Synthesis of Sunscreen with ZnO/TiO_2 nanoparticles for Broadband UV blocking

Understanding the regulatory barriers to sunscreen development in the United States

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By
Sherie Rillera

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Technical Team Members: Mackenzie Klepsig, Jalen Pryor, Elaina Lee

On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

ADVISORS

Kent Wayland, Department of Engineering and Society

Eric Anderson, Department of Chemical Engineering

INTRODUCTION:

How are FDA regulations on sunscreens influenced and how do they impact sunscreens currently produced in the United States?

Sunscreens protect from the sun's ultraviolet (UV) light rays, yet American sunscreens fall behind global standards. Two types of UV rays reach the Earth's surface and can have detrimental effects on people after long exposure. Some of these include sunburns of varying degrees, premature aging, and skin cancers (*Ultraviolet (UV) Radiation*, n.d.). As a result, sunscreen needs to be formulated to be broadband or offer protection from both types of UV rays.

Since sunscreens are meant to be a preventative measure applied to the skin, they are subjected to regulations to ensure the safety of their users. This includes the active ingredients that can be used in these sunscreens. 16 active ingredients are approved by the Food and Drug Administration (FDA), and two of them are metal oxides, zinc oxide (ZnO) and titanium dioxide (TiO_2) (21 CFR 352.10). These ingredients are found to be generally recognized as safe and effective by medical professionals and can commonly be found in American-branded sunscreens. However, these sunscreens can leave visible residues on the skin that may make the product less appealing to consumers. The technical project will address this issue by creating a sunscreen that minimizes residues while maintaining efficacy.

While the FDA's list may seem long, this list is only about half the length of the list found in the European Union (EU). There are a total of 34 ingredients (Regulation 1223/2009). This difference in list length comes primarily from the classification of sunscreen. In the EU, sunscreen is considered a cosmetic while in the US, it is a drug. As a result, this affects the speed at which ingredients can get approved. The last ingredient approved by the FDA was back in the 1990s and

eight other ingredients have been awaiting approval since 2002 (Printz, 2015). However, the FDA may not be solely responsible for this lack of sunscreen advancement. There have been rules proposed by the FDA both in 2019 and 2021 to strengthen UV protection in the US but did not take effect. While regulatory delays play a significant role, new scientific findings, such as the environmental impacts of certain sunscreen ingredients, and a lack of consumer advocacy also hinder progress. This causes American sunscreen to not be able to provide the best protection against UV rays and leave Americans to be more prone to effects from the sun. The STS project will explore the network of factors influencing FDA regulations and the broader reasons behind the stagnation in sunscreen innovation. Addressing these barriers is essential to improve sun protection and reduce the risks associated with UV exposure.

TECHNICAL PROJECT:

What steps can be taken to create sunscreens that follow FDA guidelines, but improve the user experience?

In 2020, the global sunscreen market was valued at 10.7 billion USD, this market is expected to grow at 4.0% each year from 2021-2028 (Grand View Research, n.d.). Sunscreen has transformed from a tedious beach day ritual to an everyday personal cosmetic. The greater popularity of sunscreen as part of people's skincare routine raises a need for sunscreen formulation to reach a wider commercial audience. Zinc oxide (ZnO) and titanium dioxide (TiO_2) are common active ingredients used to absorb, reflect, and refract UV rays. They are used in many sunscreen formulations to avoid skin irritation and allergic reactions that chemical sunscreen ingredients can cause.

Some compounds in chemical sunscreen have been found to harm coral and, in response to this, oxybenzone and octinoxate have been banned in places such as Hawaii and the U.S. Virgin Islands due to the coral-bleaching effects they have (Miller et al, 2021). However, zinc oxide and titanium dioxide are considered reef-safe, largely due to their low solubility in water. This also means that they last longer on the skin which contributes to their overall desirability (American Chemical Society).

As of 2021, zinc oxide and titanium dioxide are the only active ingredients Generally Recognized As Safe (GRAS) by the U.S. Food and Drug Administration (FDA). Other mineral and chemical ingredients have insufficient data to be considered as GRAS. However, mineral-active ingredients have the downside of leaving a white cast on the user's skin, discouraging people from regular usage. Nanoparticles are particles so small they are invisible to the human eye and

show promise to minimize or eliminate the white-cast mineral sunscreens can cause. Therefore, this capstone project aims to model a synthesis process for broad-spectrum sunscreen from direct precipitation of zinc oxide and titanium dioxide nanoparticles.

