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Thermal analysis of cyclodextrins and their inclusion compounds

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Abstract

This review examines the literature concerning the thermal properties of natural and semisynthetic cyclodextrins and their inclusion compounds. Particular emphasis is given to recent results of investigations by thermal methods of the hydrated forms of cyclodextrins. The limitations and advantages of the applications of thermal analyses concerning water- and drug-cyclodextrin interactions are also discussed.

Keywords: Cyclodextrins; Inclusion compounds; Thermal analysis

Quorum, ita texturae ceciderunt mutua contra ut cava conveniant plenis haec illius illa huiusque inter se, iunctura haec optima constat. (Titus Lucretius Caro, 96-55 BC, De Rerum Natura, Liber VI)

Bodies, that interact in structural harmony to fill each other's voids, combine most perfectly. (Translation by James Grant, 1896-1966, English poet)

1. Introduction

Cyclodextrins (CDs) are natural or semisynthetic cyclic oligosaccharides with a central cavity able to host foreign molecules. Their importance to pharmaceutical formulation and delivery is well documented by the increasing number of marketed or approved medicinal products containing CDs (Table 1).

The main applications are related to their solubilizing properties and to dissolution rate enhancement. A thorough solid-state characterization of these materials is of great interest considering the possible implications for patenting and marketing. In this context thermal methods are widely used to characterize CDs and their inclusion compounds.

Cyclodextrins are generally marketed as hydrates with differing water contents depending on the preparation procedures and storing conditions. TGA and DSC represent, therefore, a first choice analytical tool for an accurate physico-chemical characterization of the solid-state of these compounds in terms of water release energetics. Particular attention has also been paid to the investigation of solid–vapor equilibria of β-cyclodextrin (β-CD). Moreover, as inclusion compounds formed by drugs and CDs are generally prepared in aqueous media, they should be considered as ternary water/CD/drug systems, when the assessment of stoichiometry, i.e. the composition of the interaction product, is involved. Many excellent reviews have already been published on CDs and related topics: a prudential estimate of reviews which appeared in scientific literature in the last 20 years gives a figure

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Table 1
Commercial pharmaceuticals with CD-based formulations

Component	Trade name	Company	Country	Formulation
PGE_1/α-CD	Prostandin 500	Ono	Japan	Infusion
	Prostavasin			
	Viridal	Schwarz Pharma	Germany	
PGE_2/β-CD	Prostarmon.E	Ono	Japan	Sublingual tablets
Piroxicam/β-CD	Brexin	Chiesi	Italy, Belgium	Tablets
	Brexidol		The Netherlands, Switzerland	Suppositories
		Robapharm	France	
		Promedica		
		Nycomed	Scandinavia	
		Launder	Germany	
OP-1206/γ-CD	Opalmon	Ono	Japan	Tablets
Benexate/β-CD	Ulgut	Teikoku	Japan	Capsules
	Lonmiel	Shionogi	Japan	
Iodine/β-CD	Mena-Gargle	Kyushin	Japan	Gargling solution
Dexamethasone/β-CD	Glymesason	Fujinaga	Japan	Ointment
Nitroglycerin/β-CD	Nitropen	Nippon Kayaku	Japan	Sublingual tablets
Cefotiam/α-CD	Pansporin T	Takeda	Japan	Tablets
New oral cephalosporin (ME 1207)/β-CD	Meiact	Meiji Seika	Japan	Tablets
		Roussel-Maestretti	Italy	
Nimesulide/β-CD	Nimedex	Novartis, Italfarmaco, Boehringer Mann.	Italy, Switzerland	Tablets
Diphenydramine HCl + chlortheophylline/β-CD	Stada Travel	Stada	Germany	Chewable tablets
Chlordiazepoxide/β-CD	Transilium	Gador	Argentina	Tablets
Hroconazole/HPβ-CD	Sporanox	Janssen	Belgium	Solution
Hydrocortisone/HPβ-CD	Dexacort		Israel	Solution

of around 600 publications. Some of these are collated in Table 2. This clearly demonstrates the tremendous number of research groups operating in this field. As stated above calorimetric and microcalorimetric methods have been applied extensively in the characterization of CDs and their inclusion compounds. A review on the applications of thermal methods to these substances might therefore be of some interest when addressing topics related to CDs.

2. Chemical and physical properties of cyclodextrins

The term CDs gathers those starch derivatives characterized by a ring built with glucose units. These compounds are obtained by means of specific enzymes with a two-step process involving the cleavage of polysaccharidic chains into oligosaccharidic and resealing of the two open ends to form a cyclic structure. Natural products include cyclic compounds formed with 6–9 D-glucose units all in α(1–4) linkages, known as α-, β-, γ-, and δ-CDs (respectively, cyclo-hexa, -hepta, -octa, or -nonaamylose). The main feature of CDs is related to their ability to form inclusion compounds in aqueous solutions with molecules able to fit totally or partially into the cavity generated by the ring shape.

Table 3 reports some of the physical and chemical properties of the principal natural members of this class of homologues. As a general consideration CDs are fairly stable compounds, as starch and other starch derivatives, due to intra- and inter-molecular hydrogen bonding.

Table 2
Reviews on CD

Topics	References
Analytical chemistry	[1–5]
Binding	[6]
Biology and medicine	[7–9]
Biosynthesis	[10]
Biotechnology and food industry	[11–18]
Catalysis and artificial enzymes	[19–24]
Chromatography	[25–29]
Complexation thermodynamics and stability constants	[30–32]
Computer-aided molecular modeling	[33]
Dissolution and bioavailability	[34–39]
Inclusion compounds	[40–46]
Industrial applications	[47–52]
Organometallic compounds	[53]
Pharmaceuticals	[54–69]
Pharmacology, toxicology and metabolism	[70–73]
Polymers	[74–77]
Preparation and manufacturing	[48–90]
Prostaglandins	[91]
Spectroscopy	[92]
Structural aspects	[93–95]

Cyclodextrins are generally marketed as hydrates either depending on the separation/preparation procedures or on water adsorption–desorption phenomena related to storage conditions. When small molecules (like water or methanol) are included into the cavity, cage-like structures are usually formed by CD molecules, i.e. both openings of each cyclic unit are closed by adjacent CD molecules, thus entrapping the guest in the cage. The inclusion of molecules larger than water or methanol can deeply modify the solid state arrangement: the host–guest complex structures itself in a head to head–tail to tail fashion. Depending of course on the nature and dimension of the guest, a variety of conformations can be adopted, from perfectly aligned to more or less displaced, possibly forming, in the most favorable case, endless channels.

Table 3
Some physicochemical properties of the natural CDs

	α-CD	β-CD	γ-CD
MW	972	1135	1297
Glucose units	6	7	8
Water solubility (g/100 ml, RT)	14.5	1.85	23.2
Cavity diameter (Å)	4.7–5.3	6.0–6.5	7.5–8.3
Total diameter (Å)	14.6	15.4	17.5
Solvation water molecules	6–7	11–12	17

3. Thermal analysis of cyclodextrins

Despite the fact that thermoanalytical techniques are considered reliable and relatively fast methods [96,97] there are only few papers on the general thermal properties of CDs. Attention has been given to investigations of the thermodynamic behavior of binary water–CD systems, especially the α-CD/water and β-CD/water systems (see relevant sections).

In addition to well-known thermoanalytical techniques routinely used for investigating the cyclodextrins and their inclusion complexes, the following coupled techniques are also gaining increasing importance: TG–Fourier transform infrared spectroscopy (TG–FTIR), TG/DTA–FTIR, TG–mass spectrometry (TG–MS), TG/DTA–MS, and DTA (or DSC)–Powder X-ray diffractometry (PXRD).

All these instrumental analyses allow the determination of mass and heat flow changes simultaneously with the structural/functional identification of the sample and/or its decomposition products.

The general thermal behavior of natural CDs is similar. Differences can be found in water content, onset temperatures of thermal degradation and the mass loss values at given temperatures.

3.1. Thermal behavior of β-cyclodextrin and its derivatives

Among the different available CDs, β-CD is by far the most popular and widely used. Its thermoanalytical profile can be generally divided into three parts: (1) water loss from ambient temperature up to 120°C depending on the experimental arrangements (open, perforated or sealed lids, static or dynamic atmosphere); (2) thermal degradation — accompanied by oxidation in air — starting above 250°C in solid phase at first and continuing in liquid state after fusion which occurs approximately at 300°C; (3) ignition takes place in air above 300°C. The melting process influences the shape of the thermoanalytical curves, since the decomposition rate decreases accordingly [98].

