Highly Stable and Fine-Textured Hybrid Microspheres for Entrapment of Cosmetic Active Ingredients

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ABSTRACT: This study details the preparation and application of supramolecular host−guest inclusion complexes entrapping bio-mineralized microspheres for long-term storage and their pH-responsive behavior. The microspheres were assembled using a CaCO3 synthesis process coupled with cyclodextrin−tetrahydro-curcumin (CD−THC) inclusion complexes, forming fine-textured and mechanically stable hybrid materials. The products were successfully characterized using field-emission scanning electron microscopy (FE-SEM), energy-dispersive X-ray spectroscopy (EDS), Fourier transform infrared (FT-IR) spectroscopy, X-ray diffraction (XRD), and particle size analysis (PSA). Various parameters such as the Brunauer−Emmett−Teller (BET) surface area, single point total pore volume, and pore size via adsorption/desorption analysis were also determined. The obtained THC-entrapped hybrid microspheres contained as high as 20 wt % THC loading and were very stable, preserving 90% of the initial concentration over four weeks of storage at different temperatures, largely limiting THC leaching and indicating high stability in a physiological environment. In addition, the pH-responsive release of THC from the hybrid microspheres was observed, showing potential use for application to weakly acidic skin surfaces. To our knowledge, this is the first demonstration of antiaging cosmetic formulation technology using biomineralization based on the co-synthesis of CaCO3 and CD−THC complexes.

1. INTRODUCTION

The use of cosmetic active ingredients is important for consumer acceptance, which is the most important preference in the cosmetic industry. These ingredients have attracted significant interest due to the increasing desire for beauty and antiaging products.1,2 To date, various active molecules have been screened for a variety of cosmetic strategies. Despite significant progress over the last decade, the unique features of promising molecules, including poor storage stability and low solubility, have restricted their application in cosmetic formulations. Thus, improved stability and solubility are required for the development of next-generation cosmetics.3,4 Encapsulation is a simple technique that is commonly used to overcome the abovementioned disadvantages.5,6 Molecules such as polysaccharides,7 synthetic and natural polymers,8 and lipids9 have been mentioned in the literature. Cyclodextrins (CDs) are naturally available cyclic oligosaccharides with hydrophobic interiors. Many studies have been reported in an effort to develop a wide variety of host molecules.10,11 The hydrophobic cavity in CDs induces hydrophobic−hydrophobic interactions by forming supramolecular host−guest inclusion complexes.12 CDs have been mainly applied to prepare complexing agents to increase the solubility,13 bioavailability, and stability of water-insoluble drugs in the pharmaceutical industry.14 By coupling the unique properties of CDs with materials such as liposomes,15 hydrogels,16,17 and, particles (organic or inorganic), novel carriers have been developed for the stabilization and delivery of small hydrophobic molecules.

Certain inorganic materials allow the easy encapsulation and protection of guest molecules due to their straightforward synthesis and feasible modifications in terms of size, shape, and surface functionalization.18,19 For example, calcium carbonate (CaCO3) crystals are widely used as a pigment in cosmetics and paper industries and for water treatment as a filtering material.20 Furthermore, these provide a promising platform for drug carriers due to their encapsulation/entrapment capability.21 In comparison with other inorganic materials, CaCO3 is preferred due to its ideal biocompatibility and biodegradability properties. CaCO3 is degraded into non-toxic products (Ca2+ and CO32−) in the body and is pH-sensitive; it is well-maintained under neutral conditions and decomposes in
acidic environments. The synthesis of CaCO₃ is of low cost and does not require any organic solvent treatment. The use of CaCO₃ as a cargo carrier inspired the principles and applications of environment-friendly biomineralization. During CaCO₃ crystallization, organic molecules are commonly incorporated inside the material as a diverse additive to simultaneously control the crystal nucleation and growth. Therefore, the synthesis of this material presents an interesting and attractive topic for scientists to investigate in terms of CaCO₃ polymorphs from the micro- to nanometer range as well as morphological shape changes. Despite the progress in research over the last decade, strategies such as the sacrificial CaCO₃-based method or the synthesis followed by subsequent entrapment (co-synthesis) have limited use for the selective encapsulation of hydrophobic/hydrophilic molecules.

