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β-CYCLODEXTRIN AS CARRIER FOR DIFFERENT GUEST MOLECULES IN BIOAPPLICATIONS – A MINIREVIEW ON THE THERMAL COMPLEXATION STUDIES BY DIFFERENTIAL SCANNING CALORIMETRY

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This work is dedicated to the memory of
Acad. Bogdan C. Simionescu (1948–2024)

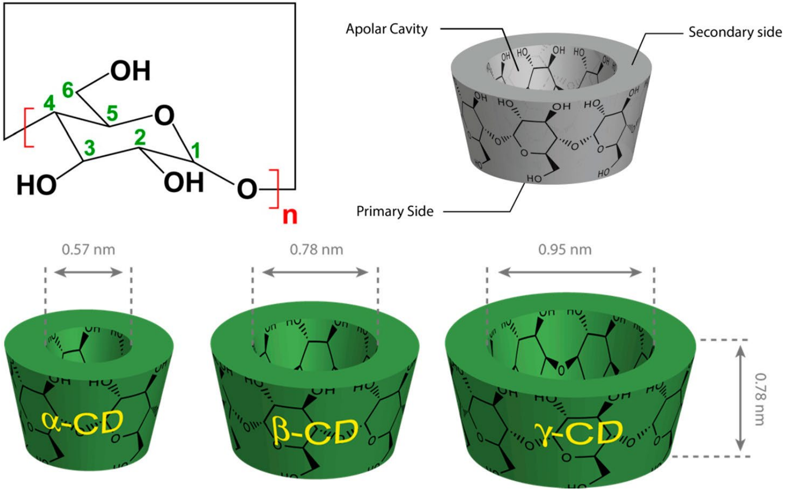
The history of cyclodextrins dates back to the end of the 19th century, when in 1891, Antoine Villiers observed the enzymatic effect of different carbohydrates, with emphasis on the butyric ferment *Bacillus amylobacter* (*Clostridium butyricum*), on potato starch. Villiers had no idea of the impact and large number of applications his discovery would generate over the next century. The most common cyclodextrins include six, seven and eight glucose units (αCD, βCD and γCD) and are generally regarded as safe, especially βCD, by the Food and Drug Administration (FDA, USA). Due to their unique structure, cyclodextrins can form inclusion complexes with a vast variety of guest molecules. The properties of the native cyclodextrins can be improved by synthesizing derivatives, depending on the desired application field. Nowadays, cyclodextrin derivatives are more than 11.000. From a practical standpoint, the degradation of cyclodextrin inclusion complexes is studied by thermogravimetric analysis (TGA), however providing information only on mass change. Differential scanning calorimetry (DSC) method reveals (changes in) other transitions as well, evidenced in the selected representative literature examples and discussed in this minireview.

Keywords: β-cyclodextrin, inclusion complex, DSC, host molecule, guest molecule, solid state interactions

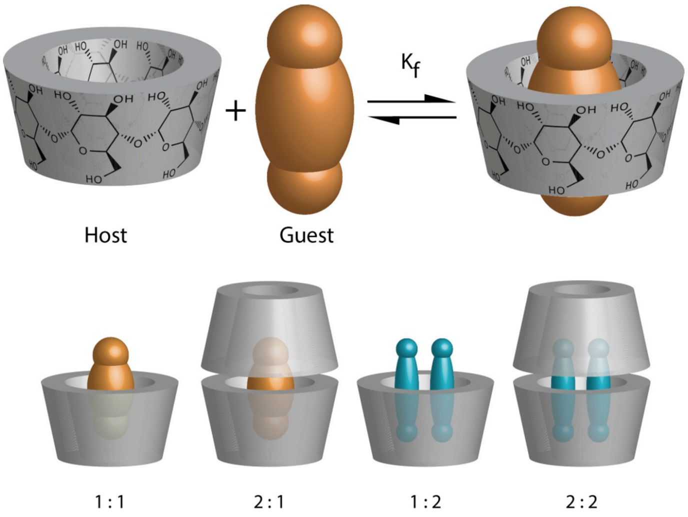
INTRODUCTION

Cyclodextrins (CDs) are applied in a wide range of industrial domains, from pharmaceuticals to foods.[1] Cyclodextrins are cyclic α-1,4-linked glucose oligomers obtained from the enzymatic degradation of starch by glucosyltransferase.[2] The most common CDs are those that possess six (αCD), seven (βCD) and eight (γCD) glucose units[3] (Scheme 1). CDs are supramolecular compounds resembling a hollow torus[4] with different polarities on its inside and outside surfaces[5,6] (Scheme 2).

