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Competing Role of Water in Inclusion of Indomethacin and Volatile Organic Compounds by Native Cyclodextrins

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The hydration was found to reduce an efficiency of drug encapsulation by native cyclodextrins (CDs) when water is added above a certain threshold level. The hydration water competes with indomethacin for solid-phase inclusion in γ-cyclodextrin (γCD) and β-cyclodextrin (βCD) with an increase of water contents to the saturation level. No competing effect was observed for α-cyclodextrin (αCD) with this drug. The hydration effect for indomethacin correlates with the influence of hydration water on inclusion of volatile organic guests by native CDs. For these guests and γCD, the competing hydration effect was estimated also by determination of vapor sorption isotherms and was found higher than that for βCD but in most cases lower than such effect for αCD. The inclusion affinity and capacity of dried γCD for water and organic guests were determined and a significant size exclusion effect was observed, which contributes to the water-guest competition. The ratio between competing and activation roles of water for the studied three native cyclodextrins correlates with the parameters of their unit cells in hydrates and in dried state.

Keywords: Cyclodextrins, indomethacin, inclusion compound, encapsulation.

Конкурирующая роль воды при инкапсуляции индометацина и летучих «гостей» нативными циклодекстринами

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Гидратация снижает эффективность инкапсуляции лекарственных средств нативными циклодекстринами при добавлении воды выше определенного порогового уровня. В насыщенных гидратах γ-циклодекстрина и β-циклодекстрина гидратная вода конкурирует с индометацином при твердофазном включении в полость этих «хозяев». Подобный эффект гидратации в случае включения индометацина коррелирует с влиянием гидратной воды на включение летучих органических «гостей» нативными циклодекстринами. Для этих гостей конкурирующий эффект гидратации γ-циклодекстрина оценивался также по изотермам сорбции паров и оказался выше, чем у β-циклодекстрина, но в большинстве случаев ниже, чем у α-циклодекстрина. В работе было определено сродство сухого γ-циклодекстрина к воде и органическим гостям, и наблюдался значительный эффект исключения по размеру «гостя», который способствует конкуренции «вода-гость». Соотношение конкурирующей и активирующей роли воды для трех исследованных нативных циклодекстринов коррелирует с параметрами их элементарных ячеек в гидратах и в высушенном состоянии.

Ключевые слова: Циклодекстрины, индометацин, соединение включения, инкапсуляция.

Introduction

The activating role of water is a key feature of substrate binding by proteins and protein mimic polymers.[1-4] For crystalline receptors, hydration of which does not plasticize their matrix as in the case of cyclodextrins (CDs), a competing role of water in guest inclusion may be relevant.[5,6] For cyclodextrins, an important issue is the efficient preparation of inclusion compounds in a solid form, which is suitable for storage and further application.[7-9] For this, water is used to activate the guest inclusion being added in a liquid form for partial or complete dissolution of the mixed components or in the form of CD hydration.[10] Depending on the used preparation procedure the formation of solid inclusion compounds of cyclodextrins with the same or similar medical drugs may be more or less successive.[11-18] This reveals the problem of whether the inclusion efficiency is changed because the activation of this inclusion process by the added water is varied or also the competition occurs between water and guest for inclusion in crystalline matrix of CD. The study of this problem may help to rationalize the common techniques of drug inclusion by cyclodextrins.

The hydration effect on inclusion process by solid CDs is a kind of molecular recognition[19] being dependent on molecular structure both of guest and CD. For example, in guest inclusion by α-cyclodextrin (αCD), the competing role of water is dominant.[5,20] For β-cyclodextrin (βCD), the hydration activates the inclusion of volatile hydrophobic guests,[6,21] while needing optimization for guests with a moderate hydrophobicity.[6] For volatile guests, their inclusion affinity for solid hosts and related size-exclusion and hydration effects can be estimated by vapor sorption isotherms.[20,22,23] These isotherms give the information in thermodynamic activity scale, which is much easier for interpretation than the data on CD-guest complexation in water solutions available in concentration scale and requiring complicated theoretical models for their description.[1,24,25] To have a complete relationship between the inclusion capacity of native CDs and their macrocycle size, the hydration effect on inclusion of volatile organic compounds by crystalline γ-cyclodextrin (γCD) was studied in the present work. Besides, this work is a first study of hydration water competition in solid-phase inclusion of medical drug indomethacin (IMC) by native CDs.

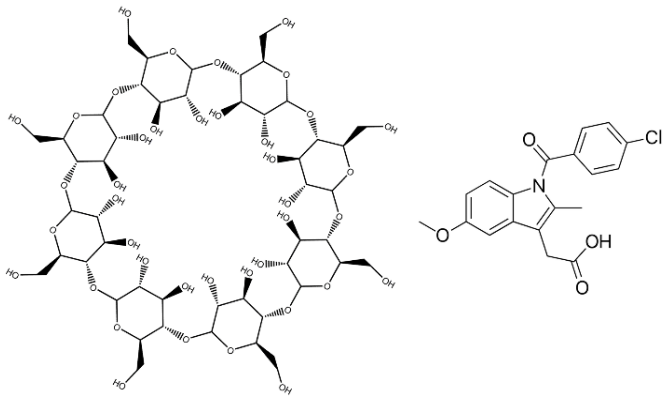

Figure 1. Structures of γ-cyclodextrin (left) and indomethacin (right).

Indomethacin (Figure 1) is a good model drug for studying the role of water in its inclusion with CD due to its high hydrophobicity and, accordingly, the need to increase its solubility by complexation with CD.[26] High thermal stability[27] of IMC and the ability of its amorphous form to crystallize upon heating[28] can be used to distinguish the encapsulated and free IMC after co-milling with CD.[11] In this work, the indomethacin inclusion was studied in the process of ball milling with native CDs having various hydration levels.

Experimental

Materials

α-Cyclodextrin (αCD), γ-cyclodextrin (γCD) and indomethacin (γ polymorph) were obtained commercially from Sigma-Aldrich with Cat. Nos. 28705, 779431 and I7378, respectively. β-Cyclodextrin (βCD) is from ICN, Cat. No. 190053. Organic guests were purified as described elsewhere[29] and additionally dried with 3 Å molecular sieves. The purity of guests checked by GC was at least 99.5%.

