Exploring the Inclusion Complex of a Drug (Umbelliferone) with \( \alpha \)-Cyclodextrin Optimized by Molecular Docking and Increasing Bioavailability with Minimizing the Doses in Human Body

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ABSTRACT: In this study, umbelliferone and \( \alpha \)-cyclodextrin host molecules have been mixed up through a coprecipitation method to prepare a supramolecular complex to provide physical insights into the formation and stability of the inclusion complex (IC). The prepared hybrid was characterized by \(^1\)H nuclear magnetic resonance (\(^1\)H NMR), Fourier transform infrared (FTIR) spectroscopy, electrospray ionization (ESI) mass spectrometry, DSC, and fluorescence spectroscopic studies. Job’s plot provides a stoichiometric ratio of 1:1 and the Benesi–Hildebrand double reciprocal plot gives binding constant values using fluorescence spectroscopic titrations and the ESI mass data support the experimental observations. The results of molecular modeling were systematically analyzed to validate the inclusion complexation. In preliminary computational screening, \( \alpha \)-cyclodextrin IC of umbelliferone was found to be quite stable based on the docking score, binding free energies, and dynamic simulations. In addition, the results obtained from \(^1\)H NMR and FTIR spectroscopy studies supported the inclusion complexation phenomenon. The results obtained from computational studies were found to be consistent with the experimental data to ascertain the encapsulation of umbelliferone into \( \alpha \)-cyclodextrin.

1. INTRODUCTION

In recent years, skin allergy and different cancers, such as basal and squamous cell carcinomas and malignant melanoma have become some of the most important health issues because of extensive exposure to sunlight as well as ultraviolet (UV) radiation. To tackle this problem, various UV-absorbing agents have been introduced as the formulations in cosmetic industries. It is important to keep in mind that the overall impact of biologically active ingredients through cosmetics with multiple product usage over a day in the skin has to be sufficiently low with a minimum side effect. Nowadays, sunscreen ingredients are produced by various metal nanoparticles (predominantly ZnO and TiO\(_2\) nanoparticles) for active UVA and UVB protection of skin, which absorb, reflect, and scatter UV radiation, along with other organic molecules as UV absorbers, for example, avobenzone and sulisobenzone. However, there is an increasing concern regarding the adverse health and environmental effects of these sunscreen ingredients and, therefore, various researchers already have started to find safer alternatives, for example, by surface coating of hazardous nanomaterials with silica layers or by enclosing different organic UV absorbers within the framework of organosilica nanoparticles. The loaded UV filter molecules encapsulated in a supramolecular matrix could easily be synthesized and dispersed so that they can be shielded from constant damage by an external mechanical force.

Owing to their wide range of photostability, excellent photosensitivity, and high color strength, organic dyes have attracted significant interest and been widely used in textiles, paints, inks, electronic devices, and metal oxide (TiO\(_2\)) photocatalysis. Coumarin belongs to a chemical class of benzopyrones, which include further naturally occurring derivatives, such as umbelliferone (UMB) (7-hydroxycoumarin), aesculetin (6,7-dihydroxycoumarin), or herniarin (7-methoxycoumarin), showing a wide variety of potential biological activities, for example, lipid-lowering ability, anticarcinogenic activity, and HIV-inhibition activity. The odor-fixing properties and sweet, warm, and vanilla-like scent of coumarin make it a promising synthetic fragrance component or a natural ingredient of various essential oils and plant extracts, such as sweet woodruff, Tonka, or lavender, in a large number of cosmetic products.
UMB, a coumarin-based molecule, has been extensively used as a sunscreen agent in cosmetics and optical brighteners in textiles. UMB is a 7-hydroxycoumarin that is a pharmacologically active agent and shows antidiabetic, antihyperlipidemic, antioxidant, anti-inflammatory, and free radical-scavenging activities. UMB has been generally introduced as the initial starting material for the preparation of more complex coumarin derivatives and is widely used as a synthon for a wider variety of coumarin-heterocycles with potential biological activity.