CDs contain primary and secondary hydroxyl groups positioned on the narrow and the wider rim.[4] The primary hydroxyl groups may rotate and reduce the CD diameter,[7] while the secondary hydroxyl groups stiffen the CDs by forming strong hydrogen bonds.[7] Due to their unique structure, CDs can incorporate a wide variety of guest molecules to form inclusion complexes. The inclusion complexation of hydrophobic structures may occur through different interactions (*e.g.* hydrophobic interactions, van der Waals or dipole-dipole) between the guest molecule and the CD cavity walls.[8] Depending on their size, one or more non-polar molecules (Scheme 2) can be incorporated into the CD cavity, enhancing their water solubility.[9] The properties of native CDs can be enhanced via the obtaining of derivatives in order to lower toxicity, increase water solubility, inclusion capacity, stability and physical properties.[10] Some of the most reported CD derivatives in the literature are hydroxypropyl–, sulfobutylether– and carboxymethyl–type βCDs.[11] CDs can bring many benefits, *i.e.*, increase the stability under (a)biotic conditions, remove bad odours and taste, as well as control reactions and the release of molecules, in domains such as food science, engineering and technology.[13] The methods of preparing inclusion complexes, their advantages and drawbacks and the analytical characterization methods were recently reviewed by Cid-Samamed *et al.*[14]



Scheme 1: Structures and dimensions of αCD, βCD and γCD (reprinted with permission from reference[6])



Scheme 2: Types of host–guest complex stoichiometry (reprinted with permission from reference[6])

To control or examine the phase-change temperature, the release and decomposition of the guest molecule are some of the most intriguing and important issues in CDs chemistry, for both practical significance as biological products, food additives and cosmetic ingredients, and knowing how to view the differences between intermolecular interactions among free, complexed, and uncomplexed CD.[15,16]

From a practical standpoint, the decomposition of βCDs inclusion complexes is mainly studied by thermogravimetric analysis (TGA), which provides information on mass change only, but what about thermal transitions that are either (right) below thermal degradation, accompany it or even overlap with it? These thermal transitions and their modification upon complexation may contribute to answering some questions in the future, such as: when and how does the guest compound exit the CD cavity? Does the release of the complexed guest influence completely or partly the thermal degradation of the complexed or uncomplexed βCD? What are the degradation modes of free, complexed, and uncomplexed βCD?

Differential scanning calorimetry (DSC) is an indispensable method in characterizing complexation phenomena occurrence in solid state host–guest interactions. The DSC method consists in recording the heat flow, between an empty crucible and a crucible containing the sample (both crucibles usually of aluminum), as a function of temperature, at a specific heating rate (*e.g.* 10 °C min^{-1}) and in an inert atmosphere (*e.g.* nitrogen).[17,18]

From a general standpoint, the inclusion of a guest molecule in the cyclodextrin cavity is evidenced by the guest molecules' melting profile, which either weakens in intensity or completely disappears, with possible simultaneous displacement.[14] In practice however, depending on various factors (structure, properties and size of the guest molecule, type of cyclodextrin (derivative), solvent, complexation method, nature of host–guest interactions) the DSC curves may show (modifications in) other transitions as well, evidenced in the selected literature examples from the authors and described in this minireview.