Between 120 and 280°C the TG curve is flat and no mass loss is detected, while, in DSC, small endo or exo or even endo–exo effects may appear at 210–240°C (Fig. 1). There is no agreement concerning the nature of this transition. Depending on the different ways of

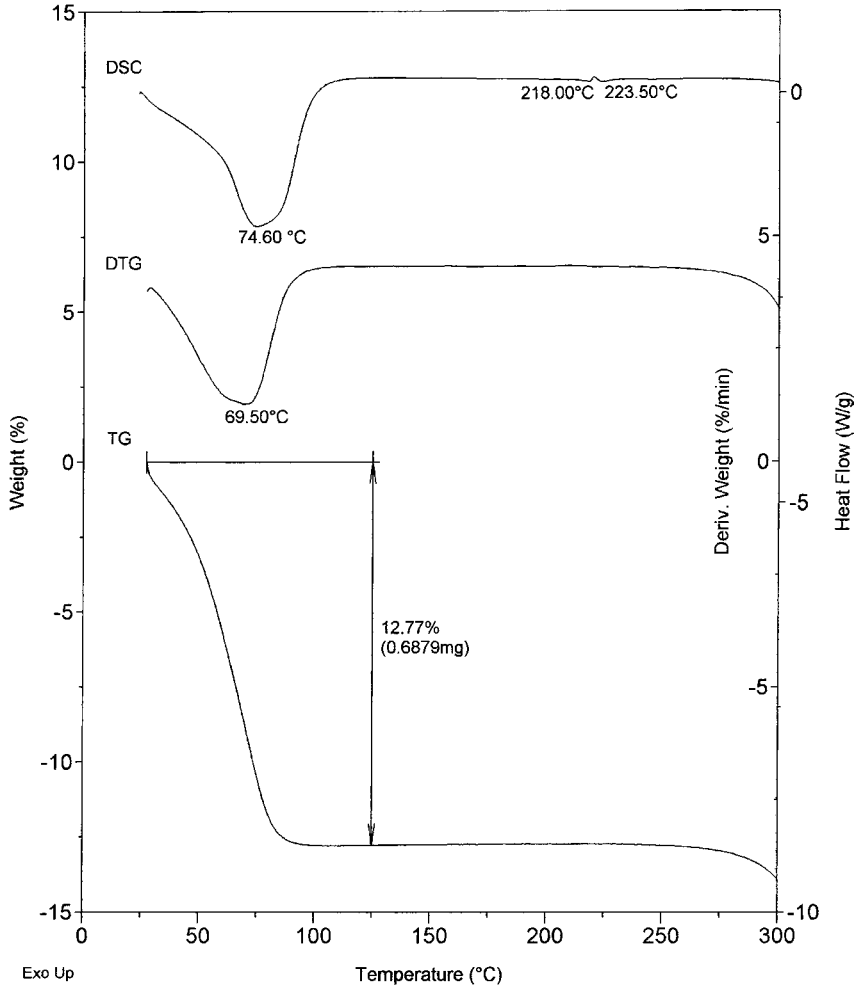

Fig. 1. Thermoanalytical profile of β-CD.

preparation and consequent hydration levels, samples of β-CD may exist in different crystal forms and some of them may more or less readily transform into each other. This peculiar behavior has been ascribed both to reversible and irreversible phenomena by different authors. Exotherm [99–101], endotherm [101,102], exo–endotherm and endo–exotherm effects [100] were found. All the above mentioned transitions were recorded [100] on commercially marketed samples of β-CD when submitted to common procedures for the preparation of inclusion compounds (grinding, kneading, and suspension techniques).

A similar endothermic effect in the same temperature range was described by Sztatisz et al. [98] who attributed it to a reversible transformation of β-CD in the solid state. Other authors reported an irreversible exothermic transition when analyzing a β-CD sample of commercial origin: the same sample exhibited an irreversible endothermic enthalpy change after rehydration. No structural transformation was evidenced by PXRD, but dimensional changes were confirmed by thermomechanical analyses [101,102].

Although the thermal profiles of the various CDs exhibit only minor differences, nevertheless crystallinity and crystal habit remarkably affect their complexing abilities. This also influences the tabletting and dissolution properties when CDs are used as excipients in the solid state [103–105].

The relationship between particle size and thermal properties of CDs was emphasized in another study [106]. Three native and a hydroxy-propylated β-CD, with a low degree of substitution, were investigated in the ''as received'' state and after storing at different relative humidities. The water contents of CDs were determined after drying at 160°C and also using the Karl Fischer method, while thermal characterization was accomplished by DSC.

Investigations on the thermal behavior of α-CD were also reported [107–109]. Studying the effects of microwave heating on dehydration it was concluded that three different energy levels are required to remove the water from α-CD. The water loss was followed by TG and a three-step process was observed between ambient temperature and 170°C [110].

3.2. Thermal behavior of α-cyclodextrin

α-CD is the smallest among natural CDs, being formed only from 6 glucose units. Owing to the dimension of its cavity, it can form inclusion compounds with foreign molecules of rather small molecular size, e.g. some organic solvents like methanol [111], ethanol [112] (generally containing also water molecules [113]), and water.

Hydrates of α-CD with 6 and 7.5 water molecules have been isolated and described. α-CD·6H_2O exists in at least two different forms (forms I and II), and their crystalline structures have been illucidated [114,115]. The authors pointed out that, despite their identical water contents, a two-step process was obtained in one case which exhibited a 188 J g^{-1} enthalpy of dehydration. The other polymorph demonstrated a three-step water loss with a remarkably higher dehydration energy (265 J g^{-1}). After its water loss a small endothermic peak appeared which was attributed to a phase change in anhydrous α-CD [109] (Fig. 2). The occurrence of phase transformation was also observed in different marketed α-CDs [100,107]. During water loss, a single step expansion was observed in the first case, whereas two distinct expansion steps (water loss and structural rearrangements) were present in the second case.

Amorphous α-CD can be prepared by grinding using a laboratory mortar grinder or by aging. The thermal properties and the rehydration kinetics under controlled conditions have been studied in detail [108,110]. TG, DSC, and TMA were used for these experiments. Grinding induced a gradual decrease of crystallinity up to complete amorphisation, in good agreement with other findings [116]. No differences were evident in the DSC curves of ground and aged samples. The dehydration of the amorphous sample took place between 30 and 130°C causing a broad endothermic peak (enthalpy change 145 J g^{-1}, 6.4 wt.% loss). ehydration of the amorphous anhydrate has been also investigated. The aged sample totally recrystallized after 3h storage at 71.5% RH, whilst the ground substance remained completely amorphous.

A detailed study was dedicated to the thermal decomposition of three native and two chemically modified β-CDs by Kohata et al. [117]. As far as water loss up to 130°C is concerned, their observations were more or less identical to those recorded by other authors. In the case of α- and γ-CDs, however, a small mass loss was reported at approximately 260–270°C and attributed to the loss of very tightly bound water. Furthermore, despite the inert atmosphere used, in the case of γ-CD an exothermic decomposition was obtained. An order for their relative thermal stability was also established for the compounds: β-CD had the lowest thermal stability, which can be explained by being the least symmetric of the three, most frequently used CDs.

Since mechanical methods such as grinding and kneading are the most commonly applied preparation techniques of CD inclusion complexes, the effects of grinding on the structure and properties of the parent CDs have been widely investigated.

The crystallization behavior of ground α- and β-CDs and ground mixtures of CDs with different drugs were studied at various relative humidities by powder X-ray diffraction and thermal analysis [118]. Ground α-CD remained in its amorphous state at RHs up to 68% but underwent recrystallization at RH values >84%.

For various reasons (enhanced water solubility, lower toxicity, etc.) chemically modified CDs have been developed [34]. Acetylated, ethylated, hydroxypropylated, methylated, and sulfobutylether derivatives are used instead of native β-CD. Few papers detail their thermoanalytical properties. In general, lower water contents are present in the modified CDs compared to their native analogues, as a result of partial replacement of hydroxyl groups following their preparation [107,118].

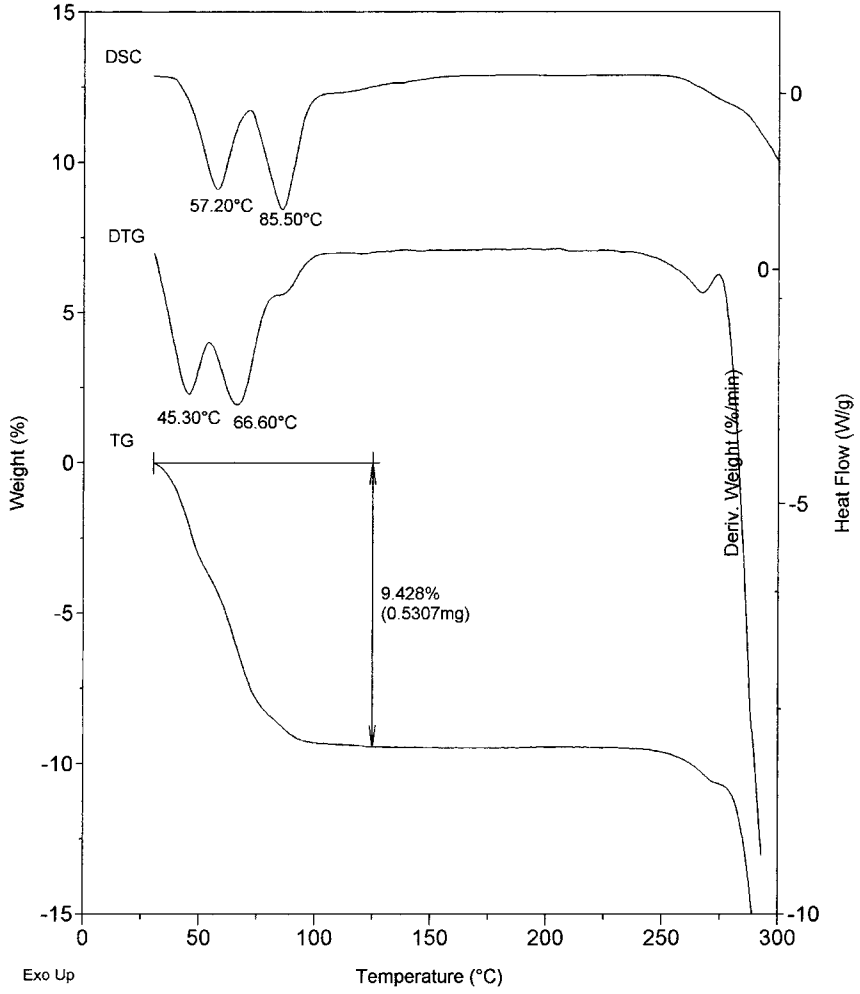

Fig. 2. Thermoanalytical profile of α-CD.

