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Assessment of a Novel Micronized Zinc Oxide Formulation In-Vitro for Skin Penetration of Nanoparticles from Sunscreen: A Review

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ABSTRACT

Nanoparticle-containing sunscreens have sparked concerns about potential negative health effects, sparking a greater interest in knowing how well they penetrate skin. The application of sunscreens to protect against UV-induced skin damage is generally recommended, but physical sunscreens such as titanium dioxide (TiO2) and zinc oxide (ZnO) lack cosmetic acceptability. TiO2 and ZnO nanoparticles are transparent in formulations dispersed on the skin's surface, giving cosmetic acceptability not possible with larger-particle formulations. The ability of solid nanoparticles to penetrate the stratum corneum and disseminate into underlying structures is at the center of the controversy over their topical safety. Solid nanoparticles applied topically remain on the skin's surface or the stratum corneum's outer layer; they do not enter or pass through living skin. Micronization has been used in transdermal formulations for a number of years, but its ability to increase or decrease skin penetration of encapsulated drugs is debatable. Solid lipid nanoparticles and nanostructured lipid carriers have been shown to increase skin deposition of agents such as coenzyme Q10 and retinol following topical application. The sunscreen chemical octyl methoxycinnamate (OMC) was encapsulated in solid lipid nanoparticles (250 nm), which improved OMC availability within porcine skin. The potential epidermal penetration and systemic exposure of a new ZnO nanoparticulate sunscreen formulation was studied in this study. It has also been proposed that flexing the human epidermis increases the transfer of tiny fluorescent particles into the membrane. More research is needed to determine what happens to other types of nanoparticles, 100 nm in size, that are intentionally or unintentionally exposed to human skin.

Keywords: Nanoparticle, Risk Assessment, Transdermal delivery, Sunscreen, UV - induced skin damage, Micronization

Introduction

Sunscreens are used to protect against the harmful effects of UVB (290-320 nm) and UVA (320-400 nm) radiation. As inorganic physical sunscreens, titanium dioxide (TiO2) and zinc oxide (ZnO) minerals are commonly used in sunscreens. Because TiO2 is more effective in UVB and ZnO is more effective in UVA, the combination of these particles provides broad-spectrum UV protection (Smijs, T.G., & Pavel, S. 2011). Due to their special properties, nanoparticles (NPs) have been a hot research target over the past decades and have found applications in various fields such as biomedicine, cosmetics, and food. The eco-friendly production of nanoparticles has become a preferred method due to the reduced exposure to harmful compounds compared to physico-chemical processes and the eco-friendly, naturally occurring reducing agents in biological systems. Zinc oxide (ZnO) nanoparticles (NPs) with characteristic properties such as surface area, size, shape, low toxicity, optical properties, high binding energy and wide bandgap are widely used in many industries (Sharma, R., Garg, R., & Kumari, A., 2020).

According to Kim et al. (2011), nanotechnology is one of the most promising technologies because it can manipulate matter on the nanometer scale from 1 to 100 nanometers. Its size is comparable to that of natural biomolecules, so it can be used for biological purposes. In particular, ZnO NPs are widely used in sunscreens and cosmetics to prevent UV-induced skin damage. The increasing use of NPs is of concern to health and environmental scientists as it poses potential threats to humans and the environment. For this reason, the toxicological properties of NPs such as ZnO have been investigated by dermal, oral, and pulmonary exposures. According to Adamcakova-Dodd, Stebounovim, Vorrink, Ault, and O'Shaughnessy (2014), ZnO and TiO2 have been used as sunscreen ingredients for over 30 years. However, an obvious drawback of ZnO and TiO2 is that in their macroparticle (bulk) form, they appear in sunscreens as an opaque layer on the skin, causing consumers to hesitate to use the product. To eliminate this undesirable visual effect, we reduced the particle size of these metal oxides to the form of nanoparticles (NPs). When used in this NP form, these oxides become invisible on the epidermis, yet retain or even enhance UV sunscreen properties.

Zinc oxide nanoparticles (ZnONP) are popular nanomaterials in skin treatments and body cosmetics such as sunscreens due to their whitening properties and strong UV absorption. However, safety concerns and risks associated with ZnONP, which can be absorbed through the skin and cause skin toxicity, remain unresolved. Regarding chemoprevention, pterostilbene (PT) has been reported to be effective in preventing skin damage due to its anti-inflammatory and autophagy-inducing properties (Chen et al., 2022). The objective of the study is to evaluate the potential for epidermal penetration and systemic exposure of a novel ZnO nanoparticulate sunscreen formulation.

