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https://doi.org/10.5109/4774220

出版情報：Evergreen. 9 (1), pp.93-101, 2022-03. Transdisciplinary Research and Education Center for Green Technologies, Kyushu University
バージョン：

Cytotoxicity of Nanoparticles Used in Cosmetic Industries: An In-depth Insight

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(Received October 28, 2021; Revised March 9, 2022; accepted March 28, 2022).

Abstract: As the incidence of skin malignancies, such as melanoma and nonmelanoma, has increased, so has the use of sunscreens. Sunscreen-mediated photoprotection relies on reducing the effects of UV, especially UV-A and UV-B. Natural & artificial tanning compounds were subdivided. Aqueous or chemical products are indeed the names mentioned in organic sunscreens. Physical, mineral, insoluble, natural, and nonchemical are all terms used to describe inorganic sunscreens. During the last decade, Octyl methoxycinnamate (OMC) was used in 90% of sunscreens as a UV filter. Organic sunscreen formulations were dominant, and this only changed in the 1990s when inorganic sunscreens started to be preferred due to their higher effectiveness. These contained microfine powders of Titania (Titanium Dioxide-TiO_2) & Zinc Oxide (ZnO). The presence of these nanoparticles, however, can have several downsides. So, by removing the hazardous entities from the materials used in cosmetics industries and with the use of some nature-based materials, cytotoxicity will be removed.

Keywords: Attenuation, Cosmetics, Cytotoxicity, Nanomaterials, Nanoparticles, Perovskite.

1 Introduction

1.1 TiO_2 (Titania) and ZnO (Zinc Oxide) NPS (Nano Particles)

Micro-sized ZnO & TiO_2 were utilized in sunscreens during the last three decades [1-2), 34-37)]. Now, due to their UV attenuation capacities. While ZnO protects against UVA, TiO_2 is effective against UVB. They act as inorganic physical UV blockers. Unlike micro-particles, nanoparticles are more bio-reactive and thus their safety is a major concern. ZnO was the most effective in inducing cell death to U87 cells followed by TiO_2, and MgO was the least effective. The induced cell death was through apoptosis or necrosis, or possibly apoptosis or necrosis-like [3), 20), 38-40)].

The stratum corneum of the epidermal layer plays an important role in barrier functioning. If this barrier is compromised, nanoparticles can penetrate the deeper viable dermal layers of the skin.

In the same line, via various research groups, there is tremendous growth in the use of perovskite kind of nanomaterials for various applications. Various experimental techniques as per the available resources and research gaps are hence applied in this work accordingly.

TiO_2 and ZnO are inherently opaque. This also adds to their light scattering benefits but is cosmetically undesirable as it leaves a recognizable chalky layer on the skin. The nanoparticles solve this undesired feature. Visible light is transmitted when particles are smaller than the optimal light scattering size (about half the wavelength), and the particles seem transparent. It is one of the very reasons NPs were popularized, other than its increased UV protection capacities.

The titanium dioxide nanoparticle market is expected to grow at a CAGR of 6.2% in the decade 2020 to 2030. Its advent has also caused a sharp decline in previously used organic substances for brightening and whitening [4-8), 41-43)]. The growing use of these NPs not only affects those directly using it but also those working in those industries, i.e., occupational exposure. It also adversely affects the environment and other species. It can cause lung damage, and digestive tract abnormalities if it crosses respiratory or gastrointestinal barriers.

Due to increasing concern about UV damaging effects of solar radiations and its early aging consequence, the ZnO-NPs, naturally being a broad-spectrum UV filter, the East Asian ZnO nanoparticle market will see a growth of about 8% by 2030 [9-10)]. Also, there is a tremendous sign of growth in the %CAGR of these ABO or AO kind nanoparticles in the next few years[44)].

1.2 Ag-NPs and Shape dependent toxicity

Silver nanoparticles have a wide range of use from cosmetic to medical purposes. This is because it is a broad-spectrum antimicrobial. Antibacterial efficacy of silver nanoparticles increases exponentially with a decrease in size [11), 20), 45-49)]. There are several potential risks to this because NPs might penetrate the skin.

There have not been many studies for testing the effectiveness of nanoparticles in skin penetration based on their shape. Even when there have been a few studies, it is sometimes questionable to what degree the results are replicable for humans as the in vitro tests have mostly been on pigs or mice.