DIFFERENTIAL SCANNING CALORIMETRY (DSC) STUDIES

Inclusion complex of a propiconazole derivative with β-cyclodextrin

The marketing of triazoles at the beginning of the 1990s was a major progress in safely and effectively treating local and systemic fungal infections.[19–23] Marangoci *et al.*[24] synthesized the antifungal propiconazole nitrate (NO_3PCZ) (Fig. 1) by the treatment of propiconazole (PCZ) with acidic nitrating agent (*i.e.*, a 1:3 molar ratio mixture of nitric and acetic acid) in chloroform for 18 h at room temperature, and purified it afterward. A yellowish–white, crystalline and odorless powder (NO_3PCZ) was obtained. NO_3PCZ is highly solubile in methanol, ethanol, DMSO, however almost insoluble in water and has a melting point of around 133.5 °C. The inclusion complex was obtained via the freeze-drying method in a 1:1 molar ratio (NO_3PCZ and βCD) in a solution of methanol and water (1/1 v/v) and stirred for 12 h. The solution was frozen afterward by immersion in liquid nitrogen and freeze–dried. The physical mixture was obtained in a 1:1 molar ratio of NO_3PCZ and βCD in a ceramic mortar.

The DSC curves of the pure drug and of the physical mixture (3.5/3.5 w/w) (Fig. 2) show two melting profiles at 126 and 137 °C, generated by the presence of a minor and a major isomer in the drug.[25,26] Both βCD and physical mixture exhibit physical dehydration through the broad endothermic peak around 110 °C. The DSC curve of the inclusion complex shows that the two endothermic peaks of NO_3PCZ coalesce into a single small peak at 140 °C, due to the formation of a new solid phase, compared to the peaks of pure NO_3PCZ.[27,28]

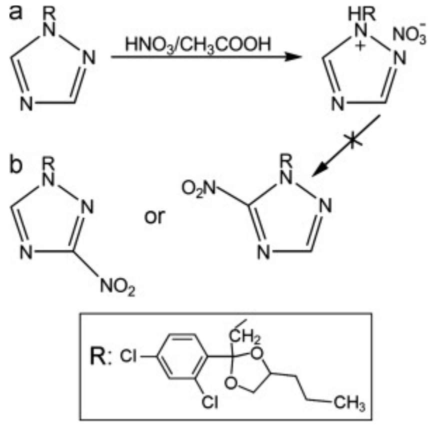


Figure 1: (a) Treatment of 1,2,4-triazoles with acidic nitrating agents and (b) proposed structure of NO_3PCZ (reprinted from reference[24] under Creative Common Attribution CC.BY.4.0)

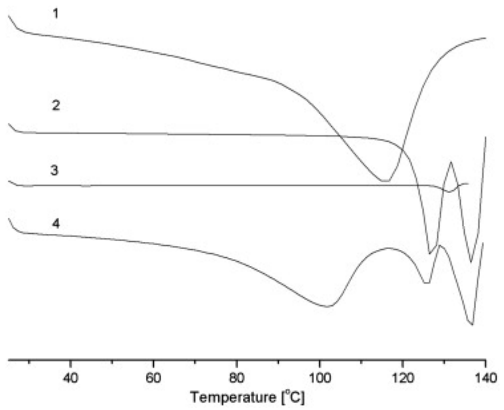


Figure 2: DSC curves of: (1) βCD; (2) NO_3PCZ; (3) βCD–NO_3PCZ; (4) physical mixture of NO_3PCZ and βCD (reprinted from reference[24] under Creative Common Attribution CC.BY.4.0)

Inclusion complexes of propiconazole nitrate with substituted β–cyclodextrins

In a further effort, the same group of Marangoci *et al.*[29] obtained inclusion complexes of propiconazole nitrate (PCZH–NO_3) with βCD and some of its derivatives sulfobutylether–βCD (SBE7–βCD), monochlorotriazinyl-β-cyclodextrin (MCT–βCD) and sulfated–βCD (βCD–SNa) in 1:1 molar ratios by the freeze–drying method as in reference.[24] Similarly to the previous case (see above), the drug molecule showed a double–peaked intense melting transition at 128 °C and 139 °C, due to the presence of a minor and a major isomer of the guest molecule. This double–peaked profile was also observed in the host–guests physical mixtures. Meanwhile, the inclusion complexes showed that the two melting peaks of the drug merge into a single and significantly reduced profile (T_m). Furthermore, this peak was displaced towards much lower temperature domains (T_m = 133 °C for βCD–SNa/PCZH–NO_3 and T_m = 120 °C for MCT–βCD/PCZH–NO_3) while completely disappearing for the SBE7–βCD/PCZH–NO_3 complex, indicating the successful formation of all three inclusion complexes.