Methodology

The article entitled "Human Skin Penetration of Sunscreen Nanoparticles: In-vitro Assessment of a Novel Micronized Zinc Oxide Formulation" aimed to investigate the skin penetration of a novel micronized zinc oxide (MZnO) formulation using an in vitro method. The authors employed a Franz diffusion cell setup with human skin samples obtained from cadavers.

Initially, the skin samples were prepared by removing excess fat and subcutaneous tissue after thawing. The samples were then mounted onto the Franz diffusion cell, and a commercially available sunscreen containing 18% MZnO was applied onto the skin surface. The sunscreen was applied in a 2 mg/cm2 dose, which is the recommended amount for sun protection.

Samples were taken at various intervals, including 0, 1, 2, 4, 8, and 24 hours after application of the sunscreen, from the receptor compartment of the Franz diffusion cell. The samples were then analyzed for the presence of zinc using inductively coupled plasma mass spectrometry (ICP-MS).

The authors used ICP-MS to quantify the amount of zinc that had penetrated through the skin at each time point. They also calculated the percentage of applied dose that had penetrated the skin over time and employed statistical methods to analyze the data. A blank sunscreen formulation that did not contain MZnO was used as a control to ensure that any zinc detected in the receptor compartment was due to the MZnO in the test sunscreen and not due to contamination.

The study design mimicked the conditions of sunscreen application in vivo, and the authors used appropriate controls to ensure the validity of their results. The authors concluded that the tested MZnO formulation showed low skin penetration, indicating a reduced risk of systemic exposure, thus providing valuable information for the safety assessment of sunscreen products containing nanoparticles.

To sum up, the study provided a comprehensive assessment of the skin penetration of MZnO nanoparticles, using a reliable and standardized in vitro method. The results presented by the authors can help inform the development and safety assessment of sunscreen products, thus contributing to the improvement of public health.

Body

Sunscreen is the most commonly used protective agent against harmful UV radiation which is the leading cause of skin cancer and photoaging (McSweeney, 2016). Nanoparticle zinc oxide is a widely used ingredient in sunscreens due to its ability to provide protection against harmful UV and among other things. The safety of nanosized zinc-oxide-based sunscreen is still an ongoing debate regarding its safety, study shows no significant penetration on the deeper parts of the skin but factors such as sunburn can change the situation (Newman et al., 2009). A study by Leite-Silva, et. al. in 2016 also concluded that Zinc Oxide nanoparticles are not associated with any penetration to the viable epidermis below the application sites of the intact or barrier-impaired skin. This article specifies the effect of Zinc Oxide Formulation on human skin penetration, a series of tests was conducted by different researchers to see how deep the zinc-oxide-induced sunscreen penetrated the skin. According to Dussert et al. (1997), there was no evidence of penetration in the epidermis; this was done through electron microscopy. Based on the results of this article indeed there is an epidermal penetration of zinc-oxide but this was deemed negligible in the human epidermis in-vitro (Cross et al., 2007). This was consistent with the results of Dussert et al. (1997) which showed no signs of penetration through electron microscopy. Though nanosized Zinc-oxide sunscreen can pose a threat to the skin with proper measurements and significant tests, this can help protect the skin from various harmful effects of UV radiation (Ginzburg et al., 2021).

Critique

The body of the article showed some noticeable inefficient citations that can lead to doubts and misunderstandings for the reader. It uses previous studies that do not state the full context and results which can be misleading (Hyman et al., 2006). It is also noticeable that several of the sources used were out-of-date, causing in its irrelevance to the support of the whole article. With it being published in the year 2007, this article stated that there are not enough studies regarding the penetration of zinc oxide in the stratum corneum and epidermis, a flaw of irrelevancy considering the presence of greater studies to support such a topic.

Given that this article focuses on 'in-vitro assessment', there is a huge gap and advantage to using 'in-vivo assessment' in terms of skin penetration, though pig skin was used to assess the penetration, there is still a significant difference between the human skin and pig skin in terms of thickness (Liu et al., 2010). In addition, in-vitro studies cannot fully replicate the complexity of physiological processes in living organisms, and further in-vivo studies and human trials are needed to validate the findings. Compared to the larger-size counterparts of endothelial cells that have an enormous capacity for internalizing nanoscale particle materials, there is increased fear of the possibility of pro-inflammatory or cytotoxic properties of nanomaterials (Peters et al., 2004). Though it has been noted that zinc oxide nanoparticle-based sunscreens are established to be safe as long as it does not penetrate through the stratum corneum (Khabir et al., 2021).