Sample preparation

Dried αCD, βCD and γCD were prepared by heating of sample for 3 h at 140 °C in vacuum (1 kPa). In dried CDs, the hydration level was less than 1% wt. according to thermogravimetry data. Intermediate hexahydrate γCD·6H_2O was prepared by heating saturated hydrate in oven at 40 °C for 20 min. Alternatively γCD·6H_2O was also prepared by saturation of dried γCD with vapor of saturated aqueous solution of K_2CO_3 having relative humidity of P/P_0 = 0.43.[30] Saturated CD hydrates were prepared by equilibration of dried CDs with a saturated water vapor (P/P_0 = 1) for 72 h.

Inclusion compounds of CDs with indomethacin were prepared by the ball milling method. For this, Narva DDR GM 9458 (30 W, 50 Hz) vibration ball mill was used, where equimolar mixtures of CD and indomethacin were shaken in 10 ml stainless steel jar with two stainless steel balls (4.06 g, 10.0 mm in diameter) for 4 h. To prevent an additional hydration from the air during the milling of indomethacin with dried CDs, the ball mill was put inside the sealed 10 L chamber with 200 g of molecular sieves 3Å. The milling increases the temperature of mixture to 42-45 °C.

For determination of the γCD inclusion capacity by thermal analysis and for the powder X-ray diffraction (PXRD) studies, the samples of dried γCD or its hydrates of 100–150 mg were equilibrated with guest vapors in sealed 15 mL vials for 72 h at 298 K. In these vials, an excess of liquid sorbate (100 μL) was placed in a separate open smaller vial and did not have any direct liquid-solid phase contact with the host powder. The solid-phase guest exchange was conducted by the same way with the initial inclusion compound prepared by equilibration of γCD hexahydrate with saturated vapor of dichloromethane and the next partial drying for 20 min at 120 °C in oven. The same saturation technique was used also to prepare samples for determination of vapor sorption isotherms of organic guests. For this, several samples of dried γCD or its hexahydrate of 100 mg were equilibrated with different amounts of liquid organic compound at 298 K as described elsewhere.[6]

For determination of the water sorption isotherm, the samples of dried γCD, 15–20 mg, were equilibrated for 120 h at 298 K with the vapors of saturated aqueous solutions of different compounds having a known water activity (humidity) a_w: CsF (a_w = 0.034), LiBr (0.064), $ZnBr_2$ (0.078), KOH (0.082), LiCl (0.11), $CaBr_2$ (0.17), $MgCl_2$ (0.33), NaI (0.38), K_2CO_3 (0.43), NaBr (0.58), NaCl (0.75), $(NH_4)_2SO_4$ (0.81), KCl (0.84).[30] Also, for a_w = 0.92, PEG-

400 aqueous solution was used as described earlier.[23] These solutions, together with the solid salts, were taken in a large excess, 250 μL of the total volume, so that only a small part of water was evaporated at equilibration with γCD sample. The prepared hydrates were analyzed using TG/DSC/MS analysis.

Static method of GC headspace analysis

Static method of GC headspace analysis (HSGC) was used for determination of vapor sorption isotherms in systems with organic guests as described elsewhere.[31] Using this method, a relative vapor pressure (thermodynamic activity), P/P_0, of organic guest in the studied systems was determined, where P is partial vapor pressure of guest and P_0 is its saturated vapor pressure. The guest uptake A (mol guest per 1 mol γCD) was determined as a difference between initial amount of guest added and its contents in vapor phase calculated from a value of P/P_0 and vapor volume. The error of P/P_0 determination is 5%. Guest uptake A was determined with an error of 5% but no less than 0.1 mol per 1 mol of γCD. Each isotherm was determined at least twice with fresh samples of γCD.

Gravimetry

Composition of saturated γCD hydrate was determined using analytical balance by weighting the hydrated sample of 100 mg before and after drying. Hydrated sample was dried for 3 h at 140 °C in vacuum (1 kPa) and then was cooled to room temperature at the same pressure before weighting.

FTIR spectroscopy

IR spectra were collected using Bruker Vertex 70 FTIR spectrometer, which was purged by dry air to remove atmospheric humidity. The interferograms were recorded with 64 scans and a resolution of 2 cm^{-1}. Spectra of solid samples were recorded using attenuated total reflection MIRacle accessory with germanium crystal (PIKE Tech.).

Thermal analysis

The device of simultaneous thermogravimetry and differential scanning calorimetry with mass-spectrometry of evolved vapors (TG/DSC/MS) Netzsch STA 449 C Jupiter with quadrupole mass-spectrometer QMS 403 C Aeolos was used to determine the composition of γCD inclusion compounds in TG/MS mode as described elsewhere.[32] This experiment was performed with heating rate of 10 K/min in argon flow of 75 mL/min. The samples in crucibles were purged with argon at room temperature until the constant weight, but no more than 15 min. For ternary clathrates with strongly overlapping MS peaks, an additional MS-calibration was used. For this, an equimolar liquid mixture of guests was sampled directly to the TG/DSC/MS device in the isothermal mode at 120 °C. A ratio of guest peaks in ion curves was used for the calculation of mass-spectrometer sensitivity for the studied guests. The contents of organic guests in inclusion compounds were estimated with an error of 0.1 mol per 1 mol γCD, and the hydration value was estimated with an error of 0.2 mol water per 1 mol γCD. The samples of indomethacin and its inclusion compounds with γCD were studied by TG/DSC method under the same conditions.

X-Ray powder diffraction

X-Ray powder diffractograms were obtained using Rigaku MiniFlex 600 diffractometer with a D/teX Ultra detector. Cu Kα radiation (30 kV, 10 mA) was used, Kβ radiation was attenuated with Ni filter. The experiments were made at room temperature in the reflection mode, at speed of 5°/min, without sample rotation. Samples were placed into a glass holder. Most of the diffractograms were determined also with addition of standard silicon powder SRM 640d, and corresponding corrections were applied to the patterns obtained.