The thermal stability of the modified derivatives is generally higher as demonstrated by their higher temperatures of decomposition compared to parent unmodified CDs. Melting can occur in roughly the same temperature range [118,119], but may also take place at lower or higher temperatures, depending on the nature of the sample. In some cases the chemical modificat-ion may result in amorphous products with T_g temperatures depending on the substitution degree [120].

Since the fusion of native CDs takes part only after decomposition has already started, these materials are not suitable to study the effects of grinding on their glass transitions. A detailed study has been presented on the amorphous transformation and glass transition of tri-*O*-methyl-β-CD, TRIMEB, showing a melting point of 156°C [120]. Grinding a crystalline sample in a vibrating mill at room temperature lead to an amorphous product. The process was followed by PXRD and DSC. On the basis of the measured enthalpies, the amorphization process was complete within 25 min of grinding; meanwhile the T_g increased linearly with grinding time from 58 to 79°C (T_g of a liquid-quenched glass). No differences were found in the X-ray pattern of thoroughly ground and liquid-quenched samples. However, their IR spectra were different in the region assigned to the rocking of the CH_3 groups at the edge of the molecule (1194 cm^{-1}).

Thermodynamic properties related to the glass transition and fusion of TRIMEB have been reported [121].

Microcalorimetry is also a technique commonly used to investigate the physico-chemical properties of CDs. The heat capacities of a set of malto-oligosaccharides, including α-, β-, and γ-CDs, both in the solid state and in dilute aqueous solution have been determined [122].

An analytical method was developed [123] using a miniaturized adiabatic calorimeter to measure the phase transition and freezing phenomenon of β-CD·11H_2O. A sharp heat-capacity peak was observed at −47°C due to the first-order phase transition while another one appeared at around −120°C due to thermal relaxation. The crystal structure of the same samples was studied with X-ray and neutron-diffraction methods.

The inclusion complex formation between β-CD, as host, and benzoic acid or its sodium salt, as guests, was investigated by microcalorimetric methods [124]. Direct calorimetric measurements were used to determine the thermodynamical values for the complex formation and for the values of the dissociation constants.

In some cases, thermoanalytical methods can be used for quality control. A correlation was found for substituted β-CD samples between their degree of substitution and T_g values [120]. In another set of experiments, EGA was used to detect technological contamination and impurities [121,125].

In addition to their uses in inclusion complex formation, CDs and their modified derivatives are commonly used as mobile and stationary phases in chromatography. Thermoanalytical properties of butylated and acetylated β-CDs have been reported [126,127]. The thermal stability of partially alkylated CDs in high temperature capillary gas chromatography was remarkably increased by trimethylsilylation of the free hydroxyl groups [128].

4. Thermal analysis of cyclodextrin hydrates and solvates

4.1. Thermal analysis of water–cyclodextrin interactions

The complex relationships between CDs and water have been repeatedly investigated by a variety of thermal methods in both solution and the solid state. As a general consideration most of the research in this direction has focused on features and properties relevant to β-CD, mainly because of availability and practical reasons but also due to some specific properties (water solubility, pseudopolymorphism, etc.) of this molecule with respect to other CDs. In other words, the interaction between water and the different CDs, and therefore the results of analytical thermal methods on this topic, cannot be easily driven within a common frame but need to be individually discussed.

4.2. β-Cyclodextrin hydrates

β-Cyclodextrin crystallizes from aqueous solutions as either its undecahydrate or dodecahydrate. The structural difference between these hydrates is mainly related to the distribution of disordered water molecules in the β-CD cavity. Water molecules are included in the cavity and also located in the interstices between the macrocycles. A neutron diffraction study [129] on the undecahydrate showed that the 11 water molecules are distributed over 16 positions, 8 in the cavity of β-CD (6.13 water molecules) and 8 in the interstices (4.88 water molecules). In fully hydrated β-CD, 7 water molecules occupy the cavity as a cluster while 5.4 molecules are located in interstitial spaces [130]. Below 15% RH the crystal structure collapses and a distinct phase is formed [131].

The dielectric investigation of β-CD hydrates by means of thermally stimulated current (TSC) methods has been performed in the 80–300 K temperature range [132,133]. The position and shape of low temperature peaks at about 145 K are practically the same for water contents between 11 and 18% (expressed as weight percent of the dry sample), while maximum current increases with water content. The high temperature region shows a very large peak at 210–220 K plus a smaller one at 250–260 K. When a β-CD sample is completely dehydrated over P_2O_5 and analyzed until it has recovered its original water content (13.3%) it has been shown that, at very low water contents (0.5%), the TSC spectrum is dominated by a very large and broad peak at 200–240 K which masks all other contributions and shifts to lower temperatures with increasing water contents. The authors [133]

moreover underline that the dehydrated sample does not recover the original dielectric characteristics, thus suggesting that complete dehydration causes an irreversible structural alteration of β-CD.

The energetics of the interaction between water and β-CD with different thermal histories and water contents has been extensively investigated by means of TG and DSC by various authors.

The apparent kinetic parameters relevant to the thermal decomposition of β-CD undecahydrate were estimated from thermogravimetric data using various calculation methods [134], obtaining a reaction order near to zero and an activation energy in the range 60–65 kJ mol^{-1}. Water was liberated in a single stage during thermal decomposition of the hydrated samples.

The thermal behavior of a commercial sample of β-CD (corresponding to the undecahydrate) was determined by TG and DSC in the −150 and +300°C temperature range [135]. According to these authors dehydration of β-CD undecahydrate occurs in two steps corresponding to the loss of 7 and 4 molecules of water. A second weak endothermic effect, already described [136] and independent of water contents, was also observed between 200 and 250°C and was attributed to a phase transition.

A comparison between the thermal behavior of β-CD samples recrystallized from water and samples with different thermal history and various water contents pointed out a linear relationship between specific interaction energy and β-CD/water ratio [137]. The high value of specific interaction energy (about 80 kJ mol^{-1}) suggests that energy contributions, arising not only from the breaking of the hydrogen bonds involving water, are also present.

Data collected from DSC, TG and TMA were compared with parallel PXRD equipped with a polythermal attachment in order to reveal possible structural changes associated with thermal events [138]. It was found that the water/β-CD system has a complex behavior above room temperature and, in all cases, water is liberated in a single step. Up to 60°C in a dry atmosphere, the release of water happens at a much faster rate than the consequent structural transition. This phase transition was shown to contribute substantially to the endothermic DSC peak usually attributed simply to dehydration. After completing its transition to the dehydrated structure, β-CD undergoes an irreversible expansion (about 15% of its initial volume), with apparently no further modification to the crystal structure.

A calorimetric and gravimetric study of β-CD hydration [139] has been performed on samples with water contents up to 14% (10 water molecules per molecule of β-CD). The enthalpy of dissolution at 298 K increased linearly with water contents, ranging from −75.6 (water content, 1%) up to 10.4 J g^{-1} (water content, 13.9%). Previous findings concerning the evolution of water in two stages [135] could not be confirmed.

Thermal measurements [131] pointed to the role of a structural transition from the hydrated β-CD (phase I) to a ''dehydrated'' form (phase II). The contribution of β-CD to dehydration equals the enthalpy of transition from hydrated to dehydrated phase. Over a wide range of hydration levels, water molecules have a liquid-like diffusion which accounts for the fast and nearly reversible dehydration of β-CD.

The obvious importance of a careful characterization in terms of water contents of partially hydrated samples of β-CD, when dealing with DSC or TGA runs to measure dehydration enthalpies, was also underlined [140]. A possible and reasonable explanation of some of the discrepancies found with the experimental results previously reported [139] probably lies in the large uncertainties in the determination of water contents in samples used by the same authors.

The inflections observed in both DSC and TGA runs during isobaric dehydration experiments in wet atmospheres are interpreted as a landmark of the instability point, taking into account that a transition occurs at 59°C at a critical saturation limit (water mol per mol of β-CD) in the order of interstitial water molecules (about 5.5) [131].

By completing thermal investigations on water/β-CD interaction with NMR [141], structural [142], and thermodynamic considerations [143], it can be concluded that water absorbed by β-CD is largely ''free'' and its fast diffusion is possible even without permanent diffusion channels through the crystal.