To further demonstrate the occurrence of complexation phenomena, the inclusion efficiency was calculated using Equation 1 and its values were close to 100% (99.90% SBE7–βCD/PCZH–NO_3, 99.69% MCT–βCD/PCZH–NO_3 and 99.73% βCD–SNa/PCZH–NO_3):

$$\% \text{ Inclusion} = 100(1 - \Delta H_{mc}/\Delta H_{mg}) \qquad (1)$$

where ΔH_{mc} and ΔH_{mg} are the melting enthalpy values of the inclusion complex and pure drug, respectively.

Inclusion complexes of hesperidin with hydroxypropyl–β–cyclodextrin (HP–βCD)

Hesperidin (HES) (5,7,3'–trihydroxy–4'–methoxy–flavanone 7–rhamnoglucoside) is a flavanone glycoside structurally composed of a flavanone (hesperitine) and of a disaccharide (rutinose) (Fig. 3a), and is the main flavonoid in lemons and sweet oranges.[30] HES is an auxiliary in many deficiencies and diseases associated with: muscle cramps (especially during the night), pain in extremities, fatigue and low capillary resistance,[31] due to its many biological and pharmacological properties and effects (*i.e.*, antioxidant, cardiovascular and anti-inflammatory).[32,33] Clinical studies have demonstrated that HES is also a vascular protector and is venotonic,[34] reduces blood pressure and cholesterol,[35,36] decreases loss of bone density[37] and fights against hemorrhoidal disease.[38] HES also shows strong neuroprotective, antiviral and antifungal properties[39] and is a suppressant of cell proliferation in oral carcinogenesis.[40] The absorption of HES occurs through the gastrointestinal tract.

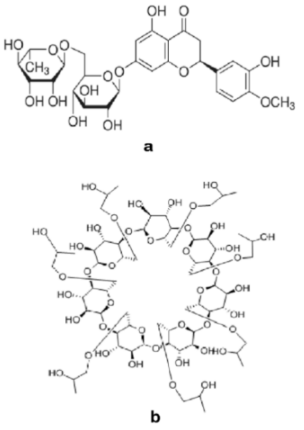


Figure 3: (a) HES and (b) HP–βCD structures (reprinted from reference[42] under Creative Common Attribution CC.BY.4.0)

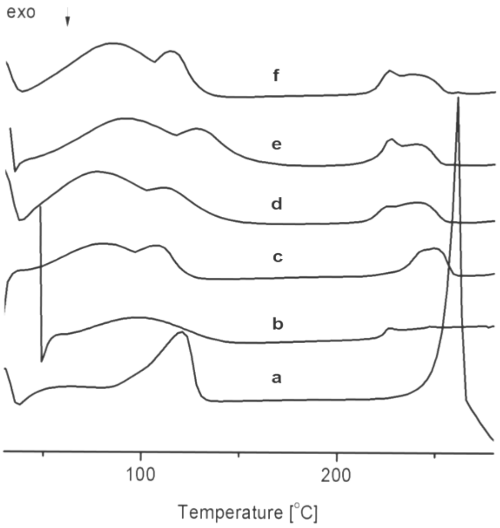


Figure 4: DSC curves of: (a) HES; (b) HP–βCD; (c) physical mixture; (d) KN; (e) CV and (f) L (reprinted from reference[42] under Creative Common Attribution CC.BY.4.0)

Unfortunately, HES reported low bioavailability (<25%) due to its low water solubility and precipitation in acidic environments.[41]

In order to surpass this impediment, Corciova *et al.*[42] obtained HES–HPβCD inclusion complexes (1:1 molar ratio) (Fig. 3b) through three different methods: co–evaporation (CV), kneading (KN) and lyophilization (L).

Figure 4 shows the DSC curves of the pristine components, the physical mixture and of the inclusion complex obtained with the three methods.