Results and Discussion

Affinity of anhydrous γCD to water and organic guests in binary systems

The affinity of dried γCD for organic compounds was determined using the static method of gas chromatography headspace analysis. By this method, the vapor sorption isotherms on dried γCD were determined in binary systems "solid host + guest vapors" at 298 K. Methanol, ethanol, 1-propanol, acetone, acetonitrile, nitromethane, propionitrile, dichloromethane, chloroform, hexafluoro-2-propanol (HFIP), pyridine, benzene and toluene were studied as guests having various molecular size, hydrophobicity and functional groups. The isotherm of water vapor sorption on dried γCD was determined by TG/DSC method for host samples equilibrated at 298 K with vapors of aqueous solutions of salts having different water activity. The isotherms obtained are shown in Figure 2, while as dichloromethane, chloroform, benzene and toluene are not included by dried γCD. The isotherms were approximated using the equation describing the sorption of guest vapors by a solid host with a phase change:[33]

$$A = SC(P/P_0)^N/[1 + C(P/P_0)^N], \quad (1)$$

where A is the solid phase composition (mol guest per mol host), S — the stoichiometry of saturated clathrate, N – cooperativity parameter and C is the sorption constant. This equation is a variant of the more general mathematical expression used to describe cooperative processes in biological and other systems.[34] Isotherms with two inclusion steps were approximated by the sum of two equations (1), as described elsewhere.[35] The parameters of the sorption isotherms are presented in the Table 1. Table 1 also contains the inclusion Gibbs energy for 1 mol of a guest transferred from its pure liquid to a saturated inclusion compound:

$$\Delta G_c = RT \int_0^1 \ln\left(\frac{P}{P_0}\right) dY = -RT(\ln C)/N, \quad (2)$$

where $Y=A/S$ is an inclusion extent.[22] The driving force corresponding to such a gain in Gibbs energy is caused by filling of empty spaces in host crystal packing:[22] a guest may fill the molecular cavity of γCD if no significant change of crystal packing is observed or guest inclusion both in the molecular cavity and interstitial spaces may occur.

The determination of guest sorption isotherm by solid host is the only method for determination of inclusion and hydration Gibbs energies. For comparison, dehydration Gibbs energy may be determined by measurement of water vapor pressure over CD hydrate. For αCD, this method gives more negative value of Gibbs energy[36] than the value from hydration isotherm for this host[20] probably because of the hydration/dehydration hysteresis.

The isotherm of γCD hydration has a stepwise shape, which means the phase transition in hydration process (Figure 1a). This isotherm determined at 298 K has two steps, like the one obtained earlier at 313 K,[37] but in a full range of the water activity (humidity), $a_w = P/P_0$. In our experiment, the threshold of the first step in terms of water activity at Y=0.5 is approximately the same (P/P_0 = 0.1) as

at 313 K, but the threshold humidity of the second step is higher (0.8 *vs*. 0.6 in Ref. [37]). Such difference can be explained by a decrease of the hydration energy barrier at the higher temperature. The hydration isotherms of αCD and βCD obtained earlier are also stepped with one step for αCD and two for βCD.[20,23]

The inclusion capacity of γCD at the first and second steps, 6 and 13 moles of water per mole of γCD, respectively, is close to the literature data.[37] The intermediate hydrate γCD·6H_2O is stable in the range of water activity 0.2–0.6. Its composition roughly corresponds to the composition of the commercial γCD.[38] According to the values of hydration Gibbs energy, the first 6 water molecules included are of "low-energy" with $\Delta G_c = -5.3$ kJ/mol, and the next 13 molecules of hydration water are of "high-energy" with $\Delta G_c = -0.6$ kJ/mol (Table 1).

The sorption isotherms of organic guests on dried γCD, as well as the hydration isotherm, are stepwise in those cases where significant inclusion is observed (Figure 2). The sorption isotherms of ethanol, acetonitrile and acetone have two steps, and the methanol isotherm has even three steps but two of them have a low discrimination. For acetone, the sorption at the first step is insignificant. The presence of more than one inclusion step shows the formation of intermediate inclusion compounds. Only isotherm of nitromethane has one step (Figure 2f). Such guests as 1-propanol, propionitrile, dichloromethane, chloroform and benzene show insignificant uptake by anhydrous γCD. The increase in guest uptake at the guest activity above 0.86 for 1-propanol (Figure 2c) and above 0.8 for the other guests is mostly because of their capillary condensation on host surface. The data obtained show that dried γCD includes efficiently only small hydrophilic molecules.

The capacity of anhydrous γCD for the same organic guests and also HFIP and pyridine at their activity close to unity ($P/P_0 \approx 1$) was also determined by TG/MS method. The examples of corresponding curves of thermal analysis are shown in Figure 3. The parameters thus obtained are given in Table 2 including the guest content in the saturated inclusion compound S_{TG}. Saturated vapors of HFIP and pyridine partially dissolve the dried γCD and the solid amorphous solution is formed as it was observed also for αCD and βCD.[20,23]

For the most organic guests studied, TG/MS data show nearly the same inclusion capacity S_{TG} of dried γCD as found by the sorption isotherms except for acetonitrile and acetone, which S_{TG} values are much lower than the S data from sorption isotherms (Table 1). Such difference can be caused by the low stability of their inclusion compounds and partial guest elimination in the argon flow at room temperature in the initial stage of the TG/MS experiment.

The affinity of dried γCD for organic guests was estimated by the values of inclusion Gibbs energy ΔG_c. Such affinity decreases in an absolute value with increase in the guest size estimated by its molar refraction MR_D (Table 1), which is a good parameter of molecular size.[22,35] No inclusion observed for larger and more hydrophobic volatile guests what means that their inclusion Gibbs energy ΔG_c is positive preventing the formation of their inclusion compounds with dried γCD. The same trend occurs for inclusion capacity S of γCD. These relationships are the result of the size exclusion effect, which was observed also for αCD and βCD.[20,23] This effect for the inclusion capacity S of γCD and the other two native CDs[20,23] is shown in Figure 4. According to this graph, γCD has a stronger size exclusion effect than αCD and βCD.