Herein, by coupling tetrahydrocurcumin (THC) with CDs as a model inclusion complex, we studied the preparation of practical and efficient hybrid microspheres for stable and pH-responsive release. In contrast to THC, glabridin (GL) affected the formation of a complex structure in terms of entrapment and release. Both THC and GL are representative cosmetically active and hydrophobic molecules derived from plant extracts. The combined use of CaCO₃, curcumin, and CDs has been reported in previous studies. In most cases, CD–CaCO₃ vehicles for hydrophobic drug delivery or curcumin–CDs for improved molecular stability have been utilized. The entrapment of a CD–curcumin inclusion complex in CaCO₃ has not been investigated for cosmetic formulation. The purpose of this study was to understand the effect of pH on the active ingredient release behavior by determining the mechanisms of CD–THC incorporation in CaCO₃ and fine hybrid microsphere formation. The use of stabilized cosmetic active molecules, to promote long-term storage, the utilization of fine-texture microspheres, arising from an appropriate size range and distribution, are important in the cosmetic industry. To the best of our knowledge, this is the first study showing the potential use of THC or curcumin as an antiaging color cosmetic formulation.

2. RESULTS AND DISCUSSION

2.1. Characteristics of the Hybrid Microspheres. THC-entrapped hybrid CaCO₃ microspheres were successfully synthesized based on the hydrophobic interaction that propelled inclusion complex structure formation, followed by subsequent mineralization, as described in Figure 1. To prepare the inclusion complex structure, the THC and CDs were vigorously mixed at RT, in the presence of EtOH, which resulted in enhanced THC solubility and biomineralization. In a previous report, curcumin–CD inclusion complexation was discussed in terms of stabilization as part of the formulation strategy in medicine and food sciences. In this study, THC-based inclusion complexes were synthesized at room temperature (RT) for the first time. Subsequent CaCO₃ crystallization entrapped the CD–THC inclusion complexes and formed micro-sized spherical particles. In cosmetic formulation, fine texture is one of the most important parameters for the application of the cosmetic product. CaCO₃ can be used to modify the texture of the pre-entrapped CDs. The fabricated CaCO₃ was successfully characterized using X-ray diffraction (XRD), scanning electron microscopy (SEM), particle size analysis (PSA), Fourier transform infrared (FT-IR), Brunauer–Emmett–Teller (BET), Baret–Joyner–Halenda (BJH) adsorption/desorption, and elemental analysis. As shown in Figure 2A, the negatively charged part of the CD–THC complexes served as a template for Ca²⁺ to attach, grow, and form micro-sized CaCO₃ particles. Interestingly, the spherical morphology adopted two different polymorphisms (Figure 2A and 3B), as indicated by the SEM and XRD analysis. The X-ray diffraction (XRD) patterns of CaCO₃ confirmed that the samples consisted of mainly mixed vaterite and aragonite phases (JCPDS nos. 33-0268 and 41-1475, respectively). Characteristic diffraction peaks were observed at approximately 20.9 (002), 24.8 (110), 27.0 (111), 32.7 (112),...
43.8 (200), 50.1 (114), and 55.8° (222) for vaterite and 20.9 (002), 29.4 (021), and 39.4° (130) for aragonite. The ratio of vaterite/aragonite was 2:1, which indicates that natural CaCO3 was obtained. The SEM images of the hybrid microspheres showed uniform spherical morphology with sizes of approximately 5−10 μm (Figure 2A). The particle size obtained by PSA indicated a defined size distribution (Figure 2C). This successful entrapment of the active ingredient was supported by the corresponding FT-IR spectrum. The FT-IR spectra of the hybrid microspheres show a broad absorption band at 3600−3300 cm−1, which corresponds to the −OH stretching between CD and CaCO3, and typical characteristic peaks at 873, 712, and 1087 cm−1, which indicate the FT-IR absorption bands of carbonate groups typically present in aragonite- and vaterite-polymorph calcium carbonate and CD−THC. The observed peaks at 1510 cm−1 originating from the C=O stretching vibration and CC=O bending indicate the presence of CD−THC complexes. Additionally, EDS was used to confirm the properties of the CaCO3 surface (Figure 2B). A key feature of CaCO3 is its mesoporosity, which is highly desirable for the loading of cosmetically active ingredients, drugs, and proteins/enzymes. The hybrid microspheres exhibited a mesoporous structure, indicating that the microspheres had sufficient...
pore volume to entrap molecules. The porous structure of the prepared samples was confirmed by the representative N₂ adsorption/desorption data using the BJH method, as shown in Figure 3C and Table 1. The BET surface area and total pore volume of the hybrid particles were 3.283 m²/g and 0.024 cm³/g, respectively (Table 1). These unique structures were favorable for the assembly of CD–THC complexes coupled with CaCO₃ crystallization for active cosmetic formulations.