These findings correlate well with results [144] obtained by infrared spectroscopy on β-CD·12H_2O samples exposed to an atmosphere of D_2O, which showed that the reversible process of the H/D exchange follows a first order kinetics. In a further

experiment aimed to demonstrate the continuous exchange of water molecules between crystalline β-CD and water vapors in the surrounding environment, a sample of H_2O containing β-CD was exposed to D_2O atmosphere and the exchange process monitored by mass spectrometry [145]. The experimental findings clearly showed that entire water molecules freely diffuse through the crystal lattice. Considering the cage-like structure of the hydrate this can happen only by taking into account conformational changes in the crystal lattice of β-CD molecules in order to open paths so that water molecules can escape from the cavity.

Heat capacity determinations [146] were effected by means of a discontinuous heating mode apparatus (adiabatic low-temperature apparatus) in the 13–300 K range on β-CD undecahydrate. A sharp heat capacity peak centered at 226 K was ascribed to a first-order phase transition, as already shown by preliminary DTA experiments [147]. Moreover, a glass transition behavior was observed around 150 K and correlated with the frozen-in disorder of two configurations of the hydrogen bonded system.

The occurrence of a first order phase transition beginning at about 200 K on β-CD undecahydrate was later confirmed by DSC and dielectric measurements [148]. The gradual reordering of protons starts at temperatures around 226 K and continues down to 150 K where the remaining disorders become frozen-in.

4.3. α-Cyclodextrin hydrates

α-Cyclodextrin is the smallest among natural CDs, being formed by 6 glucose units. Much less information concerning the interaction of α-CD with water and the relevant thermal analyses, when compared to β-CD, is available.

Three crystal forms of α-CD hydrates, with differing water/α-CD ratios, have been identified and described; in particular, two polymorphs of a hexahydrate [114,115] and a non-stoichiometric hydrate [149] with 7.57 water molecules per α-CD molecule.

The water content has been determined by isothermal dilatometry [150]. Solid α-CD has 6–6.7 mol of water per molecule. Conformational changes seem also to be involved in the water absorption mechanism at different degrees of hydration [151]. Recrystallization from water is reported to lead to a hexahydrate whose dehydration shows two distinct steps by TGA and is completed by 150°C [152]. According to other authors [117], DTA and TGA on α-CD samples recrystallized from water gave good evidence for the existence of a heptahydrate. The physicochemical characterization of anhydrous and hydrated (6 or 7.5 water mol per α-CD molecule) was carried out on the basis of X-ray diffraction and thermal properties [107]. Differences in the pattern of dehydration endotherms of two polymorphs of α-CD hexahydrate were found by DSC as well as through thermogravimetric and thermomechanical analyses [108].

Dehydration patterns of commercial α-CD hexahydrate have been recently investigated by conventional and high resolution (both dynamic and constant reaction rate) TGA [153]. Approximately four water molecules are lost during stages 2 and 3 of the overall process (stage 1 was attributed to surface water loss), while two water molecules are released over stage 4 and the following continuous mass loss. The resolution performed either by conventional TGA at low heating rates ($<1\ K\ min^{-1}$) or by high resolution thermogravimetry was related to differences in bond energy for interstitial and cavity water molecules.

4.4. γ-Cyclodextrin hydrates

When γ-CD is recrystallized from water and stored at 93.6% RH, crystals containing 17 molecules of water per molecule of γ-CD are obtained [154]. Thermogravimetric analyses have shown two distinct weight losses up to 150°C. An intermediate solid phase containing 7 water molecules per molecule of γ-CD was evidenced both during dehydration and rehydration. A hydrate with 8 water molecules per molecule was claimed in another paper [117] for samples of γ-CD recrystallized from water solutions. On heating, 7 water molecules are lost up to 130°C, while one molecule is lost at a much higher temperature (274°C).

Two major endothermic events have been associated [155] with the heating of γ-CD samples, namely, dehydration at 100°C and fusion/decomposition at 300°C. The relevant DSC traces, according to the authors, were identical to those of other CDs (Fig. 3).

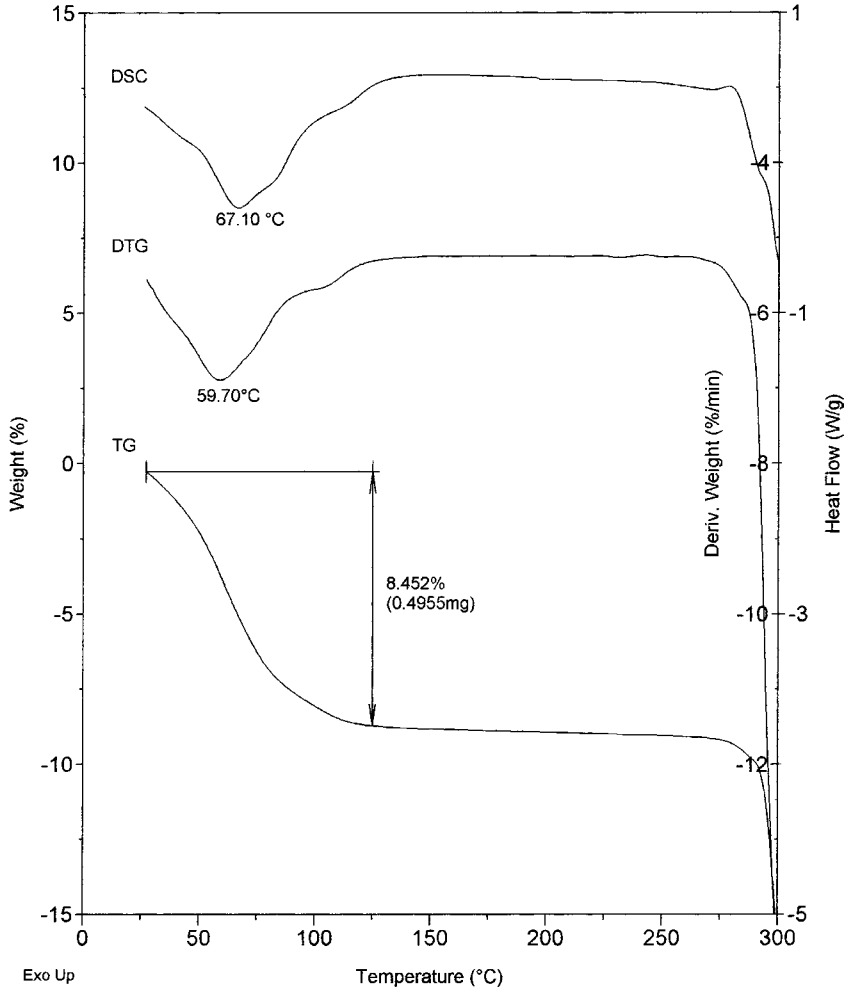

Fig. 3. Thermoanalytical profile of γ-CD.

5. Thermal characterization of inclusion compounds

In the preceding section, reports of the thermal properties and applications of thermal methods to the investigation of natural and semisynthetic CDs as single substances in the solid state were described.

This section will consider in some detail the thermal behavior and analyses of multicomponent systems containing CDs and particularly of their inclusion compounds.

As a preliminary consideration it should be pointed out that thermal methods (mainly DSC and/or TGA) represent a very popular and wide spread analytical approach to the characterization of multicomponent systems such as inclusion compounds in the solid state. This is well documented by the overwhelming number of citations that any database concerned with the topic of this review outputs when using keywords such as *inclusion compound* or *thermal analysis* (or DSC, TGA and so on).

A critical examination of such a large number of experimental data regarding the thermal properties of host–guest binary systems immediately prompts some considerations. Thermal analysis is commonly used as a routine method for a rapid preliminary qualitative investigation. In this case the approach is almost always the same: comparison of the thermal behavior

of single components, their physical mixture and the inclusion compound candidate prepared according to a variety of standard procedures (kneading, grinding, spray-drying, coprecipitation, etc.) (Fig. 4). The purpose consists of providing evidence that differences between the physical mixture and the putative inclusion compound exist. In the great majority of cases the relevant curves show the disappearance of the melting peak of the crystalline guest from the scans for a physical mixture with the CD when the same physical mixture is processed. Little or no speculation is dedicated to quantitative considerations. In some cases, moreover, the flattening of the DSC profile in the melting region of the crystalline guest is *tout–court* taken as conclusive evidence of inclusion compound formation. Generally, however, this information is more correctly reached after the joint use of thermal analyses with other analytical approaches, namely, phase-solubility analysis, spectral methods, and, where possible, single crystal structure determination.

