens, gels, and anti-acne products, with several related patents already filed.
Titanium nanocarriers: is widely used for its brightness, high refractive index, and stability, and its nanoparticle form (nano-TiO_2) is increasingly applied in skincare. Nano-TiO_2 serves as a UV filter in sunscreens and cosmetic products and shows promise in chemopreventive nanogels for protecting against UVB-induced skin damage.	**Solid lipid nanocarrier:** are nanosized carriers made from lipids and stabilized with surfactants, designed to enhance skin penetration and controlled delivery of active ingredients. They are widely used in cosmetics like sunscreens, deodorants, and vitamin E formulations due to their biocompatibility, UV protection, and low toxicity.
Zinc oxide nanoparticles (ZnO NPs): are versatile metal nanomaterials with strong UV-absorbing, antimicrobial, and anticancer properties. Biocompatible, cost-effective, and safe for use in cosmetics and drug delivery, they offer advantages over other metal oxide nanoparticles in nanomedicine and personal care products	**Polymersome as a nanocarrier:** are stable synthetic vesicles with both hydrophilic and lipophilic regions, enabling the delivery of diverse drugs and biomolecules. In cosmetics, they are being explored for enhancing skin elasticity and cell activation, with several patents already filed.
	Hydrogels as nanocarriers: are 3D hydrophilic polymer networks with strong cross-links that can swell in water and act as versatile drug carriers. Their biocompatibility, ability to protect sensitive molecules, and potential in targeted therapies—such as skincare and melanoma treatment—make them promising nanocarriers in cosmetics and medicine.

In addition to inorganic NPs, the biocompatibility of organic NPs has also been examined through assays like MTT, comet assay, ROS determination, and eye irritation

potential. Edlich and co-workers investigated polyglycerol-based NGs to determine their inhibition of cell proliferation capability. No toxicological effect was observed on skin for concentrations in the range 50 to 500 mgmL @ 1 . Polyglycerol based NGs were compared to a true positive control and the results indicated that the NGs did not increase ROS production levels at a concentration of 500 mgmL @ 1 . Further jf more, to evaluate their potential to modify genetic material, comet assay was performed which showed no mutagenic effect in Langerhans cells. Similarly, chitin NGs loaded with curcumin have been found to exhibit low toxicity at 1 mgmL @ 1 in HDF and A375 cell lines using similar assays. With the current trend of organic NPs for topical applications, synthetic polymers like PLA or PLGA have been explored and combined with chitosan to improve their biological properties. To analyze the immune response of these materials, in vivo inflammatory models have been developed by Singh et al. Allergic contact dermatitis was quantified by measuring the reduction of ear swelling in inflamed mice ears. The studies revealed that the thickness of ear swelling was reduced after 3 days, from 106.56 mm to 56.23 mm after the application of NGs for three consecutive days. Table 3 summarizes approaches and results from different nanotoxicological studies using different nanomaterials.

Table 2. Summarizes approaches and results from different studies using different nanomaterials.

Ref.	Result	Material
[123]	Gold nanorods inhibit cell proliferation	Gold nanospheres, nanorods
[123]	Accumulation in the hair follicle	Polystyrene nanoparticles
[124]	Aggregation on surface of SC, increases cytotoxicity	15 nm gold nanospheres
[124]	No aggregation, no increase of cytotoxicity	6 nm gold nanospheres
[129]	Silver nanoprism, with PVP ligand, no cytotoxicity, no aggregation	Silver nanoparticles
[133]	Reduction of swelling of inflamed mice ears	(PLA, PLGA)-chitosan particles
[127]	Epidermis inflammation	TiO_2 nanoparticles
[131,132]	No cytotoxicity from 50–500 mgmL@1; No mutagenic effect; No increase in ROS levels	Polyglycerol-based nanogels
[130]	Less cytotoxicity when the ligand is present	SiO_2 nanoparticles

Nano carriers properties and their role in the Dermatological Treatment- Angew. Chem.

