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Preparation of antibacterial TiO_2 particles by hybridization with azelaic acid for applications in cosmetics

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ABSTRACT

To apply as the antimicrobial agent in cosmetics, azelaic acid, a skin lightening material with anti-inflammatory and antimicrobial properties, has been employed to functionalize TiO_2 microspheres. Prior to the functionalization process, TiO_2 microspheres were modified with NaOH to introduce hydroxyl groups on the surface of TiO_2 as chemical binders. Hybridization was performed by condensation reaction between hydroxyl groups introduced on the surface of TiO_2 by hydroxylation process and the hydroxyl groups of azelaic acid. The azelaic acid-TiO_2 composites showed high antimicrobial activities towards both gram positive and gram negative bacterial strains, which are *Staphylococcus aureus and Escherichia coli*.

Introduction

Skin inflammation has been a common disorder experienced by many individuals from all over the world [1]. It can be caused by many factors, included disorder of pilosebaceous follicles, hormone imbalance, bacterial infection, immune hypersensitivity and genetic influences [2,3]. Among all the factors that have been mentioned, microbial colonization has been revealed as one of the most common underlying causes of skin irritation and skin inflammation [4,5]. According to previous researches, the presence of certain bacterial species has been proven to exacerbate skin problems such as acne, eczema and rosacea which can further lead to secondary local inflammatory responses [6,7]. Consequently, a variety of skin care cosmetics have been developed for the treatment of skin inflammation. Topical skin lightening agents with antimicrobial properties such as azelaic acid for acne therapy have been received much research attention in order to apply in cosmetics [8–10]. Azelaic acid was reported to have a desirable effect on inhibition of microbial growth [11]. However, azelaic acid is usually facing problems such as low thermal stability and low mechanical strength, resulted in insufficient efficiency of skin penetration to get a desirable effect [12,13].

Organic/inorganic hybrid composites materials have drawn various research attentions due to their possible broadened functionalization such as whitening, anti-inflammatory, anti-oxidant or improved dispersibility upon hybridization of organic and inorganic materials [14]. Specifically, inorganic materials such as TiO_2 and ZnO, with high thermal stability and mechanical strength can serve as a substrate to improve the durability of topical skin lightening materials [15]. Thus, improvement of skin lightening materials delivery in order to obtain desirable functions could be achieved. Also, chemical binders between organic skin lightening materials and inorganic materials allowed more even spreadability when applied as cosmetic products [16]. The ester bond that formed between azelaic acid and TiO_2 could be broken by esterase that present in human skin, thus enables penetration of azelaic acid into stratum corneum of human skin to carry out its functions [17,18]. On the other hand, TiO_2 microspheres will remain on the skin surface to provide photoprotection over harmful UV rays as shown in Fig. 1 [19,20].

In present study, a strategy has been developed to prepare hybrid organic/inorganic composite with antimicrobial properties, which is azelaic acid-TiO_2 composites. The surfaces of TiO_2 substrates were coated with topical skin lightening materials, azelaic acid, which able to inhibit the growth of harmful microbial. On the other hand, the TiO_2 substrates, which have been widely applied as pigments and as raw materials in sunscreen products due to their brightness and high refractive index, are able to provide photoprotection against harmful UV rays [21,22]. It is expected that synthesized azelaic acid-TiO_2 hybrid particles will have the whitening, antimicrobial properties as well as photo-protection against harmful UV rays. The strategy could be served as an effective way to prepare multifunctional materials, which offer numerous potential applications, ranging from cosmetics to medical fields.

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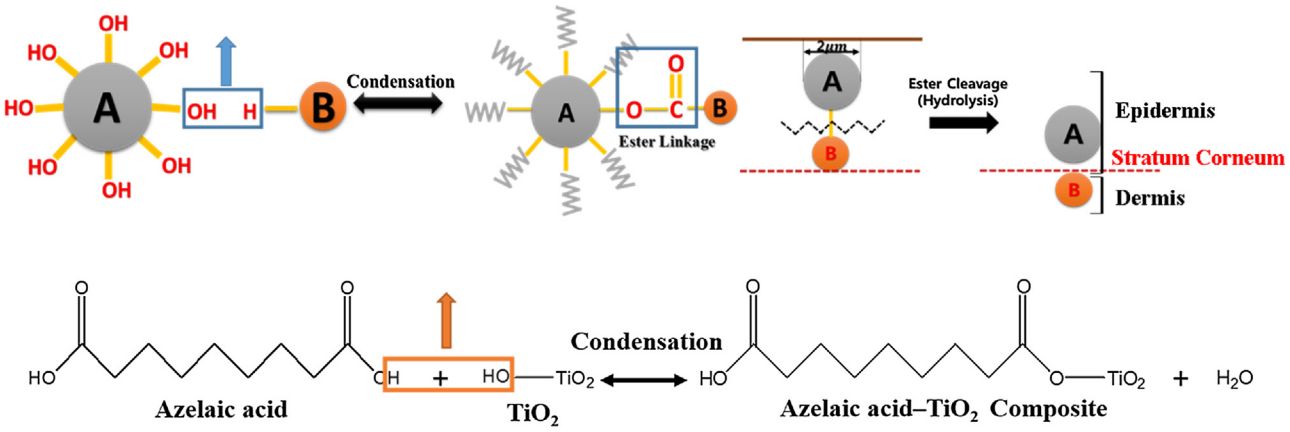

Fig. 1. Schematic illustration of ester linkage formation between azelaic acid and hydroxylated TiO_2 microspheres (A:TiO_2, B: azelaic acid).