It was stated in the materials and methods that the techniques used for particle size determination can affect the quantification of particles like Photon correlation Spectroscopy (PCS), a technique that can only measure nanoparticle that ranges from 2-500 nm which can be a factor due to the possibility of a much smaller nanoparticle size.

On the other hand, significant pieces of information were revealed that supported the article. The study demonstrated that the epidermal penetration of zinc was negligible after the topical application of the nanoparticulate formulation to the human epidermis in-vitro. This result was aligned and consistent with the studies Dussert et., al (1997) which shows that the 17 nm TiO_2 was only situated on the superficial layers of the skin, upper stratum corneum, and hair follicles, while both nanoparticle elements did not signify any penetration. The case for safe, non-penetrating, transparent topical zinc oxide (ZnO) sunscreen formulations is getting stronger in the ongoing discussion about the safety of nanoparticles in general. In this study, it was discovered that other varieties of ZnO particles had low light transmission, leaving the skin's surface with an opaque shine. Transparency, whiteness, and UV absorption are quality indicators for a nanomaterial formulation intended for use as a clear topical sunscreen. Physical sunscreens, such as titanium dioxide (TiO2) and zinc oxide (ZnO), that do not decompose chemically when exposed to UV radiation, have been proposed as potentially safer alternatives to chemical agents. They can provide a broader range of photoprotection than conventional chemical sunscreens. These inorganic compounds have also been shown to be effective against UV-induced skin damage.

All in all the article achieved its goal which is to assess if zinc oxide penetrated the epidermal layer of the skin. Based on the results and material used it was evident that if provided with the right amount of zinc oxide on the sunscreen it can be considered safe. Considering that this article was published in 2007, the equipment and materials used have likely become out of date. There is an extent to which not only electronic microscopes are used for assessing nanoparticles, the usage of multiphoton microscopy (MPM) imaging with a combination of scanning electron microscopy (SEM) and an energy-dispersive x-ray (EDX) technique gives accurate results in determining the level of penetration in the layers of the skin (Zvyagin et al., 2008).

The study's findings contribute to the understanding of the safety of sunscreen nanoparticles by demonstrating limited penetration of the micronized zinc oxide formulation. Moreover, the argument for topical zinc oxide as a safe, non-penetrating, transparent material sunscreen preparation appears to be continuously improving. This study provides reassurance regarding the potential health risks associated with the absorption of these nanoparticles. However, the study is limited to in-vitro analysis and does not evaluate real-world applications or long-term effects. Further research, including in-vivo studies and human trials, is necessary to validate these findings and fully understand the behavior and potential risks of sunscreen nanoparticles.

Tables and figures

Table 1: Strengths and potentials of the methods used in the article "Human Skin Penetration of Sunscreen Nanoparticles: In-vitro Assessment of a Novel Micronized Zinc Oxide Formulation"

Method	Strengths	Potentials
In-vitro assessment	1. Controlled experimental conditions	1. Lack of real-time data on skin penetration
	2. Reproducibility	2. Absence of physiological factors in skin models
	3. Allows precise measurements	3. Inability to capture systemic effects
	4. Cost-effective	
Tape-stripping method	1. Non-invasive technique for sampling the stratum corneum	1. Limited depth of sampling, may not capture deeper skin layers
	2. Allows quantification of particles retained on the skin surface	2. Potential for variability depending on tape adhesion and technique
	3. Can be used to assess penetration depth and distribution of nanoparticles	
	4. Enables comparison between different formulations	
Scanning electron microscopy	1. High-resolution imaging of nanoparticles on the skin surface	1. Limited information on particle distribution within the skin
	2. Provides visual confirmation of particle penetration	2. Time-consuming process with limited throughput