Mineral Nanoparticle Synthesis

Zinc oxide has the ability to reflect both UVA (320-400 nm) and UVB (280-320 nm) rays of ultraviolet light away from one's skin. This is important because UV radiation can damage the DNA in skin cells and pose a significant cancer risk. Although ZnO nanoparticles do not scatter visible light, the particles still are able to reflect and scatter UV light.

The ZnO needed for our sunscreen will be synthesized through direct precipitation. The advantages of the direct precipitation method are the small range of particle sizes it produces, cheap raw materials, and the ability to be done in a continuous operation. Common precipitation precursors are zinc sulfate and zinc nitrate (Ghorbani et al. 2015). Zinc nitrate will be used in our process because it is significantly cheaper to purchase. Using zinc nitrate as the precursor, it is combined with a hydroxide such as NaOH, KOH, or LiOH. A precipitation reaction occurs when these precursors are mixed, yielding $Zn(OH)_2$. This is then filtered, washed with distilled water and alcohol, and then calcined in an oven at high temperatures over several hours. The $Zn(OH)_2$ is dehydrated in the oven and is then recrystallized to produce ZnO on the nanoparticle scale (Wang et al, 2010).

$$Zn(NO_3)_2 + 2XOH \rightarrow Zn(OH)_2 + 2XNO_3$$

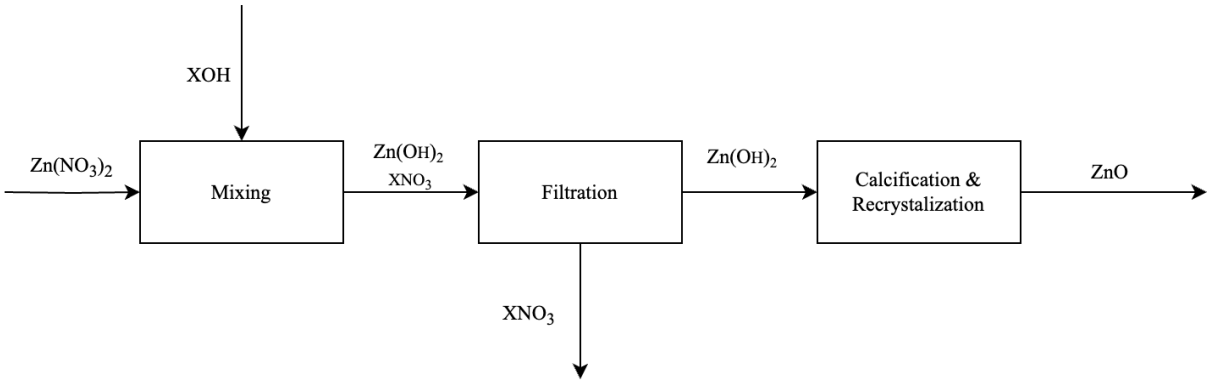

Figure 1: Process flow diagram of direct precipitation of ZnO from $Zn(NO_3)_2$.

TiO_2 will be synthesized in a similar manner as ZnO using titanium (IV) isopropoxide, isopropyl alcohol, and distilled water as a precursor. This produces a white precipitate of TiO_2 and $(CH_3)_2CHOH$, aka rubbing alcohol, which can be separated and sold for profit. The properties of our TiO_2 product can be controlled by the amount of water, reaction conditions, and the presence of additives to obtain our desired particle size and composition. Magnesium oxide is a common substance used to neutralize this reaction and yield TiO_2 in the desired crystal structures (Li et al. 2008). The white precipitate is filtered out and dried into a powder.