Effect of Biodegradability on Dermal Drug Delivery

Biodegradable polymeric nanoparticles, made from natural or synthetic polymers like chitosan, alginate, PLGA, and PCL, are promising drug delivery systems due to their safety, biocompatibility, and controlled degradation. Chitosan, in particular, offers

excellent mucoadhesive properties and biodegrades into non-toxic products, though its limited stability restricts wider pharmaceutical use

pH-Responsive Behavior in Drug Delivery

pH is an important trigger for drug release from nanocarriers, since the skin surface is acidic while deeper layers and follicles are closer to neutral. Skin diseases can further alter pH, allowing targeted release in pathological regions. Polymers such as cellulose derivatives, Eudragit L100, and chitosan are commonly used to design pH-responsive systems. Research has shown that Eudragit L100 nanoparticles improve penetration and release above pH 6, particularly through hair follicles. Chitosan-based nanogels also release drugs efficiently in acidic environments, offering high and sustained delivery for treatments such as cancer and psoriasis

Electrostatic interactions in gen delivary

The net surface charge of nanocarriers plays a crucial role in dermal gene delivery, with positive charges enabling transport through skin layers and binding to negatively charged genetic material, protecting it from enzymatic degradation. Since many skin-related monogenic diseases lack effective treatments, gene therapy has emerged as a promising approach by modulating or repairing faulty genetic sequences. However, clinical translation faces challenges such as delivery barriers, immunogenicity of viral vectors, enzymatic degradation, and poor bioavailability. Topical gene delivery offers advantages over systemic administration but must overcome the skin's protective barrier. Nanocarriers—including liposome-based, polymer-based, and hybrid systems—provide a promising solution due to their high loading capacity, lower immunogenicity, and protection against premature degradation.

Effect of physical properties on vaccinations efficiency

Advanced Therapeutic Strategies

Beyond simple encapsulation, modern nanomedicine employs intelligent design for precision medicine.

Targeted Drug Delivery: This strategy minimizes off-target effects and maximizes drug accumulation in tumors.

Passive Targeting: Leverages the Enhanced Permeation and Retention (EPR) effect, whereby the leaky vasculature and impaired lymphatic drainage of tumors allow nanoparticles to extravasate and accumulate preferentially.

Active Targeting: Nanoparticles are decorated with ligands (e.g., antibodies, peptides, aptamers, folic acid) that bind specifically to receptors overexpressed on skin cancer cells (e.g., Epidermal Growth Factor Receptor (EGFR)), promoting receptor-mediated cellular uptake.

Stimuli-Responsive Drug Release: "Smart" nanoparticles release their payload only upon encountering specific triggers in the tumor microenvironment (TME).

pH-Responsive: The slightly acidic TME (pH ~6.5-7.0) can trigger the degradation of pH-sensitive polymers or linkers.

Enzyme-Responsive: Overexpressed enzymes (e.g., matrix metalloproteinases) can cleave specific peptide sequences, unlocking the drug.

Light-Responsive: This is exceptionally suited for accessible skin tumors.

Photodynamic Therapy (PDT): Nanoparticles deliver a photosensitizer (PS) to the tumor. Upon irradiation with specific light, the PS produces cytotoxic reactive oxygen species (ROS), inducing apoptosis.

Photothermal Therapy (PTT): Light-absorbing nanomaterials (e.g., AuNPs, graphene) convert photon energy into heat upon laser irradiation, inducing localized hyperthermia and thermal ablation of the tumor.

Gene Therapy: Nanocarriers can protect and deliver genetic material to overcome pathways of carcinogenesis and drug resistance. This includes the delivery of small interfering RNA (siRNA) to silence oncogenes and microRNA (miRNA) to restore tumor-suppressor pathways.

Combinatorial Therapy: A single nanocarrier can be co-loaded with multiple therapeutic agents (e.g., a chemotherapeutic drug + a siRNA or a photosensitizer). This enables synergistic effects, overcomes multidrug resistance, and simplifies treatment regimens.