Cyclodextrins are well-known cyclic oligosaccharides consisting of six, seven, or eight α-(1 → 4)–D-glucoside moieties, giving rise to α-, β-, and γ-CDs, respectively. Owing to their nontoxic nature and complexation ability, CDs are generally regarded as safe and have received widespread attention for application in food, agriculture, cosmetics, and pharmaceutical industries. Recently, various works have been carried out with different organic UV-absorbing agents with cyclodextrins, for example, Mori et al. shown that octylmethoxycinnamate and avobenzone have been formulated with different cyclodextrins into cosmetic sunscreens. These kinds of chemical modifications through supramolecular complexation possibly will enhance the substance concentration in the upper skin layers by reducing its percutaneous penetration. Previously, a similar kind of inclusion complexation studies has been done by Meltida and Kumari and Wang et al. with UMB and β-CD as well as HP-α-CD. Herein, we have designed three different inclusion complexes and, thereafter, different kinds of characterization techniques been applied to check the formation of the inclusion complex. In this study, we report the synthesis and characterization of the UMB + α-CD inclusion complex and our main objective was to determine the influence of complexation with α-CD in improving thermal stability as well as photostability (Scheme 1).

2. EXPERIMENTAL SECTION

2.1. Materials. Both UMB and α-cyclodextrin were obtained from Sigma-Aldrich Pvt. Ltd. (India). All reagents were of analytical reagent grade and were used without further purification (Table S1). Doubly distilled water was used in all experiments.

2.2. Instruments. All the fluorescence titrations were carried out on a bench top spectrofluorometer from Photon Technologies International (PTI) QuantaMaster-40, USA. Solution-state nuclear magnetic resonance (NMR) experiments were performed on a Bruker AVANCE DRX 400 NMR spectrometer operating at 400 MHz for obtaining the 1H NMR spectra. Fourier transform infrared (FTIR) spectra were obtained using a PerkinElmer spectrometer with a resolution of 4 cm⁻¹. All DSC spectra were recorded using a PerkinElmer Pyris DSC 6 with 1.2 mg of the sample in all cases by heating in the range of 30–300 °C at a rate of 10 °C/min under a N₂ gas flow of 40 mL/min. All samples were prepared with spectroscopic grade KBr, which constituted a 100:1 ratio with respect to the total sample.

2.3. Sample Preparation. The inclusion complexation of UMB with α-CD was prepared by applying the coprecipitation method. A solution of α-CD (1.38 g) and UMB (0.2 g) was prepared in 25 mL of double-distilled water in a 1:1 molar ratio and stirred at 35 °C for 48 h. The resulting clear solution was evaporated to dryness. Then, the white precipitate was filtered cautiously and washed with ethanol and water four times to eliminate uncomplexed UMB and α-CD. The resulting precipitate was then dried in a hot air oven at 50 °C for 12 h. The obtained inclusion complex was kept in a desiccator prior to analysis.

2.4. Preparation of 3D-Structures of UMB and α-Cyclodextrin. The crystal structures of UMB (CCDC code: 1139276) and α-CD (CCDC code: 125105) were collected from Cambridge Crystallographic Data Center (CCDC). The missing hydrogen atoms and atomic charges to CDs as well as UMB were added and energy minimization was carried out with force field MMFF94x and gradient 0.05 kcal·mol⁻¹·Å⁻¹ using MOE 2015 software. These structures were used as a starting point to perform the computational studies.

2.5. Molecular Docking and Simulations. In supramolecular chemistry, molecular docking is a computational process of searching for a guest that is able to fit both geometrically and energetically in the cavity of the host moiety. This is a process by which two molecules fit together in 3D space. The aim of docking is to predict the predominant binding mode for a guest with a host of a known three-dimensional structure. An established docking protocol for host–guest system implemented in MOE was applied. The docking was carried out with the default parameters, that is, with the triangle matcher method and ordered with the London ΔG scoring function. The top five produced poses were ranked as per their docking scores and saved in a separate database file in a .pdb format. The build-in scoring function of MOE, S-score, was used to predict the binding affinity (kcal·mol⁻¹) of the optimized structure of the inclusion complex.