From Figure 4, one can observe that the pure HES exhibits a dehydration peak at 121 °C, followed by a sharp an intense melting peak at 262 °C.

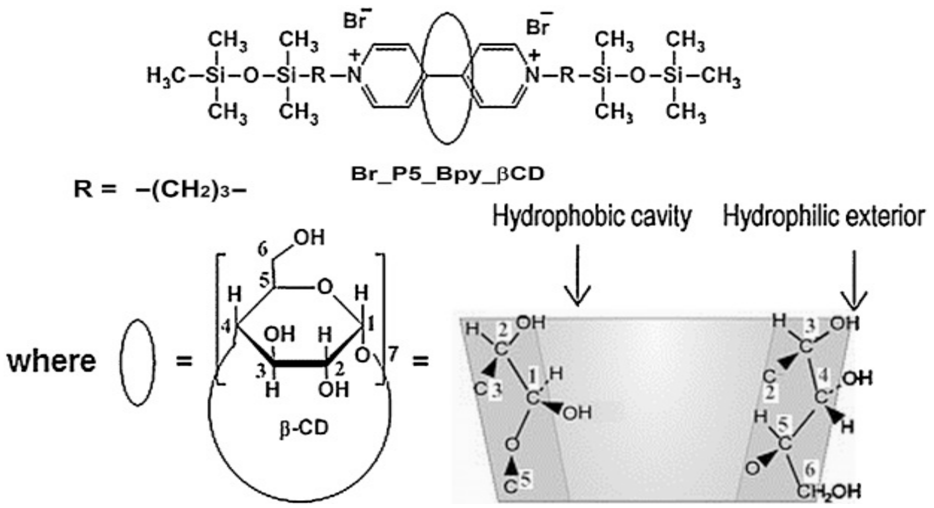
The pure HP–βCD underwent water loss from its cavity, as shown by the broad endothermic peak at 97 °C. In the DSC curve of the inclusion complexes, the dehydration peak of HP–βCD appears at a lower temperature, which is the first indication of an interaction between HES and HP–βCD. Also, in the case of all the inclusion complexes, the dehydration peak of HES also appears reduced in intensity and seemingly shifted compared to that of pristine drug dehydration (121 °C). The two glycosidic entities in the pure drug may couple to the hydrophilic exterior and/or the hydroxypropyl entity of HP–βCD through OH groups with hydrogen bonding, while the rest of the drug molecule enters the guest molecule cavity. The HP–βCD molecule showed an endothermic transition at 224 °C, consistent with a glass transition (T_g), being in good agreement with reported literature.[43–45] The T_g of an amorphous structure is known to be sensitive to the presence of other molecules, especially if physical host–guest interactions occur. This is why in the DSC curves of the inclusion compounds, the T_g of HP–βCD significantly broadens in intensity and shifts to different temperatures. To confirm this aspect, the heat capacity (ΔC_p, J g^{-1} °C^{-1}) values increased in the following order: HP–βCD (0.402) < KN (0.656) < L (0.806) < CV (0.935). This broadening and displacement of the T_g is consistent with an increase in amorphous phase due to inclusion complex formation.[46] Moreover, the melting profile of pristine HES disappears, with the forming of a new endothermic peak in the DSC curve of the inclusion compound, which slightly coalesces with the T_g. This aspect is an indication of possible complexation phenomenon or an interaction between host and guest molecules in solid state through the formation of a new amorphous phase.[47]

βCD–pseudorotaxanes host–guest architectures

Differential thermal analysis (DTA) is a technique similar to DSC, except that it measures the temperature difference between the empty crucible and the one with sample as a function of temperature increase.

The differential thermal analysis (DTA) method was applied simulatenously with thermogravimetric analysis (TGA) to a supramolecular inclusion complex.[48] In this sense, there was obtained the βCD–caged 4,4′–bipyridinium–bis(siloxane) inclusion complex [2]{[1][(1,1′–di(propyl–3–pentamethyldisiloxane)–4,4′–bipyridinium]–rotaxa–[β–cyclodextrin]}, as a potential pharmaceutical candidate in two stages: (i) the complexation between βCD and 4,4′–bipyridine (BPy), via co–precipitation, followed by (ii) the quaternization of the nitrogen atoms of the caged 4,4′–bipyridine, through the bromide atom of the presynthesized 1–(3–bromopropyl)–pentamethyldisiloxane[49] (Scheme 3).