Topical and Transdermal Delivery: The skin's accessibility allows for non-invasive treatment. Nano-engineered systems (e.g., ethosomes, niosomes, SLNs) can overcome the skin's barrier function (stratum corneum), providing high local drug concentrations with minimal systemic exposure, thereby drastically reducing side effects.

Advanced biocompatible and biomimetic NPs

A particle’s biocompatibility corresponds to its potential to avoid causing unpleasant reactions in the host biology, as many of such adverse reactions are products of undesirable interactions with nanomaterials. Obviously, any clinical application requires a high degree of biocompatibility. However, NPs materials of frequent clinical use, such as PEGylated NPs, may be less biocompatible than previously assumed. Many investigations have discovered a significant incidence of anti-PEG antibodies in patient sera [93, 189], showing that PEGylation is relatively immunogenic. As a result, we must perfect and enhance currently available nanomaterials. Fundamental elements of pristine identity, including physicochemical properties, shape, geometry, and density, significantly affect NPs biocompatibility and thus should be tailored to meet different requirements and help modulate the Nano-Bio interactions. For example, it is known that deformable disc-shaped and hemispherical polymeric particles outperform rigid and spherical particles in terms of biocompatibility, possibly because they mimic the shape, size.

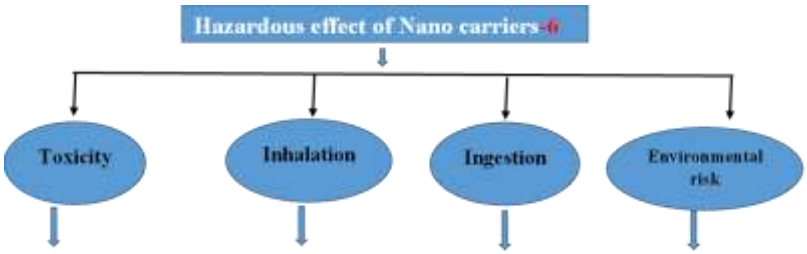
Apart from employing synthetic nanomaterials, another strategy for improving biocompatibility is incorporating biomaterials into the NP design. This approach could be beneficial by mitigating adverse off-site ancillary effects associated with NPs, as endogenous materials are far less likely to elicit unpleasant reactions. The NP can be masked with a biomimetic exterior by cloaking it in native material using natural biomolecules.

Another method is to conjugate the NPs surface to cell membrane/platelet-derived vesicles, or even to whole cells, to effectively ’hitchhike’ the NPs and conceal

them via the associated cell membrane, as is the case of the NPs conjugated with erythrocytes. However, this approach might trigger unintended NP-induced effects on the carrier erythrocytes and thus requires the refinement of NPs [193]. Encapsulating the NPs into cell membrane-derived microvesicles generated from the host's own collected cells is another innovative variation of this approach [194]. The microvesicle-enveloped NPs have an exterior identical to and indistinguishable from any other endogenous vesicle. In this situation, the NPs are encased in a cell-derived membranous 'ghost' that degrades upon uptake into the targeted tissue to expose the NP's core.

Hazardous effect of Nano carriers

In recent years there has been a rapid development in the field of nanotechnology as it has proved to be a boon in the field of cosmetics, food, and agricultural industry. They have also brought a great impact in the field of medicine and other industries due to its electrical and physicochemical properties. They are now widely used in making instruments for drug delivery including systems for monoclonal antibodies. Due to its wide usage, humans have been directly exposed to nanoparticles since birth and thus this new field of development is posing a threat to the existence of human beings. Although there are few proven facts which show that along with being harmful to human beings, they are also highly toxic to algae, bacteria, invertebrates and fishes. Scientific experiments show that these harmful effects can even cause harm to their embryonic development and even curb reproduction. The summaries of Hazardous Nano carriers are shown in the flowchart below.