3. RESULTS AND DISCUSSION

3.1. Job’s Plot. A very reliable continuous variation method also known as Job’s plot was performed in order to
validate the stoichiometry of the inclusion complex.\(^\text{30}\) The sum of the concentrations of both components was kept constant ([UMB] + [αCD] = 1.0 × 10^{-4} M) and the molar fraction of UMB (R = [UMB]/([UMB] + [αCD])) varied from 0.0 to 1.0 (Table S2). In order to calculate the stoichiometry, the fluorescence emission intensity variations (F) of UMB were plotted versus the molar fraction (R).\(^\text{31}\) Figure 1 illustrates the continuous variation spectra of the αCD/UMB system examined by fluorescence titrations.

![Image](https://dx.doi.org/10.1021/acsomega.0c04716)

**Figure 1.** Fluorescence emission spectra of UMB by varying both host and guest such that the sum of the concentrations of both components was kept constant ([UMB] + [αCD] = 1.0 × 10^{-4} M).

The plot observed in Figure 2 showed the maximum at a molar fraction of about 0.5, indicating that the stoichiometry of the complex UMB + αCD was 1:1 in agreement with the linear plot obtained from the Benesi–Hiludebrand method.

### 3.2. Association Constant Calculations

The stoichiometry and formation constant of the UMB and αCD complex was studied by using fluorescence emission titration.\(^\text{32}\) Association constants (K\(_n\)) of host–guest inclusion complexes were calculated using the modified Benesi–Hiludebrand equation (eq 1) from the fluorescence experimental data. The addition of α-cyclodextrin to an aqueous solution of UMB resulted in a decrease of the measured fluorescence intensity. The fluorescence signal of UMB is highly sensitive to the addition of the αCD solution.

\[
\frac{1}{F_o - F} = \frac{1}{(F_o - F_{max})} \times K_n \times [CD]^n + \frac{1}{F_o - F_{max}} \tag{1}
\]

where \(F\) and \(F_o\) denote the fluorescence intensity of UMB on adding αCD and pure UMB, respectively. \(F_{max}\) is the saturation fluorescence intensity. \(K_n\) is the association constant obtained by dividing the intercept by the slope. \(n\) is the binding stoichiometry between αCD and UMB.

The binding constant of the complexes assumed with the use of eq 1 can be verified by plotting the double reciprocal plot of 1/(\(F_o - F\)) versus 1/([αCD]) (Table S3); this plot will be linear in the case of 1:1 complexation, but will be curved if higher-order complexes occur.\(^\text{33}\) Figure 3 shows the double reciprocal plot, demonstrating the highly linear plot, with \(R^2 = 0.9992\), confirming 1:1 complexation for this αCD.

![Image](https://dx.doi.org/10.1021/acsomega.0c04716)

**Figure 3.** Double reciprocal Benesi–Hiludebrand plot of 1/(\(F_o - F\)) vs 1/([αCD]) at 298.15 K.

Figure 4 depicts the fluorescence spectra of UMB with increasing concentration of αCD. There is a decrease in the fluorescence intensity of UMB with αCD addition, indicating the formation of an inclusion complex between UMB and αCD. From this fluorescence titration, we had estimated the binding constant shown in Table 1, using the intercept and slope, it was found to be 6.86 × 10^{3} M^{-1} at 298.15 K and Gibbs free energy was −5.21 kcal·mol^{-1}.

### 3.3. FTIR Spectral Analysis

The solid inclusion complex formation is analyzed by FTIR spectroscopy. FTIR spectroscopy is used to confirm the formation of the solid inclusion complex by considering the deviation of the peak shape position and intensity.\(^\text{34}\) Figure 5 depicts all the spectra of pure UMB, αCD, and the UMB + αCD inclusion complex. The FTIR spectrum of pure UMB disclosed typical absorption bands at 3177 cm\(^{-1}\) for phenolic (−O−H stretching), 1603 cm\(^{-1}\) for (C=O stretching), 1684, 1567, and 1510 cm\(^{-1}\) for (aromatic C=C stretching), and 1319 and 1135 cm\(^{-1}\) for (C−O−C stretching).\(^\text{35}\) In the case of αCD stretching vibration of O−H at 3398 cm\(^{-1}\), stretching vibration of −C−H from −CH\(_2\) at 2926 cm\(^{-1}\), bending vibration of −C−H from −CH\(_2\) and