The DTA curves of the studied structures, recorded simultaneously with the TGA ones (not shown) are depicted in Figure 5.[48]



Scheme 3: Structures of the compounds (reprinted with permission from reference[48])

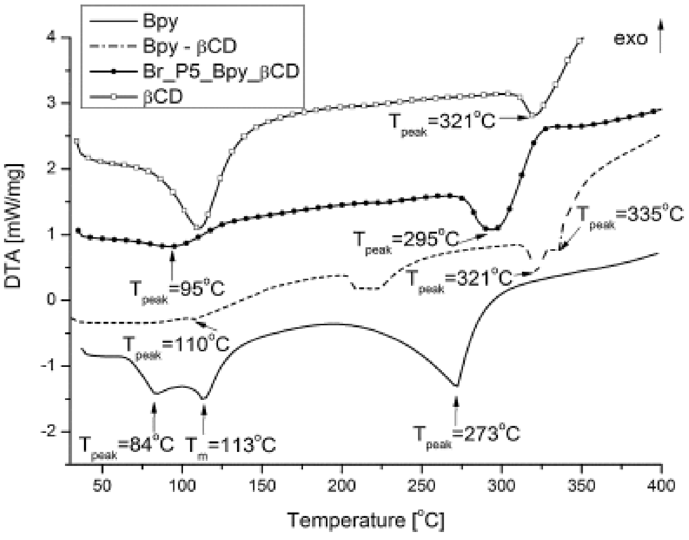


Figure 5: DTA thermograms of the compounds (reprinted with permission from reference[48])

According to Figure 5, the thermal degradation of Bpy is described by the broad endothermic profile peaked at 273 °C (ΔH = 332 J g^{-1}), describing the overlapping of the boiling point (around 305 °C) and thermal degradation processes.[50,51] Looking further, in the case of Bpy–βCD inclusion complex, the DTA curves clearly indicate that the pure Bpy broad endothermic degradation profile is significantly reduced (25 J g^{-1} vs. 332 J g^{-1}) and shifted toward a higher temperature (321 °C), almost coinciding with that of pristine βCD (321 °C, 20 J g^{-1}). The only difference is the one between ΔH values and the two peaked endothermic profile of Bpy–βCD (321 °C and 335 °C) occurred due to volatilization of complexed Bpy at a higher temperature.

From the DTA curve of the guest compound, one may observe that Bpy exhibits a two peak endothermic profile corresponding to thermal history removal (84 °C) and melting point (T_m = 113 °C). In the DTA curve of Bpy–βCD, the two endothermic peaks of Bpy merge into one less intense peak shifted toward a lower temperature (110 °C), indicating a new solid phase.[52,53] The inclusion complex Br_P5_Bpy_βCD similarly shows a less intense melting peak toward an even lower temperature (T_m = 95 °C) as that of Bpy (T_m = 113 °C), also consisting with the formation of a new solid phase.

CONCLUSION

The supramolecular structures of cyclodextrins allow them to form inclusion complexes with a wide palette of guest molecules and the properties of cyclodextrins can be enhanced by synthesizing derivatives. The decomposition of cyclodextrin inclusion complexes is mainly studied by TGA, which provides information only related to mass modification. The DSC method reveals (modifications in) other transitions also, hence DSC is a very useful tool in studying and confirming inclusion complex formation. For this minireview, the authors have selected some representative studies from their own works: (i) inclusion complex of a propiconazole derivative with β-cyclodextrin; (ii) inclusion complexes of propiconazole nitrate with substituted β–cyclodextrins; (iii) inclusion complexes of hesperidin with hydroxypropyl–β–cyclodextrin and (iv) a β–cyclodextrin–pseudorotaxanes host–guest architecture.

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