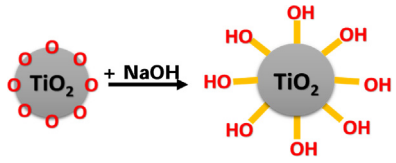

Fig. 2. Schematic illustration for hydroxylation of TiO_2 under basic condition.

Experimental sections

Hydroxylation treatment of TiO_2 surface

The modified sol-gel method reported in our previous study was employed to prepare TiO_2 microspheres [20]. The particles were calcined at 450 °C for 5 h to remove the residual impurities. The morphological properties of synthesized TiO_2 particles were observed by field emission scanning electron microscope (FE-SEM, JEOL, JSM-6700F). Chemical composition of samples was analyzed through energy dispersive X-ray spectroscopy (EDS) equipped by FE-SEM. Identification of the functional groups in composites was carried out by Fourier transform infrared spectroscopy (FT-IR) analysis, recorded by the attenuated total reflection (ATR) technique using a FT-IR spectrometer (Thermo Scientific).

To introduce hydroxyl groups on the surface of TiO_2 as a chemical binder, the 2.5 g of calcined TiO_2 powders were dispersed in 350 mL at different concentrations of aqueous NaOH solutions at 70 °C for 24 h as shown in Fig. 2. The resultants were rinsed with water for three times to remove impurities prior to the hydroxylation of TiO_2. The untreated and the hydroxylated samples at different concentrations (1, 3, and 5 M) of NaOH were named as BT, HT-1, HT-3, and HT-5, respectively. X-ray photoelectron spectroscopy (XPS, VG Multilab ESCA 2000 system) was used to observe the chemical changes of samples before and after hydroxylation treatment.

Preparation of organic azelaic acid/TiO_2 composites

The preparation routes of organic azelaic acid-TiO_2 hybrid particles were carried out through the esterification reaction between hydroxyl groups on the surface of hydroxylated TiO_2 and hydroxyl groups (–OH) of azelaic acid. The hydroxylated TiO_2 particles were re-dispersed in IPA of 750 g under magnetic stirring at 80 °C for 30 min and H_2SO_4 (0.1 wt.%) was added into TiO_2 suspension. Next, the reactant solution was prepared by dissolving 2.5 g of azelaic acid (Alfa Aesar Company, 99%) in 25 mL IPA. The solution was mixed with TiO_2 colloid under vigorously stirring at 80 °C for 3 h. The resultant suspension was cooled to an ambient temperature and repeatedly washed with deionized water and absolute EtOH for several times to remove the impurities. The hybrid composite prepared with azelaic acid, which was identified as AAT, was dried in an oven at 80 °C for 24 h for the further removal of any residues.

Evaluation of antimicrobial efficacy

Antimicrobial performances of prepared AAT were evaluated by agar diffusion method [23]. The agar diffusion method investigates the antimicrobial sensitivity of bacteria. It uses antimicrobial plates to test the extent to which bacteria are affected by those antibiotics. In this method, plates containing antibiotics are placed on an agar plate where bacteria have been placed, and the plate is left to incubate. The applied test strains were gram negative *E.coli* (ATCC 8739) and gram positive *S. aureus* (ATCC 6538P). *E. coli* suspensions with 1.3×10^5 CFU/mL and *S. aureus* suspensions with 1.1×10^5 CFU/mL were prepared in 1:500 nutrient broth (Mueller Hinton Broth, MHB). Dilutions of bacteria suspensions were used and the number of bacterial colonies appearing on the coated plates was actually counted under a microscope for quantitative testing. The sample plates were kept in an incubator at 37 °C for about 24 h. Then the number of viable cells in the sample was determined by choosing the appropriate dilution of the sample onto the agar plates and counting colonies that appeared on the plates under a microscope. An average number of viable cells was obtained by averaging the numbers in the three replicate plates.

$$\text{Antibacterial activity (log)} = \log(M_B/M_A) - \log(M_C/M_A) \quad (1)$$

$$\text{Percentage of bacteria reduction (\%)} = (M_B - M_C)/M_B \times 100 \quad (2)$$

M_A is the average number of bacteria of the standard sample immediately after inoculation. M_B is the average number of bacteria on the untreated substrate after 24 h of incubation. M_C is the average number of bacteria on the treated substrate after 24 h of incubation. The antibacterial activity was shown in Eq. (1) and the percentage of bacteria reduction was shown in Eq. (2).

Results and discussion

Morphological properties

Conventional TiO_2 particles have excellent UV screening properties and they have been widely applied in cosmetics applications [24]. However, many researchers have revealed that TiO_2 particles at nanoscale could exhibit cytotoxicity towards

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