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bending vibration of O−H and C−O−C at 1416 and 1154 cm⁻¹, respectively, were found. Stretching vibration of C−C−O and skeletal vibration involving α-1,4 linkage at 949 cm⁻¹ appeared at 1129 cm⁻¹. When, the UMB + αCD inclusion complex is formed, −O−H bond-stretching frequency of the hydroxyl group of cyclodextrin was observed at 3394 cm⁻¹, the C−O group of lactone moiety got shifted to 1706 cm⁻¹, the phenolic O−H part of UMB observed in pure guest at 3177 cm⁻¹ has been diminished, and aromatic C=C stretching vibrations that appeared at 1684, 1567, and 1510 cm⁻¹ in pure UMB are absent after inclusion complexation (Table S4).

From the above data, it can be concluded that the aromatic part of UMB has been inserted into the cavity of α-cyclodextrin.

3.4. ¹H NMR Studies. The ¹H NMR spectra of UMB, αCD, and the inclusion complex (in D₂O) are shown in Figure 6. In the spectrum of the UMB + αCD inclusion complex, appreciable chemical shift changes were observed for protons of UMB as well as αCD in the inclusion complex with respect to the spectra of the free UMB and αCD, respectively. The chemical shifts of the αCD protons in the absence and presence of UMB are listed in Table 2. From the spectra, it is observed that changes in the signals of H-1, H-2, and H-4 protons on the outer surface of αCD are negligible with Δδ values of −0.00, −0.03, and −0.04, respectively. However, complexation of a hydrophobic guest causes significant chemical shift changes of H-3 and H-5 protons that are present in the inner cavity of αCD and in this case it was found to be an upfield shift of −0.10 and −0.06 ppm for H-3 and H-5 protons, respectively. It is to be mentioned that the chemical shift variation for H-3 was higher than that for H-5 after the formation of the inclusion complex.

To further explore the possible inclusion mode of UMB + αCD, we compared the ¹H NMR spectrum of UMB in the absence and presence of αCD. Chemical shift changes for different protons in UMB with the inclusion complex are listed in Table 2. Here, it is observed that aromatic protons such as H-S, H-6, and H-8 are highly upfield shifted and found to be −0.09, −0.011, and −0.07 respectively. Based on these ¹H NMR results, we deduced the aromatic group of UMB deeply inserted into the cavity of αCD and the possible inclusion modes for the UMB + αCD complex are illustrated in Scheme 2.

3.5. DSC Analysis. A further insight into the interaction of host, guest, and complexed state can be assigned via the DSC study. A shift or change in the intensity of the peak or disappearance of melting, boiling, and sublimation points is observed in DSC curves because of the inclusion of a drug in cyclodextrin. Thermogram of pure UMB {Figure 7a} exhibited a single endothermic peak in the temperature range of 30−300 °C. The peak appeared at around 233 °C was sharp and strong. Formation of this peak indicates the purity as well as crystalline character of UMB. Whereas, in the case of αCD, an endothermic peak appeared at around 108 °C, which corresponds to the release of water molecules bound with different energy in the cavity of cyclodextrin (Figure 7b). When the inclusion complex was formed, the peak appeared at 233 °C in pure UMB got slightly shifted to a higher temperature of 244 °C (Figure 7c). Therefore, from the comparison of the above three thermograms and their shifted peaks, it was elucidated that some weak interactions, which could be hydrogen bonding, van der Waals, or electrostatic interactions, occurred between UMB and αCD.

3.6. ESI-MS Studies. A suitable estimation of the relative gas-phase stabilities of the inclusion complex was evaluated by electrospray ionization mass spectrometry (ESI-MS). In Figure S1, the peaks observed at m/z 681.56, 1135.96, and 1157.99 are related to the molecular ions, [UMB + αCD + H]⁺, and [UMB + αCD + Na]⁺, respectively. As can be seen from this figure, in the positive mode there are peaks centered at m/z 1157.99 (Table 3, Figure S1), which clearly denote the stability of the inclusion complex as compared to the free UMB and αCD.
formation of the singly charged ions of the [UMB + αCD + Na]$^+$ complex.

