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Enhancement of the photostability of oxyresveratrol using oxyresveratrol-encapsulated microparticles based on microfluidics

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1. Introduction

Oxyresveratrol (*trans*-2,3',4,5'-tetrahydroxystilbene, OXY), a natural polyhydroxy stilbene, is widely distributed in plants such as Morus alba L. and Artocarpus heterophyllus Lam. It has garnered significant attention due to its potent biological activities, particularly its tyrosinase inhibitory effects. Tyrosinase, a key enzyme in melanogenesis, catalyzes the rate-limiting steps of melanin synthesis, making its inhibition crucial for addressing hyperpigmentation in cosmetics.[1] Studies demonstrate that the inhibitory effect of OXY on tyrosinase was almost 25 times that of kojic acid, a conventional inhibitor.[2] However, similar to resveratrol, OXY is thought to be an extremely photosensitive compound that is easily affected by the external environment, including light, temperature, pH, and oxidants, and undergoes oxidative degradation or isomerization.[3], [4] OXY exists in the *trans*-form and *cis*-form, and the *cis*-structure generally exhibits lower biological activities than *trans*-forms. These two isomeric forms can be transformed into each other. When under ultraviolet radiation, *trans*-form OXY is easily isomerized into the *cis*-structure.[5], [6] Therefore, in order to preserve the biological activity of OXY, it is desirable to inhibit its photosensitivity.

Microfluidics is a promising technology for the fabrication of microcapsules, with excellent flow and particle size control, it has been used to encapsulate a variety of actives, and it is widely used in the medical and pharmaceutical field.[7], [8] To enhance the photostability of oxyresveratrol, a novel microfluidic-assisted encapsulation technology has been developed, utilizing graphene oxide (GO) as a protective carrier matrix for compound encapsulation. GO, a graphene derivative with oxygen-rich functional groups (e.g., hydroxyl, epoxy, carboxyl), exhibits exceptional dispersibility, high surface area, and tunable surface chemistry. [9], [10], [11] Studies show that GO can slow down the photodegradation of polymers by absorbing UV light, scavenging free radicals, acting as a physical barrier to hinder oxygen diffusion into the polymer matrix, and possibly increasing polymer crystallinity.[12] Meanwhile, the excellent biocompatibility and nontoxicity of GO make it a promising material for carrier substances.[13], [14]

In the present study, the preparation of OXY-GO/alginate microparticles has been carried out, and its morphology, encapsulation efficiency, and particle size have been characterized. Moreover, the photostability of free and encapsulated OXY has been evaluated.

2. Materials and Methods

2.1 Materials

Oxyresveratrol was purchased from Naturalis Srl., Graphene oxide was kindly provided by Shenzhen University. Unless otherwise specified, all other chemicals and reagents used were of analytical grade.

2.2 Synthesis of OXY-GO/ALG microparticles

Oxyresveratrol nanoparticles were synthesized via a coaxial microfluidic system by dissolving 40 mg 1,8-octanediol and 70 mg oxyresveratrol in 1,3-butanediol under dark conditions (300 rpm stirring). The inner phase (6 mL/h) containing this solution and outer phase (600 mL/h, deionized water) were co-injected through 0.1 mm/1 mm capillaries, inducing anti-solvent precipitation of nanoparticles, which were lyophilized after collection. GO was exfoliated via pulsed ultrasonication (200 W, 5 s on/off cycles, 15 min). For hydrogel microspheres, 5 mg nanoparticles (inner phase, 3 mL/h) and a mixture of 1 mg sodium alginate (ALG), 3 mg GO, and 0.5 mg cellulose (outer phase, 6 mL/h) were co-extruded using nitrogen gas (1 MPa, 15 NL/min) into core-shell droplets. These droplets were crosslinked in 0.6 g/mL $CaCl_2$ under stirring (300 rpm), forming ALG-GO hydrogel microspheres encapsulating oxyresveratrol nanoparticles. All photosensitive steps were conducted in the dark.

2.3 Encapsulation efficiency percentage (%EE)

The encapsulation efficiency was determined by quantifying total OXY present in the microparticles and in the supernatant, using Eq. (1).

$$\%\mathrm{EE} = \frac{OXY_{total} - OXY_{supernatant}}{OXY_{total}} * 100 \quad (1)$$

2.4 Characterization

The morphology analysis of microparticles was performed by confocal fluorescence microscopy. Images were obtained using an optical microscope, and particle size analyses were carried out by examining 100 microparticles using the ImageJ program. Whereas, Fourier-transform infrared (FTIR) spectroscopy was performed for functional group analysis.