5.1. Determination of the interaction stoichiometry by DSC

The drug–CD physical mixture generally shows an endothermic effect at a temperature corresponding to the melting point of the crystalline guest candidate. The interacted mixture generated by kneading, or

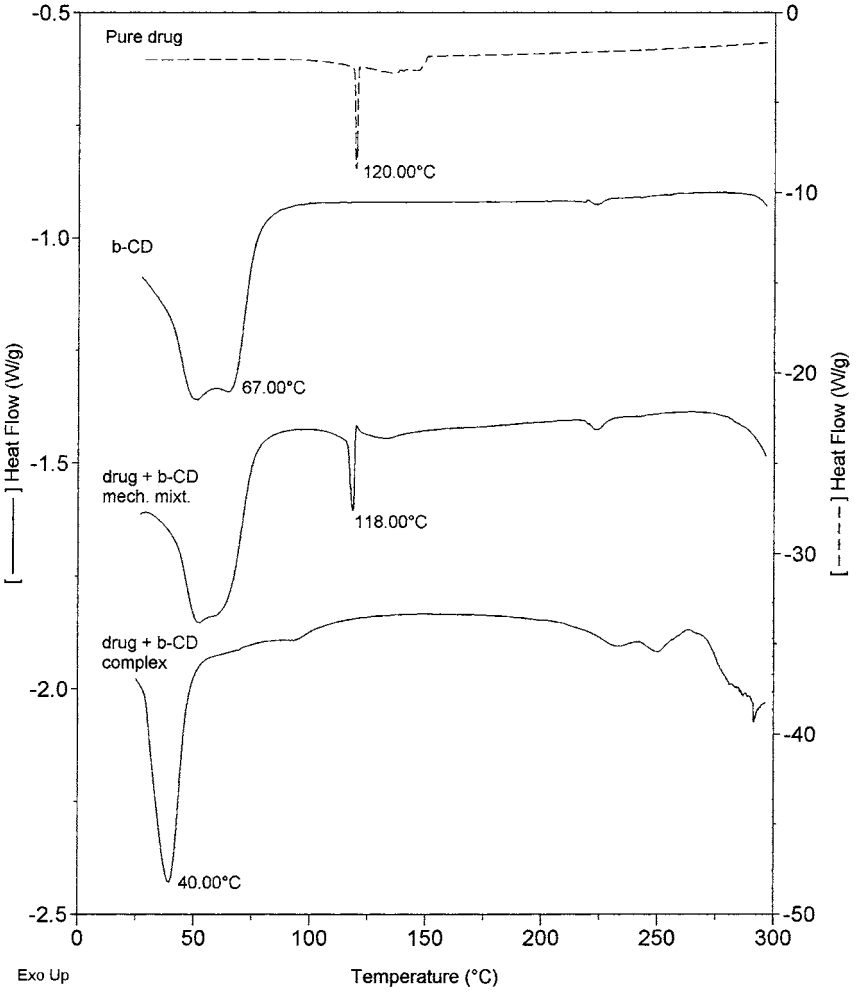

Fig. 4. Thermoanalytical profile of a drug–β-CD system. From top: pure components, mechanical mixture and inclusion compound.

other complexation procedures shows a flat profile in the same temperature region, provided the two components are in the stoichiometric ratio of interaction or an excess CD, the complexing agent, is present. When, on the other hand, excess crystalline drug is contained in the mixture after interaction, its enthalpy of fusion can be measured and, through simple calculations, exploited in order to assess the stoichiometry of the complex (vinburnine–γ-CD and paracetamol–β-CD [156]). Naproxen–β-CD [157] and 2,4-dichlorophenoxyacetic acid–β-CD [158] binary systems were also investigated by this method and the relevant stoichiometries of the complexes assessed.

5.2. Methods of preparation of drug/cyclodextrin inclusion compounds

Simple unit processes are used for the preparation of drug/CD inclusion compounds. Precipitation, kneading, spray- or freeze-drying are generally applied to solutions or suspensions of the components in suitable liquid phases. As an alternative, grinding of solid mixtures in special high energy mills is also claimed to give products with acceptable mechanical and biopharmaceutical properties. Depending on the adopted preparative procedure, the solid state properties both at a molecular and bulk level of the resulting phases reflect, in terms of crystallinity, particle size, residual solvent contents, etc. the preceding history of the sample, whether on a laboratory or industrial scale. In this respect, thermal methods are heavily employed in the assessment of solid phases aiming essentially to put into evidence significant differences between traces obtained scanning the untreated mixture (generally termed ''mechanical mixture'') and those from the interacted mixture (generally indicated ''inclusion compound'').

The following table collects information on the thermal properties of interaction and inclusion compounds with CDs. The majority of guest compounds can be found among substances of pharmaceutical interest (Tables 4 and 5).

Table 4
Keys to Table 5

Preparation methods	Host compounds	Methods of analysis
Alkaline solution (ALKS)	Alfa-cyclodextrin (ACD)	Circular dichroism (CD)
Aqueous solution (AS)	Beta-cyclodextrin (BCD)	Cross polarization magic angle spinning (CP/MAS)
Aqueous suspension (ASSP)	Carboxymethylcellulose (CMC)	Differential scanning calorimetry (DSC)
Co-evaporation (CE)	Diethylbetacyclodextrin (DEBCD)	Differential thermal analysis (DTA)
Co-lyophilization (CL)	Dimethylbetacyclodextrin (DIMEB)	Evolved gas analysis (EGA)
Co-melting (CM)	Ethylbetacyclodextrin (ETBCD)	Fluorimetry (FL)
Co-precipitation (CP)	Ethylcellulose (ETC)	Fourier transformed infrared spectroscopy (FTIR)
Evaporation (EV)	Gamma-cyclodextrin (GCD)	Gas chromatography (GC)
Freeze-drying (FD)	Hydroxyethylbetacyclodextrin (HEBCD)	High performance liquid chromatography (HPLC)
Grinding (GR)	Hydroxypropylbetacyclodextrin (HPBCD)	Hot stage microscopy (HSM)
Granulation (GRN)	Hydroxypropylmethylcellulose (HPMC)	Infrared spectroscopy (IR)
Kneading (KN)	Microcrystalline cellulose (MCC)	Isothermal titration (IT)
Mixing (MX)	Polyethylenglycol (PEG)	Mass spectrometry (MS)
Sealed container (SC)	Polyvinylpyrrolidone (PVP)	Nuclear magnetic resonance (NMR)
Spray-drying (SD)	Methylbetacyclodextrin (RAMEB)	Positron lifetime spectroscopy (PLS)
Solvent evaporation (SE)	Tetramethylbetacyclodextrin (TMBCD)	Phase-solubility (PS)
Sealed heating (SH)	Trimethylbetacyclodextrin (TRIMEB)	Raman spectroscopy (RMN)
Saturated solution (SS)		Solution calorimetry (SC)
Neutralization (NE)		Scanning electron microscopy (SEM)
		Thermal analysis (TA)
		Thermofractography (TFG)
		Thermogravimetry (TG)
		Thin layer chromatography (TLC)
		Titrimetry (TT)
		Ultraviolet–visible spectroscopy (UV–VIS)
		XRD diffractometry (XRD)

Table 5
Analysis of different inclusion compounds

Guest compounds	Host compounds	Preparation methods	Instrumental methods of analysis	References
Acetic acid, 4-diphenyl	BCD, HPBCD, DIMEB, TRIMEB		UV–VIS, ^{1}H NMR, XRD, DSC, IR, CD	[159–161]
Acetylsalicylic acid	BCD, DIMEB		XRD, UV–VIS, IR, TG, NMR, DSC, TA	[162–165]
Albendazole	ACD, BCD, GCD, DIMEB, HPBCD		DTA, XRD	[166]
Aldicarb	BCD	AS	UV–VIS, IR, ^{1}H NMR, ^{13}C NMR, DSC	[167]
Aminophenazone	BCD	CP	XRD, DTA	[168]
Amobarbital	DIMEB	CP	PS, UV–VIS, IR, DSC, XRD	[169]
Amphotericin B	GCD		XRD, TA, UV–VIS	[170]
Anethole	ACD, BCD		XRD, DTA, TG	[171]
Aniline, *p*-ethyl-	BCD		DTA, DSC, XRD	[147]
Aniline, *p*-iodo-	BCD		DTA, DSC, XRD	[147]
Aniline, *p*-nitro-	ACD	SC	XRD, IR, DSC	[172]
Anisaldehyde	BCD		TG, DSC	[173]
Antineoplaston A 10	BCD		IR, DTA, HSM	[174]
Atractylodin	BCD		DSC, XRD, GC–MS	[175]
Baicalin	BCD	CP	DTA, SEM	[176]
Beclomethasone, 17-monopropionate	BCD		TG	[177]
Beclomethasone, dipropionate	BCD, DIMEB, HPBCD		XRD, PS	[178]
Bencyclane, fumarate	ACD, BCD, GCD		DSC, XRD, TLC	[179]
Bendrofluazide	BCD		NMR, XRD, DSC	[180]
Bendroflumethiazide	BCD, HPBCD, HEBCD, DIMEB	FD	PS, XRD, DSC	[181,182]
Benzalconium chloride	ACD, HPBCD, GCD		DSC	[183]
Benzaldehyde	ACD, BCD, GCD		IR, XRD, TA	[184]
Benzene	BCD		TG	[163]
Benzene, 1,3,5-triphenyl-	TRIMEB	GR	DSC, XRD	[185]
Benzoate, 4-amino-butyl-	BCD, GCD	CP		[186]
Benzoate, 4-amino-propyl-	BCD, GCD	CP		[186]
Benzoic acid	TMBCD, DIMEB, BCD, ACD	SC, GR	XRD, IR, DSC, UV–VIS, ^{1}H NMR, TA	[162,164,172, 187–190]
Benzoic acid, *m*-hydroxy-	ACD	SC	XRD, IR, DSC	[172]
Benzoic acid, *p*-hydroxy-	ACD, TRIMEB	SC, GR, GR	XRD, IR, DSC	[172,185,191]
Benzoic acid, *p*-hydroxy-, esters	DIMEB, HPBCD, ACD, BCD	AS	DSC, IR, XRD, PS, TA	[189,192,193]
Benzoic acid, *p*-nitro-	TRIMEB	GR	DSC, XRD	[185,191]
Benzoxazolidinone, 6-benzoxyl-	BCD		XRD, TA, IR, NMR	[194]
Benzyl	BCD		TG, DTA, XRD, UV–VIS	[195]
Benzyl acetate	BCD		TG, DSC, XRD	[196]
Benzyl alcohol	BCD		TG	[197]
Berberine	BCD	CP	DTA, SEM	[176]
Beta-caryophillene	BCD		DTA, XRD	[198]
Biphenyl	BCD		TG, DSC, TG–DTA, XRD, NMR, IR	[199,200]
Biphenyl, 2,2′-dihydroxy-	BCD		TG–DTA, XRD, NMR, IR	[200]
Biphenyl, 4,4′-dihydroxy-	BCD		TG–DTA, XRD, NMR, IR	[200]
Biphenyl, *p*-hydroxy-	BCD		TG–DTA, XRD, NMR, IR	[200]
Bromazepam	ACD, BCD, GCD, DIMEB, TRIMEB	CP, AS, GR	XRD, IR, DSC	[201,202]
Budesonide	BCD, GCD	CP		[186]