Nanoparticles, widely used in medicine, cosmetics, food, and agriculture, can pose significant risks to humans and the environment due to their small size and bioactive properties. They can penetrate biological barriers, disrupt physiological processes, and harm embryos, reproduction, and various organisms, giving rise to the field of Nano toxicology, which studies their potential hazards and pathways of toxicity.	nanoparticles can deeply penetrate the lungs, particularly the alveoli, where they disrupt macrophage function and cross into the bloodstream, spreading toxicity to other organs. Particles like TiO_2 may cause pulmonary inflammation and increase reactive oxygen species, leading to DNA damage	Ingestion is a major route of nanoparticle exposure, occurring directly through food or indirectly via contaminated containers. Nanoparticles travel through the gastrointestinal tract, where they may interact with digestive enzymes and fluids, potentially disrupting gut function and interfering with nutrient absorption	nanoparticle production has rapidly increased, raising concerns about environmental pollution and toxicity. Their small size allows prolonged retention in the environment and the body, posing public health risks, prompting international efforts to regulate safe disposal and minimize nontoxicity

Figure 2. Shown the Hazardous Nano carriers

Physicochemical Characteristics of NPs and Their Safety Testing

As far as the safety of NMs in cosmetic products is concerned, the first note that should be taken resides in the nanoscale issue. In fact, the NM's incredibly small size can have an impact on numerous properties, when compared to its micro or normal size correspondent. A nanoscale material may not only have the physicochemical properties different, but also the biological ones, thus potentially affecting several domains such as quality, safety, effects, and activities. This way, it is comprehensible the possible lack of applicability and adequacy of the traditional testing assays normally used to test an ACI's safety [11], [12].

NP's safety assessment is of utmost importance and despite the need for more studies and guidance to establish a definitive and robust safety assessment, the first major topic should be the assessment of its characteristics. Morphology and solubility can play a key role in immune cells' uptake, as in the case of nanofibers, and dermal permeability respectively. Both FDA and the Scientific Committee on Consumer Safety (SCCS) have provided useful information on the specific requirements and relevant testing methodologies for safety evaluation.

Once the chemical and physical properties have been properly evaluated, toxicological assessment is extremely important, concerning the routes of exposure, possible uptake and absorption, using a variety of in vitro or in vivo tests that best fit each case. Thereafter, FDA recommends at least, acute, repeated dose, and subcronic toxicity testing, skin and eye irritation testing, as well as genotoxicity or mutagenicity, skin sensitization, and dermal photoirritation testing. Similarly, the SCCS, in the "Guidance on the safety assessment of NMs in cosmetics", emphasizes the importance of characterization to identify and entail its particular properties and to detail its toxicological profile and safety issues, building upon previously studied physicochemical peculiarities. Physicochemical characterization can be summarized, according to the previously mentioned guidance, in the following Figure 1 representation.

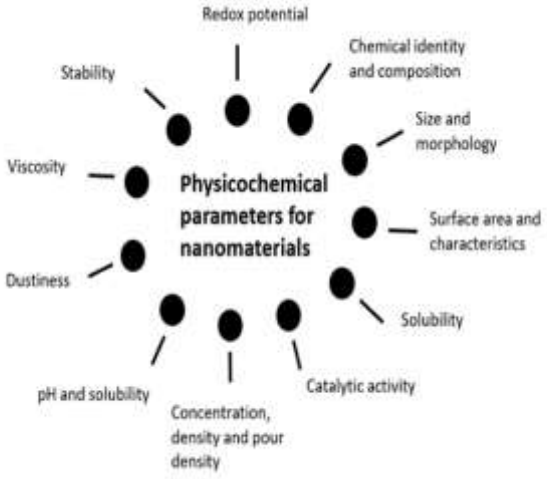


Figure 1. Physicochemical characterization for nanomaterials (NMs).

Taking on the SCCS's checklists for applicants submitting dossiers on ACIs to be evaluated by the SCCS, a final section is dedicated to addressing NMs principal assessments. Divided into three main "checklist" sections, offering a guide for the information previously mentioned and described characteristics, parameters, and general information regarding the NMs for cosmetic use, including in a cosmetic formulation, as seen summarily in Figure 2—checklist for NM's characterization, hazard assessment as toxicological data and the checklist for information on exposure, exposure assessment that is adapted from the document, noting the importance of addressing a description regarding the raw material (the produced pristine NPs); the NPs in the finished cosmetic formulation and the NPs present under toxicological investigations and exposure assessment.

