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Preparation, characterization and molecular modeling studies of the inclusion complex of Caffeine with Beta-cyclodextrin

Samikannu Prabu [a, c], Meenakshisundaram Swaminathan [d], Krishnamoorthy Sivakumar [e], Rajaram Rajamohan [a, b, *]

[a] Research and Development Centre, Bharathiar University, Coimbatore 641 046, Tamilnadu, India
[b] Department of Chemistry, SKP Institute of Technology, Tiruvannamalai 606 611, Tamilnadu, India
[c] Department of Chemistry, SKP Engineering College, Tiruvannamalai 606 611, Tamilnadu, India
[d] Department of Chemistry, Annamalai University, Annamalainagar 608 001, Tamil Nadu, India
[e] Department of Chemistry, SCSVMV University, Kanchipuram 631 561, Tamilnadu, India

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ABSTRACT

The formation through supramolecular interaction of a host–guest inclusion complex of caffeine (CA) with nano-hydrophobic cavity beta-cyclodextrin (β-CD) is achieved by a physical mixture, a kneading method and a co-precipitation method. The formation of the inclusion complex of CA with β-CD in solution state is confirmed by UV–visible spectrophotometer, fluorescence spectrophotometer and time-resolved fluorescence spectrophotometer. The stoichiometry of the inclusion complex is 1:1; the imidazole ring and pyrimidine ring of caffeine is deeply entrapped in the beta-cyclodextrin as confirmed by spectral shifts. The Benesi–Hildebrand plot is used to calculate the binding constant of the inclusion complex of CA with β-CD at room temperature. The Gibbs free energy change of the inclusion complex process is calculated and the process is found to be spontaneous. The thermal stability of the inclusion complex of CA with β-CD is analyzed using differential scanning calorimetry. The crystal structure modification of a solid inclusion complex is confirmed by scanning electron microscopy image analysis. The formation of the inclusion complex of CA with β-CD in the solid phase is also confirmed by FT-IR and XRD. The formation of the inclusion complex between CA and β-CD, as confirmed by molecular docking studies, is in good relationship with the results obtained through different experimental methods.

1. Introduction

We consume caffeine day-to-day in coffee, tea, cocoa, chocolate, some energy or soft drinks, chocolate milk, as well as in many painkillers and antimigraine drugs. Moderate consumptions of caffeine pose no health risks. We are consuming daily up to 1000 mg of caffeine, which poses no risks to human health [1]. Caffeine is the most broadly used drugs in the world and the most common caffeine delivery vehicle is coffee. The pharmacological properties of caffeine have been reconnoitered for many years and a variety of different pharmacological mechanisms have been attributed to caffeine. Young grown-ups and elderly population are differently affected by the intake of caffeine during brain development in learning and memory rates, hence more attention. The structure of the caffeine molecule limits the solubility in water because of the self-association of caffeine molecules by hydrophobic interactions [2–8] It is used as a therapy for a diuretic, but an excessive consumption of caffeine may cause several adverse effects, such as sleep deprivation, risk of cardiovascular diseases, reduction of fertility rates and increasing miscarriages [9].

It is well-known that β-cyclodextrins (β-CD) are non-toxic macrocyclic oligosaccharides consisting of (α-1,4)-linked α-L-glucopyranose units with an inner side of the cavity being hydrophobic and the outer side hydrophilic and can encapsulate model substrates to form host-guest complexes of supramolecular species. The Cyclodextrins (CDs) are well-known in supramolecular chemistry which is that discipline of chemistry which involves all intermolecular interactions where covalent bonds are not recognized between the interacting species [10,11]. The majority of these interactions are of the host-guest type determined by several weak forces, including Van der Waals, hydrophobic dipole–dipole and

* Corresponding author. Department of Chemistry, SKP Institute of Technology, Tiruvannamalai 606 611, Tamilnadu, India.
E-mail address: rajmohanau@gmail.com (R. Rajamohan).

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hydrogen bonding interactions [12,13]. The most important feature of cyclodextrins is their capability to form solid inclusion complexes with a very wide range of solid, liquid and gaseous compounds by a molecular complexation. The cyclodextrins (CDs) are torus-like macro-rings made from glucopyranose units. They are able to form inclusion complexes with a wide variety of guest molecules [14,15]. The guest molecule has been the most favorable changes in the physicochemical properties, like stability, dissolution rate, solubility, and bioavailability due to inclusion complex formation between the drug molecules with CDs [16–18]. The cyclodextrins are used in food [19], pharmaceuticals [20], cosmetics [21], environment protection [22], bioconversion [23,24], packing and the textile industry [25], drug delivery [26], nano-structures [27], supramolecular polymers [28], self-healing materials [29], amphiphiles [30], bioactive materials [31] or in the solubilization of hydrophobic monomers or RAFT agents [32,33].

The drug can be present in the different parts of the CD depending on the type of inclusion mode and thus their spectral characteristics may vary. The reason for choosing β-CD is that CDs have different nano cavity size and thus will be able to encapsulate the drug molecules in different manner and may form a different type of inclusion complex. Structural and thermodynamic information such as stoichiometry and geometry of the inclusion complex and association constant are necessary to draw a complete pictorial representation through the driving forces governing the drug-CD interaction.