The relationship between the observed size exclusion effect and changes in the crystal packing of γCD upon inclusion of various guests was studied by PXRD method. The determined diffractograms of dried γCD and its binary inclusion compounds with organic guests are shown in Figure 5. The observed diffraction patterns indicate that the smaller is the guest molecule, the greater is the packing change compared with that of dried γCD. Inclusion compounds with small hydrophilic guests — methanol, ethanol and acetonitrile — comprising more than 3 mol guest per mol γCD have the same unique crystal packing (Figure 5d-f), which differs from the packings of dried γCD (Figure 5a) and its hydrates (Figure 5g,h). For the larger guest nitromethane, which is included in significant amounts to form inclusion compound γCD·2$MeNO_2$, the packing (Figure 5c) is a mixture of the dried γCD packing and a packing of γCD clathrates with the smaller hydrophilic guests. The product of γCD saturation with acetone γCD·0.3$(CH_3)_2CO$ has a crystal packing (Figure 5b) close to that of dried γCD apparently because of a small included amount of acetone. Not included guests such as 1-propanol and propionitrile do not change the crystal packing of the anhydrous γCD.

Table 1. Parameters of sorption isotherms on anhydrous γCD.

Guest	S, mol/mol [a]	ΔG_c, kJ/mol [a]	N [b]	δ [c]	S_{TG}, [d] mol/mol	MR_D, [e] cm^3/mol
H_2O	19.6 (6.6, 13.0) [f]	–2.3 (–5.6; –0.6)	2.3; 10.3	0.014	18.7	3.72
MeOH	6.7 (2.0, 2.2, 2.5) [g]	–4.1 (–7.5; –4.4; –0.9)	2.3; 4.5; 20	0.009	6.3	8.24
EtOH	4.5 (3.3, 1.2) [g]	–2.8 (–3.3; –1.2)	6.3; 36	0.012	4.3	12.95
MeCN	4.4 (1.9, 2.5) [g]	–2.8 (–3.9; –1.9)	10.6; 2.5	0.09	3.2	11.06
$MeNO_2$	2.3 [g]	–2.7	4.8	0.023	2.0	12.61
Acetone	0.9 (0.2; 0.7)	–1.6 (–1.8; –1.5)	0.8; 8.6	0.013	0.3	16.17

[a] In brackets, ΔG_c and S values for separate inclusion steps are given;
[b] Parameters of separate inclusion steps;
[c] δ is a standard deviation calculated as given in Ref.[35];
[d] TG/MS data on guest contents in saturated inclusion compounds;
[e] the values of MR_D were calculated using the Lorenz-Lorentz equation $MR_D = (M/d)(n_D^2 - 1)/(n_D^2 + 2)$, in which M, d and n_D are the guest molar weight, density and refraction index at 20 °C, respectively;
[f] The sorption isotherm was measured by TG/MS data for samples prepared by saturating anhydrous γCD with water vapor with known activity;
[g] TG/MS data on guest contents in a saturated clathrate were used in the isotherm fitting.