Hazard assessment	**Material investigation**	**Exposure details**
o Bio kinetic behiover	o Chemical	o Total area of skin
o Genotoxcity	identification	contact
o Acute toxicity	o Morphology	o Duration of exposure
o Internal exposure	o Surface area	o Quantity of cosmetic
	o Particle size	product

Exposure Assessment

NMs are widely used in products, such as cosmetics, so exposure and toxicity are important parameters to consider for their risk assessment. It is required by the EU chemical legislation, acknowledged as Regulation on Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH), to do a consumer exposure assessment when there is a substance with a high hazard risk.

Nowadays, there is still no agreement regarding the methods to expect the consumer exposure assessment as mentioned above. Predicting the consumer exposure assessment is difficult once it is required to know the nature, amount, exposure routes, and the intended use of the products, which makes it hard to monitor after the product is sold. For example, the application of hair dyes requires the use of gloves, but there is no way to monitor this after selling the product.

Safety Testing

Different studies can be encountered with regards to safety testing of metal-oxide NMs [37], carbon NMs [38,39], and gold NMs. Delayed-type hypersensitivity is one of the reasons why ACIs are retired from the market. Testing methods to predict delayed-type hypersensivity were performed in a recent study, where several methods and strategies for testing engineered NMs were described and proposed, such as the human cell line activation test (hCLAT) and the myeloid U937 skin sensitization test (MUSST or U-SENS). Regarding the hCLAT and MUSST tests, the in vitro expression of surface markers CD54 and CD86 in THP-1 and U937 cell lines, respectively, was evaluated. The in vitro tests consist in calculating the expression of the surface marker by flow

cytometry. The fixed minimum stimulation index was 3, so values above 3 are considered as having a positive stimulation. Generally, the MUSST test is more sensitive than the hCLAT.

There are several nanocarriers for nanocosmetic delivery, allowing the successful improvement of not only the cosmetic formulation's properties at a completely different level but also toward a set of key-concepts such as toxicity, permeability, controlled-release, and efficacy. Therefore, the relevance of both the variety of the vehicles on display and the clear advantages of the more conventional normal sized forms, confers an attractiveness to the field of cosmetics, allowing the fusion of nanotechnology and cosmetology into one unique and enthralling concept.

Regarding the physicochemical characteristics of NMs, as described above, and the lack of safety testing evidence about these nanosized particles, it is important to perform more studies that also consider their long-term impact on safety.

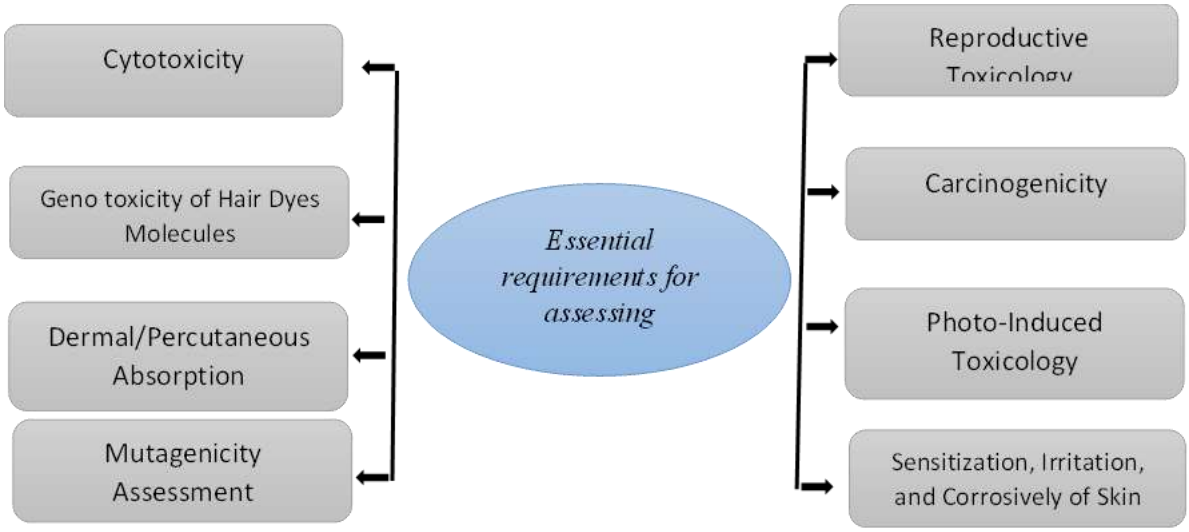
The following Table 1 presents a compilation with examples of models and testing performed on NPs for safety testing.