2.2. pH-Responsive Release Behavior and Long-Term Storage Stability. The obtained THC-entrapped hybrid CaCO₃ microspheres contained a THC weight percentage of up to 20% (Figure S1). The encapsulation efficiency of the microspheres calculated via high-performance liquid chromatography (HPLC) measurements was ~0.124 g, indicating 62% of its theoretical loading and the successful encapsulation of the CD–THC complex in the CaCO₃ microspheres. Leaching of THC from the CaCO₃ microspheres was also prevented, and these effects were further investigated. The stabilities of the THC and hydrophobic cosmically active GL as a control were estimated by incubation in an aqueous buffer under shaking (200 rpm) at RT. The entrapped THC in the microspheres exhibited good stability, as shown in Figure 4A. The initial concentration of the THC in the hybrid microspheres was 100% and the residual concentration of THC was defined as the ratio of the concentration at the specific time point to that of the initial concentration. As shown in Figure 4A, the residual concentration of THC was largely retained. After 8 h, >87% of the relative concentration was preserved. Only THC was entrapped in the CaCO₃ microspheres. The entrapped THC was released from the CaCO₃ microspheres. It was not stabilized in the microspheres because the CaCO₃ microspheres were mesoporous. However, CD–THC, the supramolecular host–guest complex, was well retained in the microspheres. We assume that a “ship-in-a-bottle”-like structure was formed, explained by the mechanism. The size distribution of the host–guest complex was ~100 to 300 nm, which indicates that the release of this complex, from the pore (<50 nm) of the microsphere, was difficult. In addition, glabridin, used as a positive control, was tested for comparison. Glabridin did not form supramolecular host–guest complexes with CDs. Thus, it completely leached from the CaCO₃ microspheres within 200 min, as shown in Figure 4A. Therefore, the THC leakage was effectively prevented, and the stability of THC was enhanced.

The biomineralization step prevented leakage of the THC active ingredient at RT, which indicates high stability in a physiological environment while retaining its pH responsiveness. First, the stabilities of cosmetics must be maintained at room temperature to confirm the stabilization of active cosmetic molecules. The formulation was performed under neutral conditions. Second, a delivery system based on the pH-responsive release of cosmetic active molecules is guaranteed under neutral conditions. The formulation was performed under pH 7.4 as a control under rigorous shaking (150 rpm). When the hybrid microspheres were suspended in aqueous solution (aqueous PBS buffers pH 7.4 or 5.5), the resulting solutions showed the characteristic absorption bands of THC at 281 nm. The released THC profiles were determined by monitoring the increasing THC concentration, suggesting that the THC dissociated from the CDs in the CaCO₃ complex in aqueous

Table 1. Physical Properties of β-CD–THC Complexes Entrapped in CaCO₃ Microspheres

|                     | S BET (m²/g) | V (cm³/g) | d ad (average) (nm) | d lo (average) (nm) |
|---------------------|--------------|-----------|---------------------|---------------------|
| hybrid microspheres | 3.283        | 0.024     | 41.373              | 15.056              |

*aS BET is the BET surface area; V is the total pore volume. bPore size, d ad and d lo were calculated using the Barrett–Joyner–Halenda (BJH) method.*
environments. As shown in Figure 4B, a higher percentage of THC release was observed at RT (25 °C) at pH 5.5, compared to that at pH 7.4, indicating differential pH release behavior. The concentrations of THC at pH 5.5 and 7.4 were calculated to be 0.054 and 0.031 mg/mL, representing 25% and 13% of the loaded THC in the hybrid microspheres, respectively (Figure 4B). To the best of our knowledge, this is the first report regarding the feasibility of CD−THC in CaCO3 microspheres for cosmetic active delivery and a highly stable carrier for THC.