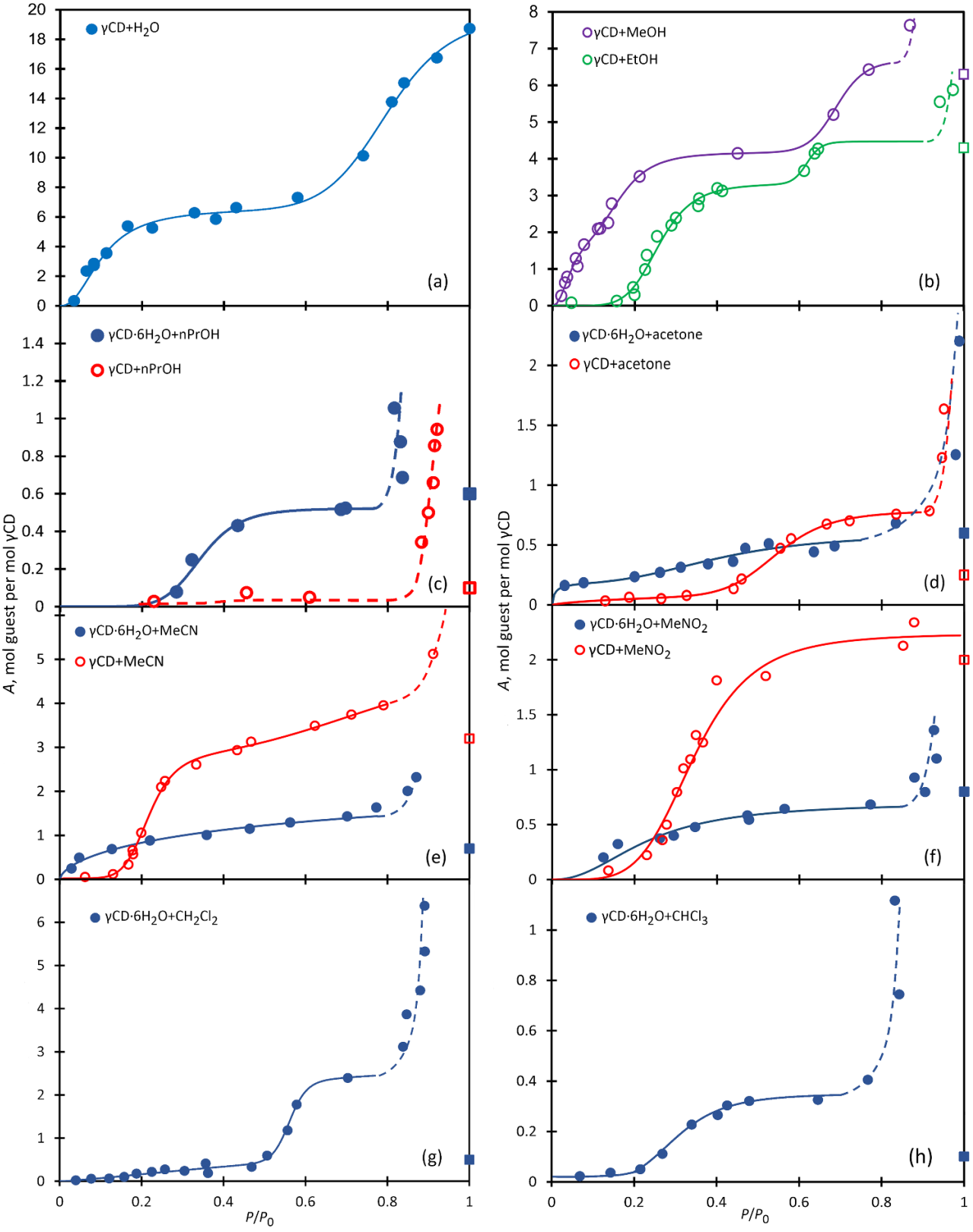

Figure 2. Sorption isotherms by initially anhydrous γCD and γCD·6H$_2$O at 298 K for vapors of: (a) water, (b) methanol and ethanol, (c) 1-propanol, (d) acetone, (e) acetonitrile, (f) nitromethane, (g) dichloromethane, (h) chloroform. The solid lines are the fitting curves calculated using the equation (1), the dashed lines are drawn by the guide of eye. Square points show the TG/MS data.

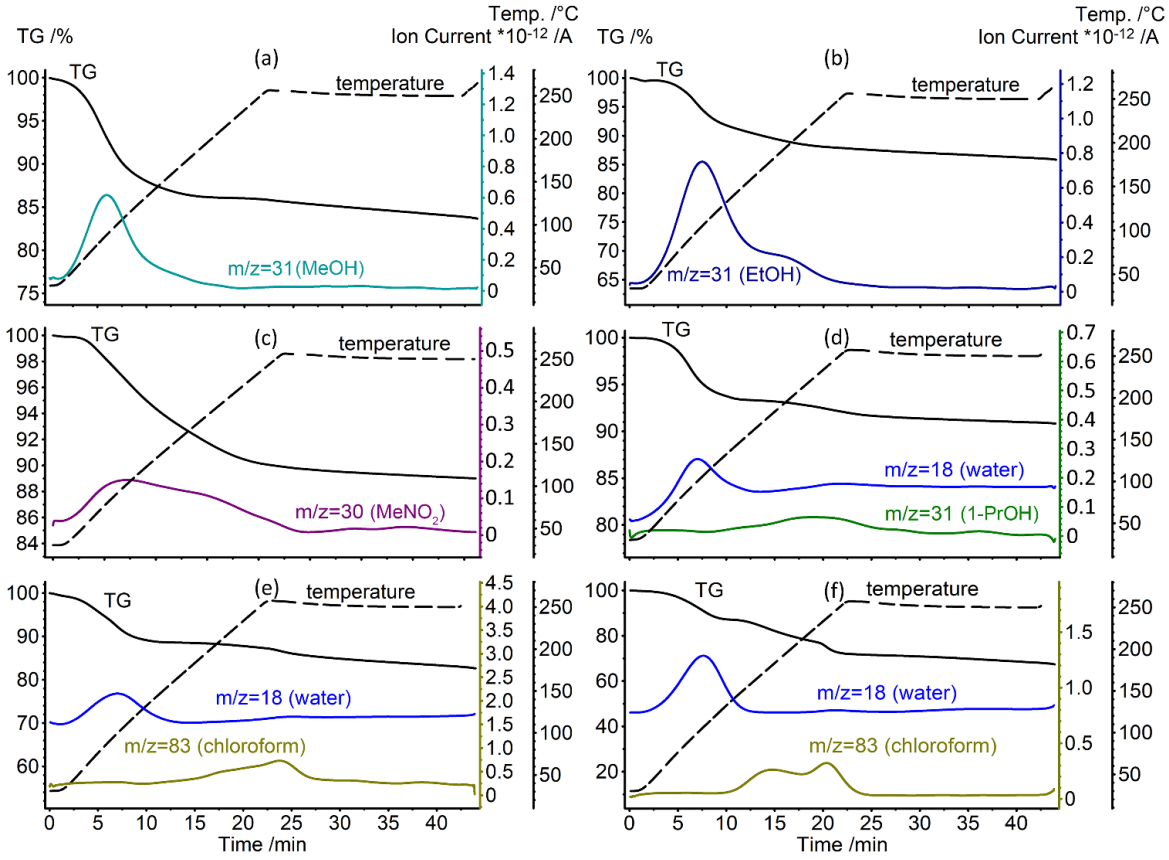

Figure 3. Curves of TG/MS analysis for clathrates (a) γCD·6.3MeOH, (b) γCD·4.3EtOH and (c) γCD·2$MeNO_2$ prepared from anhydrous γCD; (d) γCD·4.4H_2O·0.6(1-PrOH) prepared from γCD·6H_2O; (e) γCD·7.8H_2O·0.3$CHCl_3$ prepared from γCD·8H_2O; (f) γCD·10.2H_2O·2.3$CHCl_3$ prepared from γCD·19H_2O.

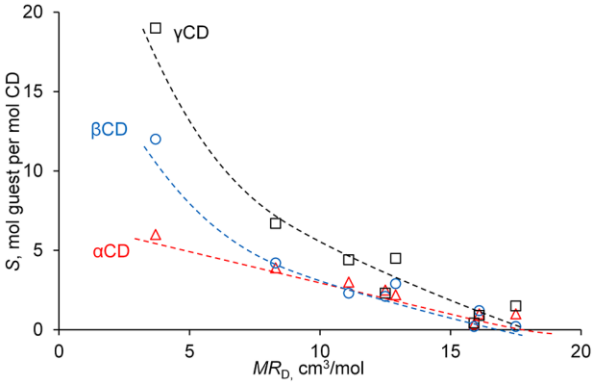

Figure 4. Size exclusion effect for native cyclodextrins: guest contents *S vs.* guest molar refraction MR_D in saturated binary clathrates with αCD,[20] βCD[23] and γCD.