$$Ti(OCH(CH_3)_2)_4 + 2H_2O \rightarrow TiO_2 + 4(CH_3)_2CHOH$$

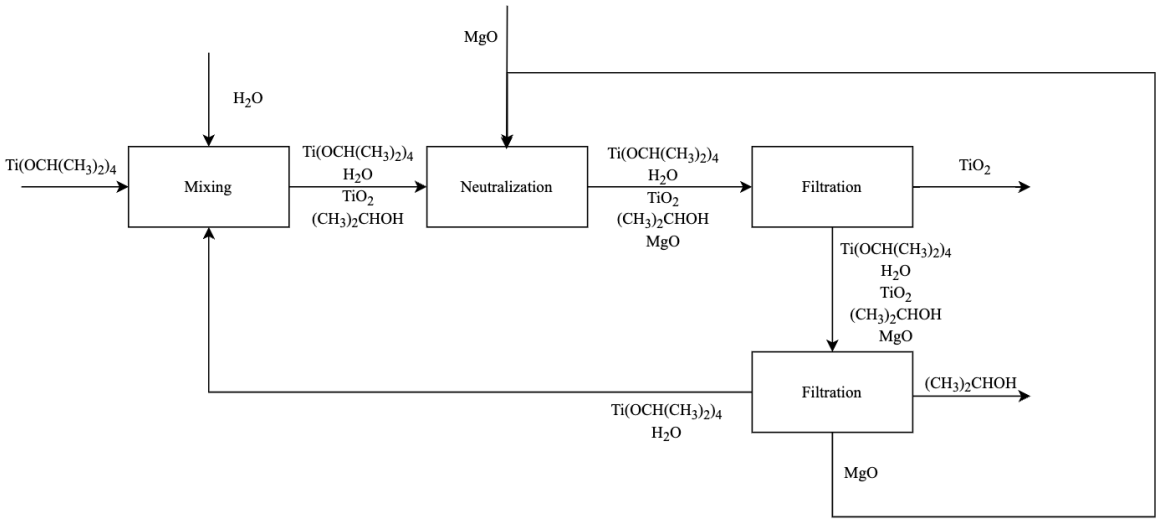

Figure 2: Process flow diagram of direct precipitation of TiO_2 from $Ti(OCH(CH_3)_2)$.

Triglyceride Synthesis

Sunscreens contain various inactive ingredients that act as emollients, dispersing agents, and antioxidants. One compound that serves these functions is caprylic/capric triglyceride. Caprylic triglyceride is a mixed triester formed from palm or coconut oils and glycerin (Mungali et al., 2021). For this process, palm oil is the best choice for making the product as affordable as possible. Palm oil is significantly cheaper, coming in at roughly $688 per MT versus $1,159 per MT of coconut oil (Bamber et al., 2016). The synthesis of caprylic triglyceride begins with saponification, followed by esterification. Saponification uses steam hydrolysis to separate the caprylic and capric fatty acids from glycerol in palm oil. This process is run at high temperatures and pressures, roughly 250 C and 50 bar respectively (Nitbani et al., 2020). Once this separation has been completed, the caprylic acid and glycerol are reacted via esterification to produce the caprylic/capric triglycerides. The conditions for this process are conducted at a high temperature

and pressure, with a catalyst (Liu et al., 2021). After, final purification is done to deodorize the product. One of the components of caprylic triglyceride that enhances its attractiveness as an additive is caprylic acid. Caprylic acid adds benefits such as increased shelf life, homogeneous dispersion of active ingredients, moisture, and free radical protection. The increased shelf life is a result of the stability of the component, which is incredibly resistant to oxidation (Mungali et al., 2021). This classifies caprylic acid as an antioxidant, which could protect the skin from damaging free radicals from the sun, and free radicals from the breakdown of the zinc oxide. Also, as an emollient, caprylic acid protects the moisture barrier of the skin and is recommended for sensitive skin (Mungali et al., 2021). Finally, capric acid allows other ingredients in the product to remain suspended and prevent any separation.

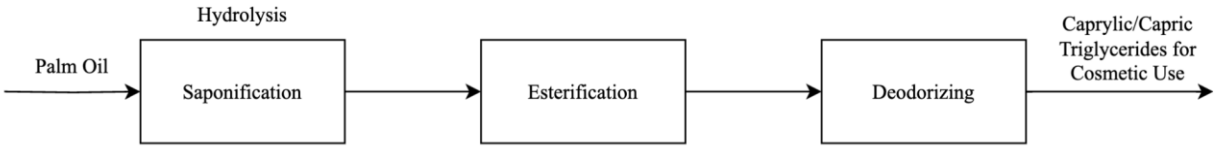

Figure 3: Process flow diagram of caprylic/capric triglyceride production.