Table 5 (*Continued*)

Guest compounds	Host compounds	Preparation methods	Instrumental methods of analysis	References
Bumetanide	ETC, HPMC, PVP, CD		DSC, XRD	[203]
Bupivacaine	BCD, DIMEB, HPBCD		IR, DSC, NMR	[204]
Butyrric acid, gamma-amino-	BCD	MX	DTA, XRD	[205]
C60	DIMEB, GCD	KN	XRD, DSC, UV–VIS, STM	[206,207]
Caffeine	BCD		TG, DTA, NMR, IR	[208]
Camphor	BCD		TA	[209]
Carbamazepine	ACD, BCD, GCD, HPBCD, PEG	CM, EV	XRD, DSC, IR, NMR, PS, UV–VIS, DTA	[210–215]
Carmofor	BCD, RAMEB	KN		[216]
Carvone	BCD		XRD, DSC	[217]
Cetostearyl alcohol	BCD	CP	DSC, XRD, IR	[218]
Cetostearyl sulphate	BCD	CP	DSC, XRD, IR	[218]
Chamomile oil	BCD, GCD		XRD, DSC, TG	[219]
Chenodeoxycholic acid	BCD		HSM, DSC, ^{1}H NMR	[220]
Chlorambucil	DIMEB		DSC, XRD, SEM, FTIR	[221,222]
Chloramphenicol	BCD		XRD, IR, DTA	[223]
Chloramphenicol palmitate	BCD		DSC, TG, XRD, IR	[224]
Chlorpropamide	ACD, BCD, TRIMEB		PS, IR, DSC, XRD	[225]
Cholesterol	BCD		XRD, TG, DSC, ^{13}C NMR	[226,227]
Cinnamate, ethyl-	ACD, BCD		TA	[228]
Cinnamic acid	ACD, BCD		XRD, TA	[229]
Cinnamic aldehyde	ACD, BCD		TA, TG, DSC, SEM	[228,230]
Cinnarizine	BCD		PS, XRD, DSC, ^{1}H NMR	[231]
Citronellol	ACD, BCD, GCD		TG, EGA	[232]
Citronellyl acetate	ACD, BCD, GCD		TG, EGA	[232]
Citrus reticulata	BCD	AS	TLC, DSC	[233]
Clobazam	ACD, BCD, GCD, DIMEB, TRIMEB	AS, SC	PS, IR, DSC, XRD	[234,235]
Clofibrate	ACD, BCD, GCD	SC, CP, KN, SC	XRD, DSC, UV–VIS, IR, TA	[236–238]
Cyclooctene	BCD		TG–DTA, GC	[239]
Cysteine	BCD			[240]
Cytochrome P 450	HPBCD, DIMEB		DSC	[241]
Danazol	HPBCD	SE, FD	DSC, XRD	[242]
Deoxycholic acid	ACD, HPBCD, GCD		DSC	[183]
Diaminostilbene dihydrochloride	ACD, BCD		NMR, CD	[243]
Diazepam	BCD, GCD	SD, CP	DSC, ^{1}H NMR	[186,244,245]
Diclofenac	BCD	AS	DSC, XRD, IR	[246,247]
Diclofenac, sodium	BCD	CP, PS, AS, ALKS, FD	XRD, TG, DSC, IR	[248–254]
Dihydropyridine	BCD, HPBCD		MS, NMR, DSC, XRD, TA	[255,256]
Dipalmitoyl-phosphatidylcholine	BCD		DSC	[257]
Dipyridyl, 4,4′-	BCD		TA, IR, XRD, TLC	[258]
Docosahexanoate, ethyl	ACD, BCD, GCD		TG	[178]
D-Oleate	ACD, BCD, GCD		XRD, DSC, GC	[259]
E 4031	ACD		XRD, DTA	[260]
Eicosapentanoate, ethyl	ACD, BCD, GCD		TG	[178]
Ethanol	BCD			[147]
Etheral oil	BCD		TG, DSC, EGD	[261]
Ethyl-*p*-aminobenzoate	BCD, GCD	CP		[186]
Eucalyptus oil	BCD		TA	[209]
Eudesmol, beta	BCD		DSC, XRD, GC–MS	[175]
Famotidine	BCD		IR, DSC, XRD	[262]

Table 5 (*Continued*)

Guest compounds	Host compounds	Preparation methods	Instrumental methods of analysis	References
Fatty acids	ACD, BCD, branched ACD and BCD			[263]
FCE 24304	BCD	KN, GR	DSC, IR, XRD, HPLC, HPLC	[264–266]
Feniramine, maleate	ACD, BCD, GCD		SC	[267]
Fentizac	BCD	CP, KN, SE, FD	XRD, DSC, IR	[268]
Feromones, olive fruit fly	BCD, TRIMEB		DSC, XRD, ^{1}H NMR	[269]
Ferrocene	BCD		DTA, TG	[270]
Flavofungin	GCD		XRD, TA, UV–VIS	[170]
Flubendazole	ACD, BCD, GCD, DIMEB, HPBCD		DTA, XRD	[166]
Flufenamic acid	Triacetyl-BCD, tri-ACD–BCD	KN	DSC, XRD	[271,272]
Flunitrazepam	TRIMEB	SC	DSC, IR, XRD	[235]
Flunitrazepam/acetone	DIMEB		XRD, DSC, IR	[273]
Flurbiprofen	ACD, BCD, GCD, DIMEB, TRIMEB		IR, DSC, XRD, UV–VIS, CD, ^{13}C NMR, TA	[246,274,275]
Flutamide	ACD, BCD		TLC, DSC, IR	[276]
FR 64171	BCD		DSC, XRD, SEM	[277]
Ganglioside	ACD		^{1}H NMR, ^{13}C NMR, DSC	[278]
Geraniol	ACD, BCD, GCD		TG, EGD	[232]
Geranyl acetate	ACD, BCD, GCD		TG, EGD	[232]
Glibenclamide	HPBCD, ACD, BCD, GCD	SA, KN, FD, SD	DSC, IR, XRD, NMR	[279–282]
Glibenclamide Na	BCD	SD	IR, DSC, XRD, ^{1}H NMR	[283]
Glibornuride	ACD, BCD, GCD	CP, FD	XRD, DSC	[284]
Gliclazide	BCD		IR, RMN, DSC, XRD, NMR, RMN	[102, 285–287]
Glipentide	ACD		DSC	[288]
Glisentide	ACD		DSC	[288]
Glutamic acid	BCD			[240]
Glutethimide	BCD, DIMEB		NMR, DSC, XRD, PS, IR	[289,290]
Glycerides, mono-, di-, tri-	ACD, BCD			[264]
Glycodeoxycholate	ACD, HPBCD, GCD		DSC	[183]
Griseofulvin	BCD, HPBCD		DSC, HSM, TG	[291]
Guaiene, alfa	BCD		DSC, XRD, GC–MS	[175]
Haloperidol	BCD polymer		DSC, NMR	[292]
Heptacaine	BCD		DSC	[293]
Hexamethylendiamine	BCD		DTA	[294]
Hexamethylmelamine	CD, PVP, PEG		TA, XRD, HSM	[295]
Histidine	BCD			[240]
Hop oil	BCD, GCD		XRD, DSC, TG	[219]
Hydrochlorothiazide	BCD, PEG	CM, solvent	IR, DSC, NMR, XRD	[180,296]
Hydrocortisone	BCD, HPBCD		XRD, IR, DSC, SEM, ^{1}H NMR, TG, TFG	[297,298]
Hydrocortisone butyrate	ACD, BCD, GCD, DIMEB		CD, UV–VIS, ^{1}H NMR, IR, TA	[299]
Ibuprofen	BCD, GCD, RAMEB, HEBCD, HPBCD	CP, MX	IR, HPLC, DSC, XRD, TG	[186,248, 300,301]
Ibuproxam	BCD		TG, HPLC, XRD, TA	[302,303]
Idebenone	BCD	CP, FD	DSC, XRD, UV–VIS, CD, ^{1}H NMR	[304]
Indomethacin	CMC, HPBCD, ACD, BCD, GCD	KN, FD, SD, CP, MS, TLC	DSC, XRD, IR, TM, ^{1}H NMR, PLS, TA	[305–316]
Indomethacin, sodium	HPBCD, BCD		DSC, NMR	[307,308]