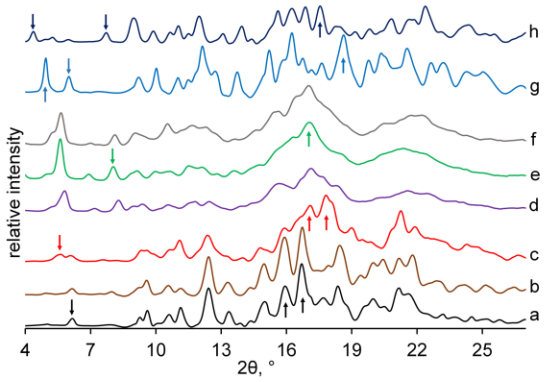

Figure 5. X-Ray powder diffractograms of (a) anhydrous γCD and its clathrates formed by equilibration of anhydrous γCD in binary systems with saturated vapors of: (b) acetone, (c) nitromethane, (d) methanol, (e) ethanol, (f) acetonitrile, and hydrates: (g) γCD·6H_2O, (h) γCD·19H_2O. Arrows indicate the characteristic peaks.

The effect of γCD hydration on its affinity and inclusion capacity for organic guests

The effect of γCD hydration on its inclusion properties was studied by comparing the inclusion affinity of anhydrous γCD and its intermediate hydrate γCD·6H_2O. Besides, the inclusion capacity of these γCD forms was compared with that of the saturated hydrate γCD·19H_2O. For intermediate hydrate γCD·6H_2O, vapor sorption isotherms of 1-propanol, acetone, acetonitrile, nitromethane, propionitrile, dichloromethane and chloroform were determined (Figure 2). Most of these guests have the smallest molecules not included or poorly included by dried γCD as shown above. Well-included acetonitrile and nitromethane were chosen to study the possible competing role of water.

Table 2. TG/MS data for inclusion compounds of γCD prepared by saturation of anhydrous γCD and its hydrates with vapors of organic guests, and by guest exchange

Guest	Inclusion compound [a]	Δ*m* /% [b]	T_{max} (guest) /°C [c]	T_{max} (water) /°C [c]
	Initial host: anhydrous γCD			
H_2O (P/P_0=0.43)	γCD·6.2H_2O	7.9	-	84
H_2O	γCD·18.7H_2O	20.6 d	-	-
MeOH	γCD·6.3MeOH	13.5	88	-
EtOH	γCD·4.3EtOH	13.1	97	-
MeCN	γCD·3.2MeCN	9.3	103	-
$MeNO_2$	γCD·2$MeNO_2$	6.4; 3.6	99; 177	-
$(CH_3)_2CO$	γCD·0.3$(CH_3)_2CO$	1.2	-	-
HFIP	γCD·1.1HFIP	12.2	113	-
Pyridine	γCD·3.7Pyridine	18.2	176, 208	-
	Initial hydrate: γCD·19H_2O			
1-PrOH	γCD·9.3H_2O·2.4(1-PrOH)	12.0; 7.4	150	90
$MeNO_2$	γCD·6.2H_2O·0.6MeNO2	8.1; 2.3	194	103
EtCN	γCD·6.3H_2O·0.6EtCN	7.9; 2.3	230	102
$(CH_3)_2CO$	γCD·5.2H_2O·0.7$(CH_3)_2CO$	7.5; 2.0	229	97
CH_2Cl_2	γCD·5.6H_2O·0.7CH2Cl_2	7.0; 4.0	193	89
$CHCl_3$	γCD·10.2H_2O·2.3$CHCl_3$	10.6; 15.8	232	97
	Initial hydrate: γCD·6H_2O (prepared from γCD·19H_2O)			
1-PrOH	γCD·4.4H_2O·0.6(1-PrOH)	6.6; 1.7	242	97
$MeNO_2$	γCD·4.8H_2O·0.8$MeNO_2$	7.2; 2.5	197	102
EtCN	γCD·5.8H_2O·0.6EtCN	7.3; 2.4	229	101
$(CH_3)_2CO$	γCD·5.0H_2O·0.6$(CH_3)_2CO$	7.0; 1.9	226	98
CH_2Cl_2	γCD·5.1H_2O·0.5CH_2Cl_2	6.5; 2.7	242	91
$CHCl_3$	γCD·5.0H_2O·0.1$CHCl_3$ [e]	6.5; 0.7	248	94
	Initial hydrate: γCD·6H_2O (prepared from anhydrous γCD)			
1-PrOH	γCD·5.2H_2O·0.4(1-PrOH)	6.7; 1.9	206	99
$MeNO_2$	γCD·4.6H_2O·0.9$MeNO_2$	7.0; 2.7	203	103
EtCN	γCD·5.4H_2O·0.6EtCN	6.9; 2.4	217	104
$(CH_3)_2CO$	γCD·5.1H_2O·0.6$(CH_3)_2CO$	6.5; 2.4	212	100
CH_2Cl_2	γCD·5.7H_2O·0.5CH_2Cl_2	7.2; 3.1	218	103
	Initial inclusion compound: γCD·0.7CH_2Cl_2 [f]			
1-PrOH	γCD·0.4CH_2Cl_2·0.8(1-PrOH)	2.3; 5.5	92	-
$MeNO_2$	γCD·1.7$MeNO_2$	9.5	119	-
EtCN	γCD·0.7CH_2Cl_2·0.2EtCN	1.9; 5.4	79	-
$(CH_3)_2CO$	γCD·0.2CH_2Cl_2·1.1$(CH_3)_2CO$	4.7; 3.2	109	-

[a] Composition is calculated from TG/MS curves where the organic guest content is less than 0.1 mol per mol γCD, if not shown and water content is less than 1 mol/mol, if not indicated;
[b] Mass loss in separate decomposition steps of inclusion compounds;
[c] T_{max} is a peak point of guest release in the corresponding MS curves;
[d] The values from gravimetric experiment;
[e] The product of γCD·8H_2O saturation with $CHCl_3$ vapor at P/P_0=1 has the composition of γCD·8H_2O·0.3$CHCl_3$;
[f] The initial γCD·0.7CH_2Cl_2 contains 1.9 mol water per mol γCD, and the guest exchange products contain 1.5 mol water per mol γCD.