The shape of NPS also has further implications beyond the cytotoxic effects on human beings. A study by Katie Lu checks the environmental implication of different shapes of disposed of nanoparticles. The study showed that both nanoplates and nanocubes are less phytotoxic than nanospheres. The inhibition difference for frond area (area of the leaf) between spherical Ag NPs and nanoplates was 6.573% and it was between nanocubes & nanospheres was 8.228%. [12),21),46-48)]. Unfortunately, almost every product containing NPS has spherical NPs. NPS also contributes to the reduction of fresh weight in plants. [12), 49)]. A study by Gorka et al stated that silver nano cubes were shown to have a 34.3 percent lower root length decrease than nanospheres [13), 50-52)]. The varied shapes release Ag+ ions at varying rates, which contributes to the differences in toxicity. Also, nanocubes are more stable than nanospheres in aquatic environments. They tend to form aggregates thus releasing much lesser amounts of Ag+ ions into the water body [12),22), 53-55)].

There is no significant difference between the antibacterial property of nanocubes and nanospheres [13), 24), 56-59)]. Thus, it is only beneficial to shift to nanocubes from nanospheres, reducing the environmental toxicity while preserving its antibacterial effect.

Another study tested the in vitro skin permeability of three different NPs- Rod-shaped NPs (RNPs), Spherical NPs (SNPs), and Triangular NPs (TNPs)- on hairless naked mice. Ag-NPs showed shape-dependent permeability concerning time. After 12 hours, 1.82, 1.17, and 0.52 g/cm^2 of silver had penetrated through the skin from RNPs, SNPs, and TNPs, respectively. TNPs had the lowest penetration rate of 2.47 g/cm^2 after 30 hours, while SNPs and RNPs had penetration rates of 3.05 g/cm^2 and 7.22 g/cm^2, respectively. [14),25), 61-63)]. Triangular NPs were found to be significantly lower in the receptor fluid after 30 hours as well [26), 64)]. On the other hand, the permeability coefficients of RNPs were significantly higher. Of all three, only RNPs were detected in the dermal layer after 30 hrs. at a depth of 224 micrometers indicating their obvious penetration capacities.

Natural desquamation, textile touch, or body wash will not remove the deposited nanoparticles [15), 27), 65-66)].

Five days of in vivo analysis by topical application of the NPS on hairless mice also revealed TNPs as the better option. Their concentration in blood (from heart) was the least (39.29±1.96ng/ml) for TNPs and highest (108.57±5.43ng/ml) for RNP. [14), 28), 67-69)].

1.3 Occupational Exposure to Nanoparticles

Inhalation of metal oxides, predominantly ZnO causes acute, reversible syndrome Metal fume fever is an acute, reversible illness caused by inhaling metal oxides, primarily ZnO. Fever, chills, painful muscles, dyspnea, nausea, and exhaustion are some of the symptoms. To prevent this the threshold limit value (TLV) was set to $5mg/m^3$ in 1962.

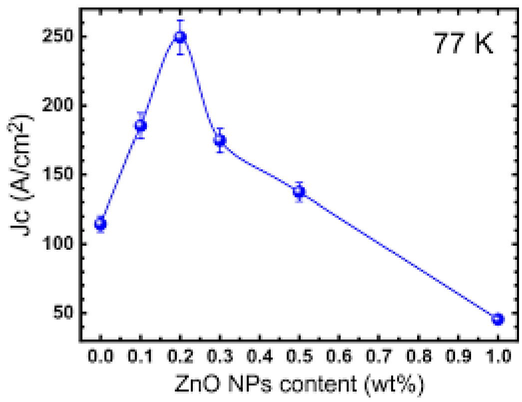

Fig.1 Fluctuation's effect of ZnO Nature [17)]

However, in a study, it was found that repeated exposure to about $5mg/m^3$ ZnO produced cellular and functional degradation in the lungs [16), 29), 70-72)].

ZnO exposure for 24 hours or above increases the production of 8-OHdG (8-hydroxy-2' -deoxyguanosine) and induces significant oxidative stress when compared with controls. It also activates inflammatory cells and neutrophils at 24 hrs. and above. Marker of cytotoxicity, LDH (Lactate dehydrogenase), is also significantly increased [17), 30)]. Hence, ZnO exposure can also cause immunotoxicity along with cytotoxicity.

While cytotoxicity has been studied much, the effect of NPs on epigenetic modification and DNA methylation has been studied very little. Patil et al did a study exactly on this. As lungs are the most affected area, they chose lung fibroblast (MRC5) to study subtle DNA methylation that happened below the sub-lethal levels. With an increase in the concentration of TiO_2.