Table 5 (*Continued*)

Guest compounds	Host compounds	Preparation methods	Instrumental methods of analysis	References
Insulin	ACD, BCD, RAMEB		DSC, ^{1}H NMR	[317–319]
Iodine	ACD	CP	UV–VIS, TT, DSC	[320]
Ipriflavone	BCD		DSC, EGA, TA	[321,322]
Iproniazide phosphate	ACD, BCD, GCD		SC	[267]
Isopyrin bitartrate	BCD	CP	XRD, DTA	[168]
Isosorbide, 5-mononitrate	BCD	SS., KN, GRN	DSC, XRD, HSM, NMR, HPLC, TA	[323–325]
Ketoconazole	ACD, BCD, DIMEB, HPBCD	FD, SE, KN, SD	PS, IR, DSC, XRD	[326–330]
Ketoprofen	ACD, BCD, GCD, DIMEB, RAMEB, HEBCD, HPBCD	FD, GR, ASSP	XRD, DSC, IR, ^{1}H NMR, UV–VIS, PS, ^{13}C NMR CP/MAS, TFG, PMR, DTA, TA	[164,232,301, 331–337]
Khellin	BCD, GCD, HPBCD		PS, UV–VIS, DSC, XRD, IR	[338]
Lemon oil	BCD, GCD		XRD, DSC, TG	[219]
Leucine	BCD			[240]
Lidocaine	BCD, DIMEB, HPBCD		IR, DSC, NMR	[162]
Limonene	BCD		XRD, DSC	[217]
Linalool	ACD, BCD		XRD, DTA, TG	[171]
Linoleic acid	BCD		TG	[178]
Lipoic acid, alpha-	ACD, BCD		UV–VIS, XRD, IR, DTA	[339]
Liposomes	HPBCD, DIMEB, TRIMEB		DSC	[340,341]
Loperamide hydrochloride	BCD		PS, XRD, IR, DSC, TG	[342]
Lorazepam	BCD, TRIMEB, HPBCD, HEBCD	FD	PS, DSC, IR, UV–VIS, XRD, DTA	[343,344]
Lysolecithin	BCD		IR, NMR, DSC	[345]
Lysophosphatidyl-choline	ACD, HPBCD, GCD		DSC	[183]
Lysozyme	ACD		DSC	[317]
Mandelic acid	ACD, BCD, GCD	ASSP, GR, KN	DSC, EGD, TG, XRD	[346,347]
Mandelic acid, benzyl ester	ACD, BCD, GCD	ASSP	TG, DSC, EGD	[346]
Mandelic acid, ethyl ester	ACD, BCD, GCD	ASSP	TG, DSC, EGD	[346]
Mandelic acid, isoamyl ester	ACD, BCD, GCD	ASSP	TG, DSC, EGD	[346]
Mandelic acid, methyl ester	ACD, BCD, GCD	ASSP	TG, DSC, EGD	[346]
Mebendazole	ACD, BCD, GCD, DIMEB, HPBCD		DTA, XRD	[166]
Meclofenamic acid, sodium	BCD		XRD, TG, DSC	[248]
Mefloquine hydrochloride	BCD		XRD, DSC, TG, IR, SEM, PS	[348]
Menadione	ACD, BCD, GCD		XRD, TG, DSC, EGD, CD, PMR, UV–VIS, CD, ^{1}H NMR, TA	[349–352]
Menthol	BCD	CP	TA, DSC, XRD, PLS	[209,313]
Menthol, L-	BCD, DIMEB		TA, XRD, TG, DSC	[248,353]
Metaprogerol	BCD		IR, TA, XRD	[354]
Metapyrilene hydrochloride	ACD, BCD, GCD		SC	[267]
Methanol	BCD			[147]
Methionine	BCD			[240]
Methoxybutropate	BCD, HPBCD	SD, GR, KN	HPLC, DSC, XRD	[355]
Methyl orange	BCD		DTA, IR, XRD	[356]
Methylcinnamate	ACD, BCD		TA	[228]
Methylparaben	ACD·H_2O, ACD, BCD	SC, GR	XRD, DSC, TA, UV–VIS, IR	[162,172,357]
Methylsalicylate	BCD		TG	[163]
Metronidazole benzoate	GCD	CP, KN	TA, IR, UV–VIS, XRD	[358]
Miconazole	BCD		DSC	[359]
Molsidomine	BCD, GCD	SD	HPLC, DSC, EGD, NIR, TA, IR, XRD	[360–363]

Table 5 (*Continued*)

Guest compounds	Host compounds	Preparation methods	Instrumental methods of analysis	References
Montmorillonite	ACD, DIMEB, HPBCD		IR, SEM, TA	[364]
Morpholinosydnonimine	BCD		NIR, DSC, EGA	[365]
m-Xylylenediamine	BCD		DTA	[294]
Mydeton hydrochloride	BCD		TA	[366]
Nalidixic acid	BCD		TLC, IR, DTA, XRD	[367]
Naphthalene	DIMEB, DIMEB, DIMEB	SC, SH	TG–DTA, TA, XRD, TA	[368–370]
Naphthylbenzene, 1,3,5-tri-alpha-	TRIMEB, TRIMEB	GR	DSC, XRD	[185,191]
Naproxen	TRIMEB, HEBCD, ACD, GCD, HPACD, HPBCD, HPGCD, RAMEB	CE, CL, CP, EV, GR, FD, SD, KN	XRD, TA, DSC, IR, NMR, UV–VIS, PS	[157, 371–380]
Negundo oil	BCD		DTA, XRD	[198]
Nerol	ACD, BCD, GCD		TG, EGD	[232]
Neryl acetate	ACD, BCD, GCD		TG, EGD	[232]
Nicardipine	ACD, GCD, RAMEB, HPBCD	KN, SH	IR, ^{13}C NMR, DSC, XRD	[255,381,382]
Nicardipine hydrochloride	BCD		HPLC, ^{1}H NMR, TA, XRD	[383]
Niclamide	ACD, BCD, GCD		SC	[267]
Nicotinic acid	ACD, BCD, GCD		SC	[267]
Nifedipine	BCD, HPBCD	KN	PS, XRD, DSC	[341,384,385]
Niflumic acid	ACD, BCD, GCD		SC	[267]
Nimesulide	BCD, GCD		DSC, ^{1}H NMR	[386,387]
Nimesulide, natrium	BCD	SD	DSC	[388]
Nimodipine	HPBCD		XRD, TA	[256]
Nitrazepam	DIMEB, TRIMEB, ACD, BCD, GCD		XRD, DSC	[389]
Nitroglycerin	DEBCD		DSC, IR	[390]
Neocloprost	ACD, BCD, GCD		^{13}C NMR, TA	[391]
Norcarane, 7,7-dibromo-	DIMEB		^{13}C NMR, IR, UV–VIS, TA	[392]
Norcarane, 7,7-dichloro-	DIMEB		^{13}C NMR, IR, UV–VIS, TA	[392]
Norfloxacin	BCD, HPBCD, PEG 60001	FD, NE	XRD, DSC, IR	[393–395]
Nystatin	GCD		XRD, DSC, IR, HPLC, TA, UV–VIS	[170,396]
Omeprazole	HPBCD, GCD	FD	UV–VIS, CD, IR, DSC, XRD, ^{1}H NMR	[397,398]
Orange oil	BCD, GCD		XRD, DSC, TG	[219]
Orthophen	BCD		TA, TLC	[314]
Oxazepam	HPBCD, GCD, BCD, DIMEB	KN, SD, AS	PS, DSC, XRD, SEM, UV–VIS, ^{1}H NMR	[399–402]
Oxodipine	BCD, HPBCD, PEG	KN, EV	IR, DSC, HSM	[403,404]
Paclitaxel	HPBCD, HEBCD, DIMEB		TA, IR, NMR, CD	[405]
Paracetamol	BCD, ACD, MCC	SD, GR	TA, XRD, DSC, IR, TLC, EM	[156,306, 406–413]
Perfume oils	BCD		DTA, GC	[414]
Phenacetin	BCD		TA	[413]
Phenol, *p*-nitro-			UV–VIS, ^{1}H NMR, XRD, IR, DSC	[164]
Phenolphthalein	TRIMEB	GR	XRD, DSC	[185,191]
Phenotiazine	BCD		NMR, DTA	[415]
Phenoxyacetic acid, 2,4-dichloro	BCD, DIMEB, ACD	CP, SD, KN	DSC, IR, XRD, SEM	[416–419]
Phenylalanine	BCD			[240]
Phenylbutazone	BCD	CP	XRD, DTA	[168]
Phenylpropionic acid	BCD		TA, IR, XRD	[420]

Table 5 (*Continued*)