2.5 Photodegradation Study

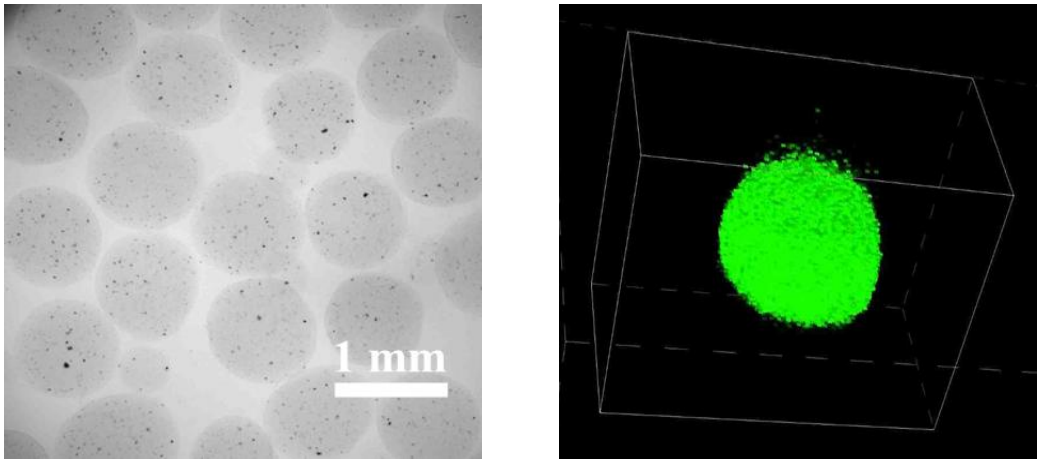
The photodegradation of OXY and OXY-GO/ALG microparticles was carried out under a UV lamp. The samples were irradiated under UV light at 365 nm for 1.5 hours. The remaining amounts of OXY were analyzed using HPLC.

3. Results

3.1 Morphology

The morphology of OXY-GO/ALG microparticles was shown in Fig. 1 and Fig. 2. According to the confocal fluorescence microscopy images, OXY-GO/ALG microparticles fabricated by

microfluidics techniques were homogeneous with diameters ranging from 700 to 1100 μm. The microspheres were spherical in shape with smooth surfaces.



(**a**) (**b**)

Figure 1. (a) The optical microscope image of OXY-GO/ALG microparticles; (b) the confocal fluorescence microscopy image of OXY-GO/ALG microparticles.

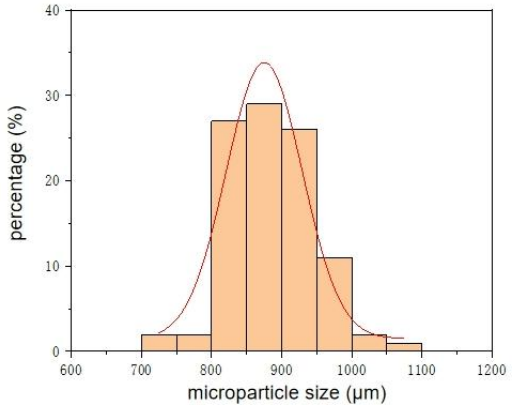


Figure 2. The microparticle size of OXY-GO/ALG microparticles.

3.2 Encapsulation efficiency and loading capacity of OXY-GO/ALG microparticles

The OXY content of the microparticles was approximately 2.0%, which corresponded to an encapsulation efficiency of 90.85%. The latter value would include not only the amount of entrapped OXY but also the fraction adsorbed on the microparticle's external surface.

3.3 FTIR analysis confirming the OXY-GO/ALG microparticles formation

The absorption spectra of the OXY, GO, GO/ALG microparticles, and OXY-GO/ALG microparticles are displayed in Fig. 3. OXY showed characteristic vibrations at 3192 cm^{-1} (O-H stretching), 1611 cm^{-1} (C=C stretching), 1325 cm^{-1} (O-H bending).*[15]* However, OXY-GO/ALG microparticles showed a significant shift at approximately 3200 cm^{-1} and 1050 cm^{-1}, which might be due to the encapsulation of OXY within the GO/ALG microparticles.