The inclusion complexes have received considerable attention because of their increasing applications in the pharmaceutical field. For example, cyclodextrin based supramolecular complex has wide applications in medicine and single molecular devices. Hence, the study of photochemical and photophysical process of guest molecules has always been a spectral interest in chemistry.

In our present work, we report the preparation and characterization of inclusion complex formed by CA with β-CD. We utilized the absorption, fluorescence spectral titration and time-resolved fluorescence techniques to determine the stoichiometric ratio and binding constant of CA: β-CD complexes. The solid inclusion complex is characterized by FT-IR, powder XRD, DSC and SEM. Further, the most probable structure of 1:1 inclusion complex is proposed by molecular docking studies.

2. Materials and methods

2.1. Reagents

β-Cyclodextrin (purity ≥ 99%) and Caffeine (purity ≥ 99%) are obtained from Alfa Aesar chemical company and used without further purification. Other reagents and chemicals are of analytical reagent grade. A stock standard solution from CA (3×10^{-4} mol dm^{-3}) is prepared by using triply distilled water. The different concentration of stock solution of β-CD (0–1.2×10^{-3} M) is prepared by using triply distilled water. All experiments are carried out with triply distilled water. The solutions are prepared just before taking UV and fluorescence and life time measurements.

2.2. Instruments

Absorption spectra are recorded from 200 to 400 nm with an SHIMADZU model UV-2450PC spectrophotometer while fluorescence spectra of each solution being recorded from 280 nm to 800 nm using with a Perkin Elmer LS-45 fluorescence spectrophotometer. Single photon counting picosecond spectrofluorimeter (TSUNAMI, SPECTRA PHYSICS, USA) is used for the measurements of fluorescence lifetime of CA. FT-IR spectra of powder samples of drug, β-CD and the inclusion complexes are measured from 4000 to 400 cm^{-1} on a Thermo Nicolet 6700 spectrometer by using KBr pellets. The morphology of the samples is inspected using a Quanta 200 FEG scanning electron microscope (FESEM). Thermal characteristics of solid inclusion complexes are measured using Mettler Toledo DSC1HT fitted with STRe software (Mettler Toledo, Switzerland); the temperature scanning range is from 40 to 1100 °C with a heating rate of 10 °C/min. Powder X-ray diffraction patterns are recorded using a PAN analytical X′ pert pro X-ray diffractometer with CuKα radiation (1.5406 A°) source. The peak intensity data is collected over the range from 20θ to 50θ using a step scan mode (0.060/s).

2.3. Molecular docking study

The most probable structure of the CA: β-CD inclusion complex is determined also by molecular docking studies using the PatchDock server [34]. The 3D structural data of β-CD and CA is obtained from crystallographic databases. The guest molecule (CA) is docked into the host molecule (β-CD) cavity using PatchDock server by submitting the 3D coordinate data of CA and β-CD molecules. Docking is performed with complex type configuration settings. PatchDock server follows a geometry-based molecular docking algorithm to find the docking transformations with good molecular shape complementarity. PatchDock algorithm separates the Connolly dot surface representation [35,36] of the molecules into concave, convex and flat patches. These divided complementary patches are matched in order to generate candidate transformations and evaluated by geometric fit and atomic desolvation energy scoring [37] function. RMSD (root mean square deviation) clustering is applied to the docked solutions to select the non-redundant results and to discard redundant docking structures.

2.3.1. Semiempirical quantum mechanical calculations

The ground state of CA molecule is optimized using ArgusLab program by AM1 method. MolSoft MolBrowser tool is used to visualize the 3D structural data.

2.4. Preparation of inclusion complex in liquid medium

The stock solution of CA (3×10^{-4} mol dm^{-3}) is prepared by using water. The β-CD solution is prepared with the concentrations from 2×10^{-3} to 12×10^{-3} mol dm^{-3}. About 0.3 ml of CA solution is added to all the β-CD concentration to reach the final concentration of CA in each flask is 9.0×10^{-4} mol dm^{-3}

2.5. Preparation of solid inclusion complexes of CA with β-CD

The solid inclusion complexes between CA and β-CD are prepared at 1:1 M ratio by the following methods.

2.5.1. Physical mixture

The physical mixture of CA and β-CD with 1:1 M ratio is prepared by continuous agitation using a mortar and pestle for 10 min. Finally, a homogeneous mixture of CA and β-CD is obtained.

2.5.2. Kneading method

Accurately weighed 0.75 g of CA and 0.75 g of β-CD are placed in a mortar and allowed to make the of homogeneous paste with a small amount of deionized water as a binding material for 10 min. The paste is further kneaded manually for 45 min. The obtained paste is dried in a desiccator under vacuum for 48 h and stored in a desiccator at −20 °C until further analyses [38].

2.5.3. Co precipitation method

The solid inclusion complex of β-CD and CA is also prepared by