Long-term storage stability is essential for cosmetically active formulations together with fine-textured properties, and THC stability was also determined. As shown in Figure 4C, the residual concentration of THC decreased to 90% over 4 weeks at 4, 25, and 45 °C as well as under cycling conditions. This was mainly due to the strong molecular structure of CD−THC complexes in the hybrid microspheres and enhanced mechanical stability imparted by the ceramic CaCO3, which prevented THC leaching and oxidation. As shown in Figure 4C, the residual THC concentration was largely retained without any peak shift in terms of retention time during the HPLC measurement. We hypothesize that the absence of a shift of the THC peak is likely due to delayed oxidation by forming polymer conjugation in the pocket structure of CDs. Furthermore, the inorganic CaCO3 microenvironment entrapped the CD−THC complexes, enabling the formation of an inorganic−organic hybrid structure. This is the first report regarding the feasibility of a CaCO3-based cosmetically active formulation application. These microspheres will inspire novel perspectives to investigate the encapsulation mechanism of supramolecular complexes during biomimetic mineralization.

3. CONCLUSIONS

In conclusion, in this study, stable and pH-responsive hybrid microspheres were fabricated using a CD−THC inclusion complex entrapped in CaCO3 for the first time. The hybrid microspheres were successfully assembled and exhibited advantages such as THC loading, high storage stability, and fine-texture properties obtained through eco-friendly biomimetic mineralization. In particular, the pH-responsive THC release, important for its application under the weakly acidic conditions of human skin, explained by the sustainable release effect of the cosmetic active ingredient, indicates the large potential of the platform, which can be employed for stabilization of cosmetically active hydrophobic molecules as well as for various delivery vehicle systems. Furthermore, this study provides a novel method for the design of CaCO3 mineralization approaches, with large potential for cosmetic formulation.

4. EXPERIMENTAL SECTION

4.1. Materials. Calcium chloride (CaCl2) anhydrate, ammonium carbonate (NH4)2CO3, ethanol (EtOH), acetone (Sigma-Aldrich), β-cyclodextrins (CDs), and 1 N HCl (Daejung, Korea) were purchased and used without additional purification. Tetrahydrocurcumin (THC) and glabridin (GL) were synthesized by Sami Labs Limited (Karnataka, India) and SK Bioland (Cheongju, Korea), respectively.

4.2. Preparation of Hybrid Microspheres. The CD−THC inclusion complex was prepared in a molar ratio of 1:2 by the co-precipitation method. Briefly, CDs were dissolved in distilled water and mixed with THC dissolved in ethanol. The mixed solution was sonicated and stirred for 150 min at 25 °C. Subsequently, 100 mM CaCl2 solution was added to the CD−THC inclusion complex solution with an additional 30 min of stirring at 25 °C. For calcium carbonate (CaCO3) mineralization, 100 mM (NH4)2CO3 solution was added and vigorously stirred for 10 min at 25 °C. Thereafter, the fabricated samples were filtered through a 220 nm Nylon membrane for separation. The hybrid microspheres were washed three times with ethanol and then centrifuged. The separated CaCO3 hybrid microspheres were collected and then
dried in a drying oven at 60 °C to ensure the complete evaporation of ethanol. After 2–3 days of drying, the samples were collected and stored at room temperature (RT) for further use. The samples for GL were prepared using the method described above for the CD–THC inclusion complexes entrapped within CaCO₃.