Importance

ZnO and TiO_2 are both white and are effective at reflecting light. As a result, mineral sunscreens can often leave a white cast, the white residue on the skin after sunscreen application. As a result, people feel less inclined to use sunscreen to avoid a pale or ashy appearance, especially for those with darker skin tones. However, this can be avoided through the use of metal oxide nanoparticles (Addae & Weiss, 2024). ZnO and TiO_2 particles should be smaller than 50 nm for them to not be visible to the human eye. However, TiO_2 also has a skin permeation threshold of

45 nanometers meaning it is important to precisely control its size (Filon et al., 2015). Because of this, nanoparticles can reduce the white cast from mineral sunscreens currently on the market.

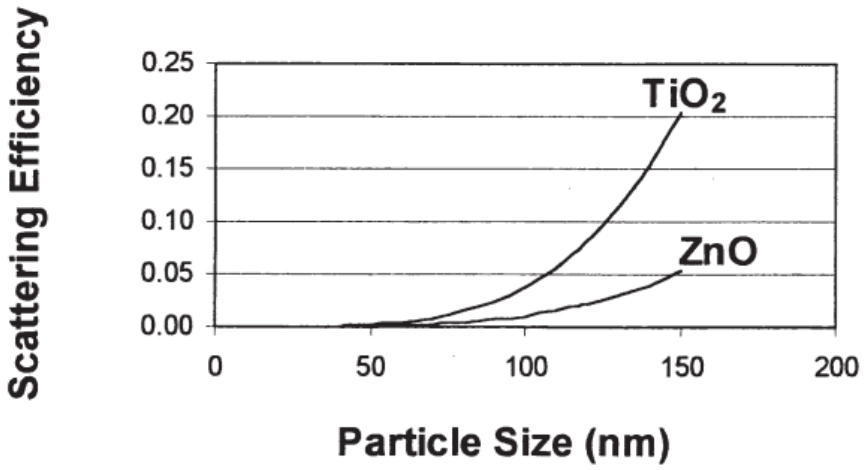

Figure 4: Scattering efficiency in comparison to nanoparticle size (Pinnell et al., 2000).

The sunscreen that will be produced is planned to be hypoallergenic and fragrance-free. Mineral sunscreens are regarded to be better for those with sensitive skin since they lack some compounds in chemical sunscreens that can be irritants. Another source of irritation can come from the use of fragrances. In a 2019 study, it was found that fragrances are the most common allergen in high SPF sunscreens found in the United States (Keyes, 2019). By making the product with ingredients that cause minimal allergic reactions, it allows anyone to use the sunscreen without discomfort. The selected ingredients are also known to be non-comedogenic, or non-pore-clogging, allowing the sunscreen to be used by those who are acne-prone.

There are a handful of sunscreens on the market that utilize mineral nanoparticles. Some of the most popular are Murad's City Skin Age Defense Broad Spectrum SPF 50 | PA++++ and La Roche Posay's Anthelios Mineral Zinc Oxide Sunscreen SPF 50. Both of these products are being sold for more than twenty dollars per fluid ounce compared to the roughly three dollars per

fluid ounce of regular mineral sunscreen; which poses an issue with the affordability of this type of product (La Roche Posay, Murad Skincare). This is, in part, due to the more complex and expensive development of these novel sunscreens, but it also significantly hinders its accessibility and marketability to a wider market. Minimizing the cost of this product through optimization of its synthesis is necessary to increase the accessibility of this product such that the average consumer can afford a visually pleasing and non-comedogenic sun-blocking product.

Execution

This work will be completed by modeling the synthesis process of zinc oxide, titanium dioxide, and triglyceride to optimize variables such as flow rates, temperature, and reaction rate. Modeling the processes themselves will be performed using Aspen Plus Version 14 with raw material thermodynamic data obtained from NIST Thermodata Engine (TDE) (Aspentech, 2017). Additionally, both safety and cost analyses will be performed to assess the viability of this product on the market. This design work will be done over the course of two semesters with a detailed deliverable in the spring of 2025.

STS RESEARCH PROJECT:

What is leading to the slowed development of sunscreens in the United States?