The isotherms of vapor sorption on γCD·6H_2O indicate a significant decrease in the inclusion capacity of γCD upon hydration for the studied most hydrophilic guests at their high activity: up to 2.5 times for acetonitrile at P/P_0>0.2 and up to 3 times for nitromethane at P/P_0>0.25 (Figure 2e,f). For acetone, a slight decrease is observed at P/P_0>0.6 (Figure 2d). At the lower activities of these guests, the γCD hydration activates their inclusion. This intermediate hydration activates inclusion of larger and more hydrophobic 1-propanol, dichloromethane and chloroform without competition. The sorption isotherms of these three guests on γCD·6H_2O have a clearly defined inclusion

threshold by their activity, in contrast to the more hydrophilic compounds (Figure 2c,g-h). The hydration of γCD does not change significantly the inclusion of propionitrile.

To estimate the inclusion capacity of γCD·6H_2O and γCD·19H_2O for organic guests at their activity close to unity, these hydrates were equilibrated with the saturated vapors of the same organic guests, benzene and toluene. The compositions and parameters of thermal stability of the saturation products were determined by TG/MS method. The results are given in Table 2, and examples of TG/MS curves are shown in Figure 3.

The products of γCD·6H_2O saturation with organic guests have the same composition as determined in TG/MS experiment and from sorption isotherms (Table 2, Figure 2) in all cases except for acetonitrile and dichloromethane. Probably the inclusion compounds with these guests are unstable in air and lose guest partially at preliminary weighing in TG/MS experiment.

The TG/MS data help to compare the hydration effect on guest inclusion capacity for the intermediate γCD·6H_2O and saturated hydrate γCD·19H_2O. This change in hydration does not affect the inclusion of small hydrophilic guests (nitromethane, acetone and propionitrile) and increases the inclusion capacity for medium-sized hydrophobic dichloromethane and chloroform (Table 2). An essentially higher inclusion capacity of γCD·19H_2O is observed for 1-propanol and chloroform included to the level of 2.4 and 2.3 mol per mol of γCD, respectively. Hydration of γCD does not activate the inclusion of large hydrophobic guests (benzene, toluene), which does not occur at all hydration levels studied.

The observed hydration effect on inclusion properties of γCD was compared with the same of αCD[5] and βCD[6] in their intermediate and saturated hydrates. Only γCD and βCD show similar behaviour with chloroform, as well as γCD and αCD with benzene at all levels of hydration and guest activity. In the first case, almost the same activation of guest inclusion is observed, regardless of the water content and the chloroform activity. In the second case, benzene is not included at any degree of CD hydration. Intermediate hydrates αCD·4H_2O and γCD·6H_2O behave in a similar way with a number of guests: such hydration activates the inclusion of acetone, propionitrile and dichloromethane by both CDs. The hydration of αCD and γCD to the level of saturation reduces the inclusion of nitromethane. For both CDs, the activating role of water is changed to a competing one with an increase in the activity of acetone and propionitrile. In the other cases studied, hydration affects the inclusion properties of native CDs in different ways.

Unlike what was observed for tetrahydrates of αCD,[5] the hydration history does not affect the crystal packing and inclusion properties of intermediate hydrate γCD·6H_2O. Its inclusion capacity when prepared by different ways (hydration of dried γCD or dehydration of its saturated hydrate) is the same within the experimental errors, Table 2.

To explain the complex and various relationships between the activating and competing roles of water for guest inclusion by native CDs, the observed dependence of their crystal cell volumes per 1 glucose unit on the CD hydration degree, V_G, (Figure 6) can be considered. These data, Table 3, were calculated by the indexation of PXRD patterns of dried γCD and hydrate γCD·6H_2O determined in this work and of powder diffractograms of dried βCD published elsewhere.[20] In addition, the earlier determined cell parameters of the dried αCD,[5] and the single crystal X-ray data for hydrates of these native CDs were used,[39-42] Table 3.

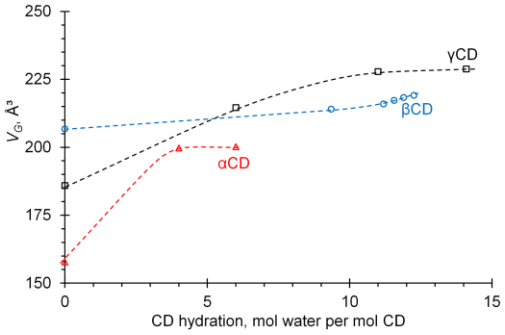

Figure 6. Dependence of crystal cell volume V_G per one glucose unit of native CDs on their hydration.

The observed hydration effect on V_G volumes of native CDs indicates that hydration of βCD only slightly increase its V_G value (Figure 6). So, the observed inclusion of relatively large hydrophobic guests by βCD hydrates[6] may be caused by tense packing of these hydrates and, respectively, with the presence of high-energy hydration water, what provides the guest inclusion without water exchange. This assumption correlates with the less negative Gibbs energies of βCD hydration[23] compared to those of αCD[20] and γCD (Table 1).

Table 3. Unit cell parameters of anhydrous natural CDs and their hydrates.

	Space group	*a*, Å	*b*, Å	*c*, Å	*β*, °	*V*, Å³	*Z*	V_{CD} [a], Å³	ΔV_G [b], Å³
anhydrous αCD [5]	P 2_1 2_1 2_1	14.135	36.030	7.437	90	3787	4	947	158
αCD·6H_2O [39]	P 2_1 2_1 2_1	14.856	33.991	9.517	90	4806	4	1201	200
anhydrous βCD	P 1 2 1	13.703	16.065	13.163	92.69	2894	2	1447	207
βCD·9.35H_2O [40]	P 1 2_1 1	20.857	10.158	15.141	110.94	2996	2	1498	214
βCD·12.26H_2O [40]	P 1 2_1 1	21.295	10.318	15.108	112.46	3068	2	1534	219
anhydrous γCD	P 1 2 1	11.784	17.731	28.519	93.16	5950	4	1488	186
γCD·6H_2O	P 1 2 1	17.213	18.714	21.648	100.06	6866	4	1717	215
γCD·11H_2O [41]	P 1 2_1 1	16.858	22.079	20.287	105.07	7291	4	1823	228
γCD·14.1H_2O [42]	P 1 2_1 1	16.847	11.098	20.271	104.97	3661	2	1831	229

[a] volume per CD molecule; [b] volume per glucose unit.