Research	Material	Applocations	ref
Cytotoxicity/Geno toxicity Photo toxicity	Micro-nano zinc oxide NPs	Human skin keratinocyte cells	[48]
Biodistribution (in vivo) Toxicology	Indium-based quantum dot NPs	Rat model	[53]
Toxicology (embryonic)	Chitosan NPs	Zebrafish	[54]
Genotoxicity (in vivo)	Fullerene	Rat lung cells	[51]
Genotoxicity	Titanium Dioxide NPs	Human bronchial epithelial BEAS-2B cells	[51]
Genotoxicity (in vivo)	Iron Oxide and Ionic Iron NPs	Earthworm Coelomocytes	[44]
Toxicology	Graphene	Caenorhabditis elegans	[52]
Genotoxicity	Titanium Dioxide NPs	Human bronchial epithelial BEAS-2B cells	[46]

Safety Assessment Testing to Evaluate Different Types of Toxicity

NMs are widely used in many fields, such as cosmetics, urging the understanding of their potential toxicity. The increase of new NPs is unfortunately not accompanied by their safety assessment. NMs unique properties, such as size, surface area, zeta potential, and aggregation, have influence over the biological reaction and can be a risk for the consumer, thus it is important to increase the knowledge regarding the potential toxicology of NPs supported by in vivo or in vitro studies.

In vivo studies are the ideal ones, once they can simulate biological mechanisms and chronic toxicology which is not possible by in vitro methods. NPs toxicology is related to the route of administration. The potential exposure routes must be identified and in vivo or in vitro studies should be conducted [13], [14], [15].



CONCLUSION

Fundamental Finding: In this Review, we have highlighted multiple examples of Nano carriers displaying enhanced penetration, retention, and the delivery of therapeutics at the diseased site. Owing to the advancements in dermal drug delivery using Nano carriers, there is a promising outlook for the translation of this technology to the market. Several products have reached the market for the topical/transdermal delivery of therapeutics; however, cosmetic Nano carriers products dominate over pharmaceutical products. We highlight the potential of the Nano carriers in overcoming the skin protective barrier for the delivery of active therapeutics. **Implication:** With this thorough revision, we want to promote research on developing nanoparticles for skin therapy using a holistic and multidisciplinary approach that takes into account the difficulties of translating technology. To address this, essential stakeholders from various disciplines, including chemistry, pharmacy, dermatology, and toxicology, can contribute their insights to surmount the existing challenges related to the effective delivery of therapeutics in skin diseases. In addition, the ecological impact must be carefully evaluated. **Limitation:** Although ongoing advances, studies and the growing body of knowledge, cosmetic and Nano carriers research continuous to face substantial challenges. Nevertheless, it is evident that considerable progress is still required to achieve safer, more effective, and innovative formulations. The toxicological impact and potential health outcomes in living organism remain insufficiently clarified, particularly as long as continuous exposure studies and the dose–exposure–response relationships are not fully established. **Future Research:** Further research is required to better understand the complex interactions between biological systems, nanotechnology and Nano carriers. Novel testing approaches are needed to better clarify and predict as accurately as possible, the toxicological behavior of cosmetic nanomaterials within both the human body and the environment. Future methodology studies should incorporate a systematic assessment of nanocarriers exposure to establish reliable exposure indices and ensure safety evaluations. Furthermore, the development of a comprehensive

database integrating standardized methods and nanoparticles is essential and should be made accessible to the scientific community.

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