American sunscreens have been behind in comparison to those from other countries. In a 2016 study, it was found that US sunscreens allowed three times more UVA rays than European sunscreens on average (Diffey, 2016). This difference in effectiveness arises from the different amounts of approved ingredients by their regulatory agencies. This also affects the types of sunscreens widely available. Physical sunscreens, which reflect UV rays, often leave a white cast, while chemical sunscreens, which absorb UV rays and release them as heat, are cosmetically more appealing. However, many high-performing chemical filters common abroad are not approved in the U.S., limiting options for consumers. However, the FDA is not simply refusing to approve ingredients. The lack of high-performing sunscreens is due to a push and pull between different groups and their approaches to sunscreen.

Background & Literature Review

A 2023 interview with Alexandria Ocasio-Cortez, a current House of Representatives member, highlighted the sophistication of sunscreens from two Asian brands (Garcia, 2023). Both brands use active ingredients not yet approved in the United States. This lag is primarily due to the FDA classifying sunscreen as an over-the-counter drug since it is "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases" (21 CFR 314.3). In contrast, regulatory bodies in the EU and Asia approve a broader range of filters, enabling faster adoption of cutting-edge sunscreen technologies. This difference in regulatory approaches leaves American consumers with few advanced options and limits accessibility to improved formulations available

elsewhere. As a result, it is reasonable to blame the regulatory body overseeing ingredients in different products.

However, the FDA may not be solely responsible for sunscreens falling behind. In 2019, the FDA requested more information from sunscreen manufacturers on ingredients that are seeking approval (84 FR 6204). The proposal aims to bring sunscreens more up-to-date, which involves more recent findings of some chemicals being absorbed into the skin. As expected, this led to a scare in the general public and demoted the general use of sunscreens. However, in response, the FDA clarified that they aimed to ensure the continued safety of already approved ingredients. Along with if other ingredients on these could be deemed as 'generally recognized as safe and effective' like some metal oxides. This is only one example of displaying the relationship between the FDA and the general public and how either side may interfere with the sunscreen market.

Current literature tends to focus on the restrictions placed on sunscreens by a singular group. One example is banning an ingredient in Hawaii after it was found to bleach coral (Raffa et.al, 2018). Another article talks about the absorption of some ingredients into the skin. However, there is not enough scientific evidence to show that there was any impact on human health in the long term (Suh et. al, 2020). Otherwise, the literature focuses on the FDA and the approaches taken as the Sunscreen Innovation Act (SIA) and the Coronavirus Aid, Relief, and Economic Security Act (CARES Act). These acts attempt to help make the approval process more efficient.

Theoretical Framework & Methodology

To examine this relationship more, an understanding of the history of sunscreen under the FDA with a focus on key legislative developments, including the SIA and the CARES Act. These laws and their implementation will provide insights into the FDA's regulatory approach and how

it influences sunscreen ingredient approval and innovation. Additionally, literature on scientific advances in sunscreen will be reviewed to understand how emerging developments interact with regulatory policies. Advances include new UV filters or improved formulation methods. This will include identifying how scientific findings have shaped or constrained ingredient approval and the availability of effective sunscreens

To fully establish the network between these different groups, actor-network theory (ANT) will be used. ANT is a theoretical framework that can analyze a complex system by focusing on relationships and interactions between human and non-human actors in a network (Callon, 1986). Some of the actors that are involved include the FDA, scientific research, the environment, and consumers. The focus will not presume the existence of an established network but will instead examine the processes and interactions that have attempted to form one.

For example, this analysis will trace how the FDA's policies interact with industry efforts to introduce new ingredients, how scientific findings influence public opinion or consumer demand, and how these forces converge (or fail to converge) to drive sunscreen innovation. By doing so, the study will identify where and why network formation has stalled or succeeded, providing a clearer picture of the challenges facing sunscreen development in the United States.

CONCLUSION

Through the technical project, this will allow for an understanding of creating large-scale processes. This is not only limited to understanding the process itself but also mitigating risk factors from reacting and combining different starting materials. This will provide insights into managing complexities and ensuring safety during product development. The STS project will examine if the FDA is solely responsible for the slow development of sunscreens or if other actors contribute to this such as scientific research and consumer advocacy groups. The use of ANT will emphasize the process of whether a network is forming. Both projects will demonstrate some of the complexities when working with regulations set in place, but be able to navigate them to successfully create a product.

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