4.3. Characterization of the Prepared Hybrid Microspheres. Morphological and elemental analyses of CD–THC inclusion complexes with entrapped CaCO₃ were determined by field-emission scanning electron microscopy (FE-SEM) equipped with energy-dispersive X-ray spectroscopy (EDS; TESCAN, Czech Republic). Pt sputtered coating (20 mA, 30 s) was performed prior to scanning electron microscopy (SEM) at an accelerating voltage of 5 kV. The Brunauer–Emmett–Teller (BET) surface area and pore volume were obtained using a Tristar II (Micromeritics) instrument. Pore-size distributions and pore volumes were calculated using the Barrett–Joyner–Halenda (BJH) equation. Fourier transform infrared (FT-IR) spectra were recorded using an FT-IR spectrometer (Jasco) over the frequency range of 4000–650 cm⁻¹. To achieve an adequate signal to noise ratio, 32 scans were collected at a resolution of 1 cm⁻¹ with a data interval of 0.964 233 cm⁻¹. All spectra were recorded in the transmission mode and were normalized and baseline-corrected. The X-ray diffraction (XRD) patterns were analyzed using a Rigaku Mini Flex 600 (Rigaku, Japan) instrument with Cu Kα radiation (λ = 1.5418 Å) at a scanning rate of 5.00 °/min. Particle size analysis was performed using a LA-960 laser scattering particle size distribution analyzer (Horiba, Japan).

4.4. Loading Calculation of the Hybrid Microspheres. The amount of THC loaded into the hybrid microspheres was determined by calculating the amount of each molecule entrapped in the particles via UV–visible (UV–vis) spectrophotometry (Eppendorf BioSpectrometer, Germany). The THC produced was analyzed using an HPLC system (Eppendorf BioSpectrometer, Germany). Pt sputtered coating (20 mA, 30 s) was performed prior to scanning electron microscopy (SEM) at an accelerating voltage of 5 kV. The Brunauer–Emmett–Teller (BET) surface area and pore size were obtained using a Tristar II (Micromeritics) instrument. Pore-size distributions and pore volumes were calculated using the Barrett–Joyner–Halenda (BJH) equation. Fourier transform infrared (FT-IR) spectra were recorded using an FT-IR spectrometer (Jasco) over the frequency range of 4000–650 cm⁻¹. To achieve an adequate signal to noise ratio, 32 scans were collected at a resolution of 1 cm⁻¹ with a data interval of 0.964 233 cm⁻¹. All spectra were recorded in the transmission mode and were normalized and baseline-corrected. The X-ray diffraction (XRD) patterns were analyzed using a Rigaku Mini Flex 600 (Rigaku, Japan) instrument with Cu Kα radiation (λ = 1.5418 Å) at a scanning rate of 5.00 °/min. Particle size analysis was performed using a LA-960 laser scattering particle size distribution analyzer (Horiba, Japan).

4.5. pH-Responsive Release Behavior of the Hybrid Microspheres. The pH-responsive release behavior of THC and GL was determined by measuring the released molecules from the hybrid CaCO₃ microspheres under two pH conditions (5.5 and 7.4). Using a UV–vis spectrophotometer, the changes in absorbance at 281 and 283 nm were measured, respectively. For the measurement, each sample (50 mg) was prepared in a physiological buffer (0.01 M PBS with 0.5 wt % Tween-80). Both the sample solutions were placed and stored in an incubator under gentle agitation (150 rpm). Aliquots were withdrawn periodically, and the released THC or GL was separated by centrifugation. The supernatant was monitored for overall changes in absorbance during the spectrophotometric measurement. The percentage of THC or GL released from the hybrid microspheres at various time points was calculated using eq 3.

$$\text{THC or GL release (\%)} = \frac{\text{released THC or GL}}{\text{total encapsulated THC or GL}} \times 100$$

All samples were measured thrice for standard deviation. The standard deviation is represented by error bars in the figure.

4.6. Long-Term Storage Stability of the Hybrid Microspheres. The long-term stability of the hybrid microspheres was examined under changing temperature conditions for 4 weeks. The temperature was set to 4, 25, or 45 °C, with an additional cycling condition. After incubating the powder samples in a vial, the residual THC concentrations at each time point were determined using an HPLC system as mentioned above. The residual concentration at each time point was defined as the percentage ratio of the residual concentration to the initial concentration for each sample. All samples were measured thrice for standard deviation. The standard deviation is represented by error bars in the figure.

# ASSOCIATED CONTENT

## Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c04609.

HPLC chromatogram for THC analysis, showing the elution profile of THC from the reaction mixture (Figure S1) (PDF)

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