### Table 2. $^1$H NMR Data for UMB in the UMB + αCD Complex in D$_2$O

| guest | position of protons | pure guest chemical shift (ppm) | inclusion complex chemical shift (ppm) (IC) | change in chemical shift | $\Delta \delta = (\delta_{IC} - \delta_{pure})$ |
|-------|---------------------|---------------------------------|---------------------------------------------|--------------------------|------------------------------------------|
| UMB   | H-3                | 6.18−6.20 (1H, d, $J = 8$ Hz)   | 6.17−6.19 (1H, d, $J = 8$ Hz)               | -0.01                    |                                          |
|       | H-4                | 7.86−7.90 (1H, d, $J = 16$ Hz)  | 7.82−7.86 (1H, d, $J = 16$ Hz)              | -0.04                    |                                          |
|       | H-5                | 7.52−7.54 (1H, d, $J = 8$ Hz)   | 7.48−7.45 (1H, d, $J = 8$ Hz)               | -0.09                    |                                          |
|       | H-6                | 6.85−6.87 (1H, d, $J = 8$ Hz)   | 6.74−6.76 (1H, d, $J = 8$ Hz)               | -0.11                    |                                          |
|       | H-8                | 6.76 (1H, s)                    | 6.69 (1H, s)                                | -0.07                    |                                          |
| αCD   | H-3'               | 3.90−3.92 (6H, m)               | 3.80−3.84 (6H, m)                           | -0.10                    |                                          |
|       | H-5'               | 3.76−3.80 (6H, m)               | 3.70−3.74 (6H, m)                           | -0.06                    |                                          |

3.7. Molecular Docking Studies. In recent years, the molecular docking has been extensively used to predict the...
Scheme 2. Schematic Illustration of the UMB + αCD Inclusion Complex

Figure 7. DSC thermograms of (a) UMB, (b) αCD, and (c) UMB + αCD inclusion complex.

Table 3. ESI-MS Analysis of the Complexes with Calculated as Well as Experimental Mass Values

| name of the complexes | calculated mass (a.u.) | experimental mass (a.u.) |
|-----------------------|------------------------|--------------------------|
| [UMB + αCD + H]⁺      | 1134.98                | 1135.96                  |
| [UMB + αCD + Na]⁺     | 1157.98                | 1157.99                  |

bound conformations of CD and various drug molecules. Docking has been carried out for five different poses as shown in Figure 8. Docking results revealed the structural orientation of UMB inside the cavity of αCD as well as the lowest energy structure of the UMB + αCD inclusion complex.

The computationally calculated binding affinities of the first five energy conformers of the UMB + αCD inclusion complex were −3.60, −3.59, −3.47, −3.42, and −3.42 kcal·mol⁻¹, respectively, which were very near to the experimentally measured values (Table 4). Docking results demonstrate that the UMB was not completely embedded into the αCD cavities in all poses because of its small cavity size. For the first two poses, that is, Figure 9a,b, the binding affinity was quite similar and the change was about 0.01 kcal·mol⁻¹. However, their structural orientation was totally different. In the first pose, the lactone moiety was located at the wider side of the αCD cavities but in the second case, the aromatic part came closer to the wider side of the αCD cavity, which was also supported by various spectroscopic methods, such as ¹H NMR, FTIR, and so forth. However, in this work, only five conformations of optimized inclusion complexes based on their binding affinity have been studied and showed. If someone closely looks at the five conformations, it can be observed that Figure 8d,e are the conformations with least binding affinity and subsequently are not being encapsulated in the cavity of αCD. Therefore, the molecular docking and free energy calculation results suggested that UMB bound to αCD with both hydrophobic and electrostatic interactions.