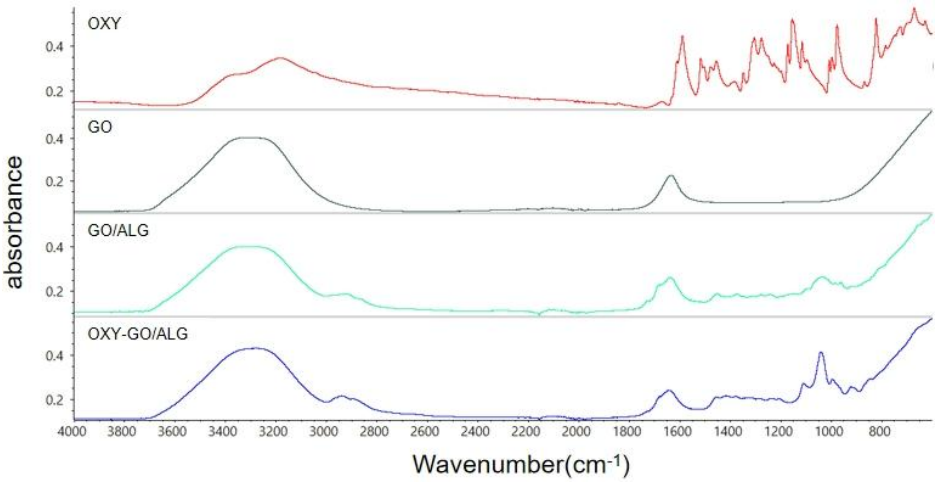


Figure 3. FTIR spectra of OXY, GO, GO/ALG, and OXY-GO/ALG.

3.4 Photodegradation Study

Photodegradation study of OXY-GO/ALG microparticles was demonstrated in Fig. 4. Free OXY and OXY-GO/ALG microparticles showed 69.8% and 3.4% degradation, respectively within 1.5 hours because of the direct exposure to the UV light. It was evident that OXY-GO/ALG microparticles showed better protection from UV light. Compared to free OXY, the encapsulated OXY-GO/ALG microparticles showed significantly enhanced protection against UV degradation, with an approximately 20-fold improvement.

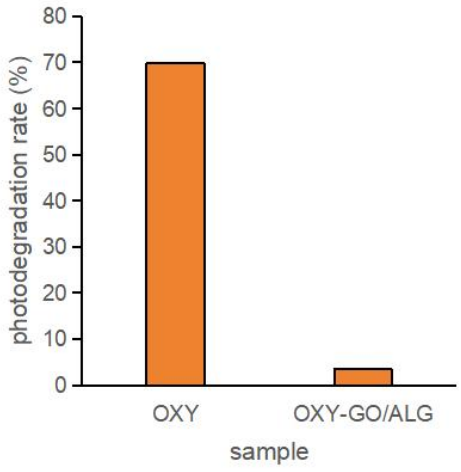


Figure 4. Photodegradation study of OXY and OXY-GO/ALG microparticles.

4. Discussion

OXY is susceptible to photodegradation. Exposure of *trans*-stilbene to light can lead to alterations in physical and chemical properties, as well as pharmacological activities and therapeutic efficacy. These effects should be considered when incorporating OXY into the products, accompanied by finding the appropriate strategies to minimize photodegradation to maintain product stability.[16]

The enhancement of the photostability of OXY-GO/ALG microparticles observed in this study can be attributed to the synergistic effects of GO and ALG in the microparticles. GO, with its

UV-absorbing properties and radical-scavenging capabilities, likely acts as a protective barrier against high-energy photons during UV exposure.

The microfluidic technique employed here offers distinct advantages over conventional encapsulation methods. By enabling precise control over flow rates and nozzle dimensions, this approach ensures uniform particle size distribution (700–1100μm) and spherical morphology, as evidenced by confocal microscopy (Fig. 1). Such reproducibility is critical for scaling up production and maintaining consistent performance in cosmetic formulations. Additionally, the high encapsulation efficiency (90.85%) underscores the effectiveness of the coaxial gas-jet system in entrapping OXY within the core-shell structure, minimizing OXY loss during preparation.

The FTIR spectral shifts observed in OXY-GO/ALG microparticles (Fig. 3) further confirm successful encapsulation. The broadening of O-H stretching bands near 3200 cm^{-1} and the emergence of new peaks around 1050 cm^{-1} suggest hydrogen bonding and electrostatic interactions between OXY, GO, and alginate. These interactions likely stabilize the composite structure, preventing premature OXY release.[17] However, future studies should investigate the long-term stability of these interactions under varying environmental conditions, such as humidity and temperature fluctuations.

While the photodegradation results are promising, practical applications may require further optimization. For instance, reducing particle size to the nanoscale could enhance skin penetration in topical formulations, while adjusting the GO/ALG ratio might balance UV protection with biocompatibility. Comparative studies with alternative encapsulants, such as polymeric nanoparticles or liposomes, would also help contextualize the advantages of GO-based systems.

5. Conclusion

In this study, OXY-GO/ALG microparticles fabricated via microfluidics demonstrated exceptional photostability, with only 3.4% degradation after 1.5 hours of UV exposure, compared to 69.8% for free OXY. The success of this approach stems from the synergistic roles of GO and ALG in shielding OXY from UV-induced isomerization and oxidative damage, combined with the precision of microfluidic encapsulation. Graphene oxide, rich in conjugated aromatic structures, provided effective UV shielding, thereby enhancing microparticle photostability. This advancement not only improves the sustainability and bioavailability of OXY in cosmetic formulations but also presents a promising strategy for developing products targeting hyperpigmentation and sensitive skin.

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