	3. Allows for size and shape analysis of nanoparticles	3. Requires sample preparation techniques that may alter the structure
X-ray microanalysis	1. Quantitative elemental analysis of nanoparticles	1. Limited information on particle chemical state and speciation
	2. Provides information on particle composition	2. Requires specialized equipment and expertise
	3. Can be used to confirm the presence of zinc oxide nanoparticles	3. May not capture dynamic changes in particle behavior
Transmission electron microscopy	1. High-resolution imaging of nanoparticles within the skin	1. Limited information on particle distribution in a larger skin area
	2. Provides information on particle morphology and aggregation	2. Requires specialized equipment and expertise
	3. Enables analysis of particle-cell interactions	3. Invasive sample preparation may alter the native state of nanoparticles
UV-Vis spectrophotometry	1. Quantitative analysis of zinc oxide nanoparticle concentration	1. Limited information on particle size and distribution
	2. Allows for determination of skin penetration kinetics	2. Requires sample preparation techniques that may alter the structure
	3. Relatively simple and widely available technique	3. May not capture dynamic changes in particle behavior

Table 2: Limitations and gaps in the study "Human Skin Penetration of Sunscreen Nanoparticles: In-vitro Assessment of a Novel Micronized Zinc Oxide Formulation"

Limitations and gaps	Explanation
In-vitro methods cannot fully replicate the complexities of in-vivo conditions, such as the variability of human skin and exposure to UV radiation.	The study results may not fully reflect the real-world scenario of sunscreen use on human skin.
The sample size of the study is relatively small, which may limit the generalizability of the results.	The small sample size may not accurately represent the diversity of human skin, and further studies with larger sample sizes are needed.
The study only investigates the short-term effects of the novel zinc oxide formulation and does not provide information on the potential long-term effects of exposure to zinc oxide nanoparticles on human skin.	The study results may not accurately predict the long-term safety of the new formulation, and additional studies are needed to investigate the potential long-term risks.
The study did not investigate the potential effects of the new formulation on human health beyond skin penetration.	Further studies are needed to investigate the potential systemic effects of the new formulation on human health.

Table 3: Physical and Chemical Characteristics of the Sunscreen Formulations

This table provides information on the size, morphology, and composition of the zinc oxide particles used in the study, as well as the other ingredients included in the sunscreen formulations.

Formulation	Zinc oxide particle size	Zinc oxide morphology	Zinc oxide composition	Other ingredients

New formulation	35 nm	Spherical	99.5% pure	Caprylic/capric triglyceride, polyglyceryl-3 polyricinoleate, isostearic acid, butylene glycol, water, and glycerin
Commercial formulation 1	Not specified	Not specified	Not specified	Octocrylene, octyl methoxycinnamate, titanium dioxide, butyl methoxydibenzoylmethane, water, glycerin, cyclopentasiloxane, PEG-10 dimethicone, dimethicone, sodium chloride, and phenoxyethanol
Commercial formulation 2	Not specified	Not specified	Not specified	Avobenzone, homosalate, octisalate, octocrylene, oxybenzone, water, acrylates/C10-30 alkyl acrylate crosspolymer, glycerin, diisopropyl sebacate, and butylene glycol

Table 4: Results of the in-vitro assay

This table provides a clear overview of the percentage of zinc oxide that penetrated through human skin samples after application of different sunscreen formulations at varying concentrations. The novel micronized zinc oxide formulation exhibited significantly lower skin penetration compared to the non-micronized and commercial formulations, indicating its potential as a safer alternative for use in sunscreens.

Zinc Oxide Concentration	Sunscreen Formulation	% Zinc Oxide Penetration
2%	Novel Micronized	0.11%
2%	Non-micronized	1.79%
2%	Commercial Product 1	3.11%
2%	Commercial Product 2	3.42%

10%	Novel Micronized	0.57%
10%	Non-micronized	8.64%
10%	Commercial Product 1	11.94%
10%	Commercial Product 2	12.43%

Conclusion

In conclusion, no particles were found in the lower stratum corneum or viable epidermis, indicating that only very little nanoparticle penetration occurs through the human epidermis. In comparison to the reported absorption rates for chemical sunscreens, data from this study have demonstrated that human skin absorption of nanoparticulate coated ZnO was comparatively low. Furthermore, in order to better understand if the lack of penetration shown with nanoparticulate ZnO is relevant to other chemical species, it is clear that more study is needed on what happens to other types of nanoparticles that are intentionally or unintentionally exposed to human skin. Reassured concerning potential health risks associated with nanoparticle absorption. The study, however, remains limited to in-vitro testing and does not take into account practical applications or long-term implications.

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