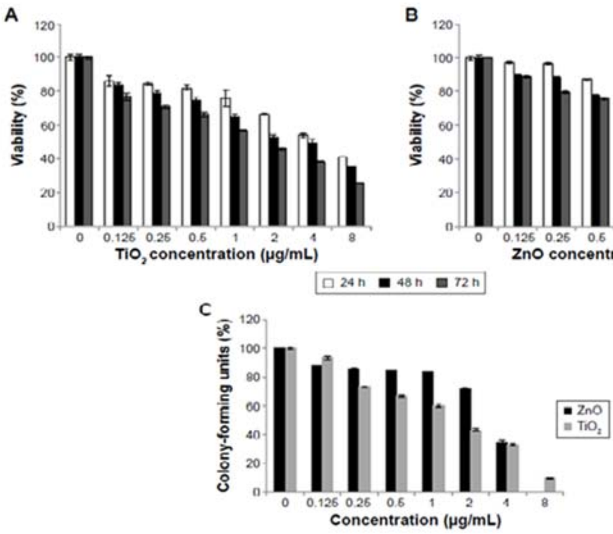

Fig.2 Cytotoxicity effects of NPs [18)]

ZnO NPs, growth, and proliferation of the cell line were effectively retarded. When cells were at 48 hours, there was only a slight decrease in DNA methylation from that in the initial 24 hours. DNA methylation was lower in the ZnO-exposed cells compared with the control. The average percentage of methylated cytosine in DNA methylation was decreased to 59% and 58.8% at 24- and 48-hours incubation with 1μg/mL (sublethal concentration) as compared with control. While the time of incubation beyond hours showed no significant difference in effect, the change in concentration did. Hence, the study concluded that DNA methylation occurred in a dose-dependent manner, but was independent of exposure time [18), 30), 73-74)].

Almost all in vitro studies occur in liquid. This does not properly replicate the nanoparticle exposure in the lungs which happens in the air-liquid interface. As a result, Lenz et colleagues developed the ALICE (air -liquid interface cell exposure) system.

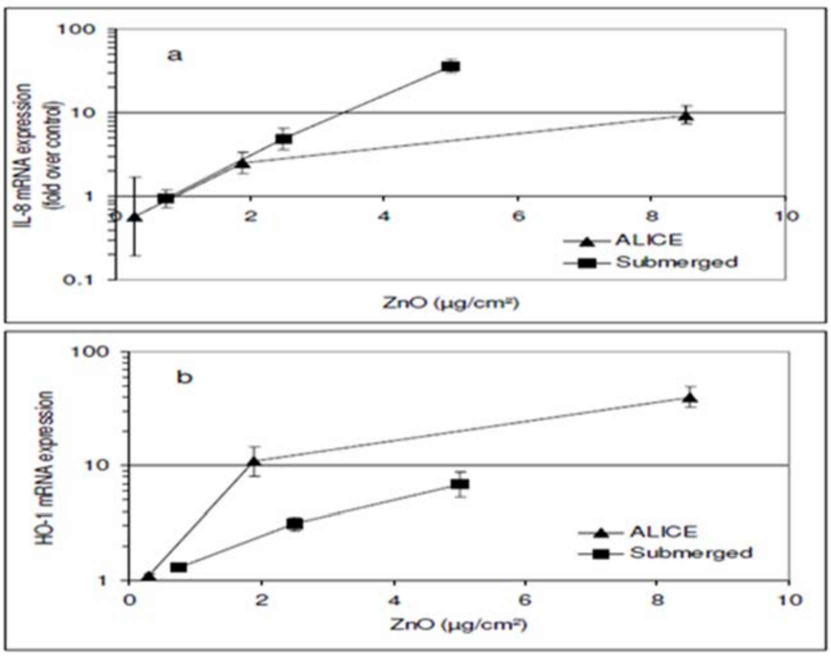

Fig.3 Cellular impacts [69)]

When comparing submerged and air,liquid interface expo sures, dose,response measurements using ZnO nanoparticles (0.3-8.5 μg/cm^2) revealed substantial changes in mRNA expression of pro-inflammatory (IL-8) and oxidative stress (HO-1) indicators. However, no cellular response was observed below 1g/cm^2 ZnO in either scenario [19), 31), 75)].

2 Negatives/ Bottle necks/ Research gaps

Photocatalysis releases reactive oxygen species that can have cytotoxic effects. According to Uchino et al., TiO_2 produces OH radicals under UV-A. The rutile crystal form (90nm in size) and amorphous form, though, produced significantly lower amounts of OH radicals than the anatase form of TiO_2. Sunscreens usually have a combination of both, the rutile crystal and the anatase form. On Chinese Ovarian Cells (CHO), the cytotoxicity of TiO_2-UV irradiation was investigated, and a proportionate connection was disc
On Chinese Ovarian Cells (CHO), the cytotoxicity of Ti O_2UV irradiation was investigated, and a proportionate c onnection was discovered.