3.8. Potential Energy Calculations of the Inclusion Complex. Potential energy calculations were carried out in order to obtain some information about the geometry and stability of the host–guest complex and to find the intermolecular interaction in αCD and UMB inclusion complexation. ΔE of the complexation was calculated for the minimum energy mode according to eq 2 and the data of $E_{\text{Complex}}$, $E_{\text{Host}} + E_{\text{Guest}}$, and ΔE are listed in Table 4. This potential energy term ($E$) is actually a summation of various different energy terms and can be stated as eq 3.

\[
\Delta E = E_{\text{Complex}} - (E_{\text{Host}} + E_{\text{Guest}}) \tag{2}
\]

\[
E = E_{\text{str}} + E_{\text{ang}} + E_{\text{tb}} + E_{\text{oop}} + E_{\text{tor}} + E_{\text{vdW}} + E_{\text{ele}} + E_{\text{sol}} \tag{3}
\]

where, $E_{\text{str}}$, $E_{\text{ang}}$, $E_{\text{tb}}$, $E_{\text{oop}}$, $E_{\text{tor}}$, $E_{\text{vdW}}$, $E_{\text{ele}}$, and $E_{\text{sol}}$ are potential energy components for bond stretching, bond angle, stretching bending, out of plane bending, dihedral torsional, van der Waals, electrostatic, and solvation energies, respectively.

The energies of the complex and its different components are summarized in Tables 5 and S5. As seen from the table, all the other energy components are unaltered but it is the van der Waals ($\Delta E_{\text{vdW}}$) and electrostatic ($\Delta E_{\text{ele}}$) energies that are responsible for the complexation. The host–guest complexation in the gas phase is driven predominantly by vdW interactions. When the inclusion complex is formed, change in vdW energy, that is, $\Delta E_{\text{vdW}} = -12.186$ kcal·mol⁻¹ is much lower than $\Delta E_{\text{ele}} = -7.839$ kcal·mol⁻¹, indicating the vdW forces play a pivotal role in the formation of UMB/αCD in an aqueous environment.

3.9. Dynamic Simulations. In this study, we used molecular dynamics to calculate the stability of the UMB and αCD inclusion complex equilibrium. The rigid microenvironment of the host inside the host cavity and the stability of the complexes have been discussed using MD simulations based on the potential energy change with time.

Figure 9 shows the plot of potential energy versus time (ps) obtained through MD simulations for the complex structure in the gas phase as well as in the solvent phase. For complex UMB + αCD in the gas phase, we noticed a potential energy change from 586.201 to 385.245 kcal·mol⁻¹ during first 100 ps; it also showed a slight variation of potential energy: 385.245 to 387.618 kcal·mol⁻¹ in the second part of the interval between 100 and 600 ps. The binary inclusion complex of UMB in the gas phase showed an initial potential energy value and high fluctuations in the potential energy, but latter got stabilized after 100 ps of time. In the solvent phase, we noticed that the UMB + αCD complex has a potential energy change from −5021.233 to −6190.101 kcal·mol⁻¹ during first 100 ps, we also noticed a variation of potential energy: −6190.101 to −6122.078 kcal·mol⁻¹ in the second part of the interval.
between 100 and 600 ps. Therefore, we observed that the complex becomes stable after 100 ps in both phases. The potential energy deviance of the complex was less for the inclusion complex in the solvent phase compared to the inclusion complex in the gas phase indicating the better stability of the supramolecular inclusion complex in the solvent phase.

4. CONCLUSIONS

In the present study, UMB + α CD was designed, synthesized, and characterized by using 1H NMR, FTIR, and ESI-MS. Job’s plot was used to confirm the stoichiometry of the inclusion complex. From the FTIR and NMR data, it is confirmed that the aromatic part has been inserted into the α-cyclodextrin cavity. Differential scanning calorimetric value for the inclusion complex confirms that it is thermally stable upto 244 °C. Thermodynamic parameters like the binding constant have been found to be favorable for stable inclusion complexation. From the molecular docking study, it is observed that when UMB inserted through the aromatic part, it showed the highest binding affinity compared to the rest of the four poses, which confirmed the preferential encapsulation and the geometry of the inclusion complex obtained from 1H NMR experiments. Thus, molecular docking as well as dynamic simulations also support the experimental evidence. Thus, the overall study concluded that the UMB-α-cyclodextrin supramolecular hybrid could lead to further developments of sunscreen agents.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c04716.

Detailed descriptions of all the chemicals used, Job’s plot table, association constant data, ESI-MS spectra of the inclusion complexes, and potential energy calculations of both inclusion complexes using computational studies (PDF)

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Notes
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