Guest compounds	Host compounds	Preparation methods	Instrumental methods of analysis	References
Phenytoin	ACD, BCD, GCD, HPBCD		DSC, XRD, IR	[421]
Phosphatidylcholine, L-β-dipalmitoyl-	ACD, HPBCD, GCD		DSC	[183]
Phosphoglycerate kinase	ACD		DSC	[317]
Picotamide	ACD, BCD, GCD		XRD, TA	[422]
Pilocarpine	ACD, BCD, GCD		SEM, DTA, XRD, IR	[423]
Pinene, alfa	BCD		DSC, XRD, GC–MS	[175]
Piperidine, derivatives	BCD		DTA, TG	[424]
Piribedil	BCD, RAMEB, HPBCD		DSC, IR	[425]
Piromidic acid	DIMEB		PS, DSC, ^{1}H NMR	[426]
Piroxicam	ACD, BCD, GCD	SD, CP, FD	SC, XRD, IR, DSC, SEM, RMN	[246,267,306, 410,427–430]
Polyethylene glycol	BCD			[431,432]
Polyrotaxane	ACD		DSC, IR, XRD	[433]
Polyvinyl alcohol, coumarin	BCD		DSC	[434]
Polypropylene glycol	ACD, BCD, GCD	AS	IR, XRD, ^{1}H NMR, ^{13}C NMR, ^{13}C CP/MAS NMR	[435,436]
p-Quaterphenyl	TRIMEB	GR	DSC, XRD	[185]
Pralidoxime chloride	ACD, BCD, GCD		SC	[267]
Prednisolone	BCD, GCD, ACD	CP	UV–VIS, CD, ^{13}C NMR, XRD, TA	[186,437]
Progesterone	BCD, GCD, HPBCD	CP, FD	PS, DSC, XRD, TG, TA	[438–440]
Propanol, *n*-				[147]
Propantheline bromide	ACD, BCD, GCD, DIMEB, TRIMEB	AS	^{1}H NMR, UV–VIS, XRD, DSC	[441]
Propofol	HPBCD	KN	PS, IR, DSC	[442]
Propylparaben	BCD	GR	PS, IR, DSC	[443]
Propylphenazone	BCD	CP	XRD, DTA	[168]
Prostaglandin E1	GCD		XRD, TA	[444]
Prostaglandin F2-a	GCD		XRD, TA, ^{13}C NMR	[445]
Psoralen	BCD, DIMEB, TRIMEB		XRD, DTA	[446]
Psoralen, 5-methoxy	BCD		FL, CD, PS, DSC	[447]
Psoralen, 8-methoxy	BCD, DIMEB	SD, KN	FL, CD, PS, DSC, TA, IR	[447,448]
p-Terphenyl	TRIMEB	GR	DSC, XRD	[185]
p-Xylylenediamine	BCD		DTA	[294]
Pyridine, 1,4-dihydro-	BCD		PS, XRD, DSC, MS, ^{1}H NMR	[449]
Pyridine, derivatives	BCD		DTA, TG	[267]
Pyrilamine maleate	ACD, BCD, GCD		SC	[267]
Quercetin	BCD		DSC, IR, ^{1}H NMR	[450]
Quinine	BCD		TA	[209]
Retinoic acid	BCD	AS, CP	SEM, CD, DSC, XRD, SEM, DSC	[451,452]
Rhodium(II), alfa-methylcinnamate	BCD		XRD, RMN, IR, UV–VIS, TA	[453]
Riboflavin	BCD		DSC, ^{1}H NMR	[454]
Rnase A	ACD		DSC	[318]
RU-46364	HP–BCD		CD	[455]
Salbutamol	ACD, BCD, GCD, RAMEB, DEBCD, ETBCD	FD	DSC, MS, CD	[456–458]
Salicin	TRIMEB	GR, GR	DSC, XRD	[185,191]
Salicylic acid	BCD, ACD	SC	XRD, UV–VIS, IR, DSC, ^{1}H NMR, TA	[162,164,172]
Spironolactone	BCD, HPBCD, HEBCD, DIMEB, PVP	GR, CP, EV	PS, IR, DSC, NMR, XRD	[182,443,459, 460]

Table 5 (*Continued*)

Guest compounds	Host compounds	Preparation methods	Instrumental methods of analysis	References
Sucrose	TRIMEB	GR, GR	DSC, XRD	[185,191]
Sulfapyridine	ACD, BCD, GCD		SC	[267]
Sulphathiazole	BCD		XRD, TA	[461]
Sulprofos	BCD	AS	UV–VIS, IR, ^{1}H NMR, ^{13}C NMR, DSC	[167]
Tangerine essence oil	BCD		XRD, TA	[462]
Taxol	HPBCD, HEBCD, DIMEB		TA, IR, NMR, CD	[405]
Tenildiamine hydrochloride	ACD, BCD, GCD		SC	[267]
Tenoxicam	BCD	GR, FD	PS, UV–VIS, IR, DSC, XRD	[463]
Terfenadine	BCD	GR, KN	PS, IR, DSC, XRD	[443,464,465]
Terpineol	ACD, BCD, GCD		TG, EGD	[232]
Terpinyl acetate	ACD, BCD, GCD		TG, EGD	[232]
Theophylline	BCD	GR, FD	DSC, XRD	[466,467]
Thiamphenicol fatty acid esters	ACD		DTA	[468]
Thiopental	GCD		UV–VIS, TA, XRD	[469]
Tiamulin	ACD, BCD, GCD		UV–VIS, CD, TA, XRD	[470]
Tolbutamide	RAMEB, PEG 6000, HPBCD	KN, CP, CM, FD	PS, ^{1}H NMR, ^{13}C NMR, XRD, DSC, DTA, IR, TA, RMN	[471–476]
Tolperisone hydrochloride	BCD, GCD, DIMEB, RAMEB, HPBCD		TG, DSC, EGD, IR, XRD	[477]
Toluene	BCD	CP	DSC, XRD, PLS	[313]
Trans-sobrerol	BCD	AS, KN	TG, DSC, TA	[478,479]
Triamterene	BCD, HPBCD	KN, SD, GR	PS, DSC, IR, SEM, XRD, HSM, DTA, SEM	[480–483]
Tricarbonylmanganese, eta-5-cyclopentadienyl	BCD		^{1}H NMR, DSC, TLC	[484]
Tripolidine hydrochloride	ACD, BCD, GCD		SC	[267]
Tritcumex	BCD		IR, MS, DSC, HPLC	[485]
Tropicamide	ACD, BCD, GCD		SC	[267]
Tumeric oil	BCD		TLC, GD, DTA	[486]
Tungstate, sodium	BCD		TA, XRD	[363]
Tyrosine	BCD			[240]
Ubiquitin	ACD		DSC	[317]
Ursodeoxycholic acid	BCD, HPBCD		HSM, DSC, ^{1}H NMR, IR, ^{13}C NMR, XRD, TA	[220,487]
Vancomycin	ACD, BCD, GCD		IT, DSC	[488]
Vinburnine	GCD		DSC	[156,489]
Vitamin A	BCD		XRD, DSC, TAS, TA	[490,491]
Vitamin A, acetate	BCD		XRD, TA, TAS	[492]
Vitamin D2	BCD	SD, KN	HPLC, DSC, XRD, NMR, TA	[491,493]
Vitamin D3	BCD		XRD, TA, MS	[491,494]
Vitamin E	BCD		TA	[491]
Vitamin E, nicotinate	BCD		TA	[491]
Vitamin K1	BCD		TA	[491]
Vitamin K2	BCD		TA	[491]
Vitamin K3	BCD		TA	[491]
Warfarin	ACD, BCD	SD	PS, TLC, IR, DSC, XRD	[306,495]
Xylidine, 3,4-	BCD		DTA, DSC, XRD	[147]
Zeolite, calcium	HPBCD		TA	[496]
Zeolite, copper	HPBCD		TA	[496]

6. Conclusions

Cyclodextrins are very popular compounds which have attracted and still attract the interest of so many researchers from different fields. Industrial applications of such compounds are found mainly in pharmaceutical and food industry, but also applications in analytical and organic chemistry should be mentioned. Thermal methods have been used and are currently employed as powerful tools in the characterization of both CDs and their inclusion compounds. Generally speaking it ought to be underlined that the features of these methods of analysis are underestimated. Most authors are satisfied with a phenomenological qualitative description of DTA or DSC traces. It should be reminded that marketed calorimeters are nowadays very sophisticated instruments. Quantitative evaluations of enthalpies of fusion or heat capacities can afford highly valuable information.

Though the ultimate proof of a real inclusion compound formation is the crystal structure determination e.g. via single crystal (when available), thermal methods can provide fast and reliable assessment of possible interactions between host and guest and are used routinely for this purpose.

It is evident, moreover, that the large majority of studies and investigations has been concentrated on β-CD. Much work remains to be performed on the thermal properties of β-CD derivatives as well as α- and γ-CD.

Any review regarding topics with high worldwide interest in many industrial fields suffers a major drawback: once published it is surpassed. Nevertheless it may have various positive tasks to accomplish for researchers involved in the same area. It can be of some help for young researchers and allow them to get an updated perspective of the state-of-art and also for experienced scientists who collect literature records in a day-by-day fashion and may compare and complete their data.

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