Exposure of titanium dioxide microparticles or NPS, concentration below 1.0 microgram/ml, for 48 hours did not affect the survival of human astrocytoma U87 cells, while prolonged exposure with concentrations higher than that decreased survival of U87 cells. A research-based suggested parameter/value of TiO_2 is about 5% in an effective sunscreen which can be extremely cytotoxic. At a concentration above 100 microgram/ml, survival of U87 cells decreased to less than 30%, but there was no significant difference between microparticulate or NP TiO_2. When the anatase concentration was above 50 microgram/ml and was irradiated with UVA, the CHO cells also showed a significant decrease in viability. [2-3), 32-34)].

The IC50 is a measure of the potential of a substance in inhibiting a specific biological or biochemical function. ZnO was significantly higher in cytotoxicity with IC50 of about 11 microgram/ml. Exposing U87 cells to NP ZnO concentrations above 20 microgram/ml decreased the cell survival to just 5% of the total cells. Death was induced in 95% of the cells. The IC50 for TiO_2 was early 40 microgram/ml. MgO on the other hand only induced decreased survival to 35% even in the highest tested concentration of 100microgram/ml. It did not significantly decrease the survival rate when used under the concentration of 50microgram/ml[3].

There are very few articles focusing on the relationship between NP size and UV attenuation [6)]. UV attenuation capacities of sunscreens change with skin-particle-light interactions, and these relations need to be studied.

The studies on the direct effect of long-term exposure of human cells to these nanoparticles are also limited, and only recently have come under scrutinization.

3 Advantages with Results and Discussion

ZnO NPs display broad absorption bands ranging from 350 to 370 nm. ZnO, Perovskite (ABO_3), and TiO_2 nanoparticles have a high photocatalytic capacity and do provide effective protection from UV-A and UV-B.

Unlike organic sunscreens, titanium dioxide and zinc oxide are hypoallergenic and inert. They are also more stable and cause much fewer adverse reactions. The penetration or diffusion of these nanoparticles can be reduced exceedingly or even completely by coating them in other porous material [5)].

The optical properties of larger particles are different than that of nanoparticles and are highly undesirable in cosmetics. However, these optical properties can be attained in larger particles through coating or other expedients. Micronized UV attenuating particles can be contained within porous particulates having pores that prevent nanoparticles from coming into direct contact with the skin or water [6)].

Nano-TiO_2 is a non-sensitizer and mild or non-irritant in the skin, according to a study by Dreno et al. Although the cytotoxicity of the substance has been demonstrated in vitro, no similar effect has been observed in a 3D human skin model [7)].

To decrease occupational exposure and adverse effects, these nanoparticles can be biosynthesized from aqueous organic extracts. The half-maximal inhibitory concentration (IC50) for ZnO NPs formed from Linum Usitatissimum (Flax) was found to be about 30.5ppm when tested against CT26 cell lines through MTT assay, which shows significantly low cell biotoxicity. They showed an 83% degradation rate thus indicating the retention of a strong photocatalytic nature [4)].

Lack of homogeneity is also another factor that prevents the overall desired photo-protective effect of these NPs. A medium or formulation that can create a homogenous distribution of these is highly desirable. A lot of nanomaterials will be well utilized within the proper rules, regulations, and hygiene checks to nullify any side effects. One example is the invention of a composition containing at least one aqueous phase, a matrix of composite particles an inorganic screening agent, and gamma-oryzanol or plant extract containing it.[10)].

4 Conclusion

Coated ZnO and TiO_2 could decrease cytotoxicity. These coatings should comprise materials that quench ROS and do not let them meet skin, especially the viable dermis. The addition of free radical scavengers such as antioxidants can also add to the benefit. There is no significant difference between the antibacterial property of nanocubes and nanospheres in Ag-NPS [13)]. Thus, it is only beneficial to shift to nanocubes from nanospheres, reducing the environmental toxicity while preserving its antibacterial effect.

Acknowledgments

Pondicherry University for providing me with the idea conceptualization and Amity University Rajasthan for the help in conceiving the progressive research data. Ms. Supriya Dash did the conception as a contributor, Dr. Sanjay Kumar Singh as design, with the execution role, and Dr. Sudhanshu Singh interpreted the reported study.

Area of Conflict: None

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