The hydration of αCD and γCD to the level of αCD·4H_2O and γCD·11H_2O hydrates, respectively, gives a significant increase of V_G value, Figure 6. For αCD, the corresponding increment of V_G per 1 water molecule is equal to 63 Å^3. This value is greater than the molecular volume of ice 32.6 Å^3 at 273.15 K, which does not depend much on temperature.[43] Such high increment may create free space for inclusion of hydrophobic guests if they are not too large. On the other hand, the ability of water to increase V_G can be due to its high affinity for these CDs, estimated from the hydration Gibbs energies of αCD[20] and γCD (Table 1). As a result, for αCD and γCD having a lower initial V_G in their anhydrous state than that of βCD, the inclusion of large hydrophobic guests by their hydrates may be hindered by the need to compete with relatively low-energy water. This results in the non-inclusion of hydrophobic guests like benzene by hydrates of γCD in this work and by αCD.[5]

Guest exchange in anhydrous inclusion compounds of γCD

The possibility to increase the inclusion capacity of γCD by the solid-phase guest exchange was also studied in this work. Dichloromethane was chosen as a "leaving guest" because it is not included by dried γCD having therefore a positive Gibbs energy of inclusion. Also, dichloromethane has a high volatility, which facilitates its removing from the clathrate upon guest exchange. The initial inclusion compound γCD·0.7CH_2Cl_2 for solid-phase guest exchange was prepared by the partial drying of γCD·5.6H_2O·0.7CH_2Cl_2. The dried γCD·0.7CH_2Cl_2 was equilibrated with saturated vapors of acetone, nitromethane, propionitrile and 1-propanol. The composition of the dehydrated γCD·0.7CH_2Cl_2 and the products of guest exchange were determined by TG/MS method (Table 2).

The data obtained on the composition of guest exchange products show that the use of dichloromethane as an activating component instead of water doubles the inclusion capacity of γCD for acetone and nitromethane in comparison with that of intermediate and saturated hydrates (Table 2). Activation with dichloromethane is also observed for 1-propanol and acetone compared to anhydrous γCD. For propionitrile and benzene, the activation with dichloromethane does not occur. The inclusion activation with dichloromethane is more effective for γCD than for αCD.[44] For comparison, strong activation of guest inclusion was found for βCD using another hydrophobic "leaving guest" — benzene.[6,23]

Competing role of water in solid-phase inclusion of indomethacin

For comparison of the hydration effect on inclusion capacity of native CDs for volatile compounds and solid guest, the inclusion of solid indomethacin (IMC) by dry native CDs and their hydrates was studied under ball milling conditions. For this, equimolar mixtures of indomethacin were ball milled with αCD, βCD and γCD of various hydration degrees. The initial states of γCD were the same as described above for volatile guests: dried γCD, intermediate γCD·6H_2O and saturated γCD·19H_2O hydrate. For αCD and βCD, their dried forms and saturated hydrates αCD·6H_2O and βCD·12H_2O were studied. The products of ball milling were characterized with TG/DSC, PXRD and FTIR spectroscopy methods. The results are shown in Figure 7 and Table 4. To estimate the inclusion degree of IMC, the initial pure γCD and IMC were also milled and studied, as well as their physical mixture.

Unincluded IMC in the ball milling products of βCD·12H_2O and γCD·19H_2O is detected by their FTIR spectra having the intensive peaks at 1690 and 1715 cm^{-1} which is observed for the physical mixture of ball milled γCD·6H_2O and crystalline indomethacin (Figure 7C). For the other ball milling products, these peaks are smaller by an order of magnitude.

DSC curves for the products of IMC ball milling with the dried native CDs and their hydrates show a complete inclusion of this drug by dried CDs, intermediate hydrate γCD·6H_2O and saturated hydrate αCD·6H_2O (Figure 7A, Table 4). The partial inclusion is observed for saturated hydrates γCD·19H_2O and βCD·12H_2O. Their ball milling products have DSC peaks with onset points T_m at 151 and 147 °C, which is close to the melting point of IMC α-polymorph.[45] So, the fraction of unincluded IMC can be estimated from the ratio of the fusion enthalpies ΔH_f of ball milled mixtures (Table 4) and of the pure α-polymorph of IMC, which is equal to ΔH_f = 92 J/g.[45] This ratio is 65% for the product from the mixture of IMC+γCD·19H_2O and 30% for the product from IMC+βCD·12H_2O. These values give the inclusion degree of IMC 35% and 70%, respectively. In the work of Salústio,[11] the ground mixture of IMC and βCD with 1.5–2 times more water added than in the saturated hydrate gives a significantly lower degree of IMC inclusion estimated by the same experimental methods.

PXRD analysis shows that the most products of IMC+CD mixtures milling are amorphous (Figure 7B). These patterns of amorphous products are close to that of amorphous α-, β- and γ-CD prepared by grinding[46] and spray drying.[47] The presence of crystalline material is observed for the products prepared from the mixtures of IMC with saturated hydrates γCD·19H_2O and βCD·12H_2O (Figure 7B, curves f,k). These milling products have PXRD patterns with narrow peaks at 2θ of 11.6°, 17.0°, 19.6°, 21.8° which correspond to γ-polymorph of IMC. Presumably, when the IMC is milled with CD hydrates having a large amount of water, it partially crystallizes into the γ-polymorph. The heating of these mixtures gives the α-polymorph, according to DSC data (Figure 7A). A similar crystallization of an amorphous IMC with the formation of α- or γ-polymorphs, depending on temperature and humidity, was described elsewhere.[48,49]

Ball milling of IMC with anhydrous γCD·0.7CH_2Cl_2 and γCD·4.3EtOH clathrates prepared as described above resulted in the same 100% IMC inclusion as for mixtures with anhydrous γCD and γCD·6H_2O, Table 4.

The low inclusion degree for indomethacin milled with γCD·19H_2O can be explained by the competing role of water. When milled with indomethacin, the hydration of γCD decreases from 19 to 8.2 mol water per mole of γCD. So, a large amount of free water released increases its activity in the system. Thus, water with high activity becomes a competitor with indomethacin for inclusion into γCD, which decreases the inclusion degree. The results for αCD

and βCD agree with this supposal. Despite the significantly higher affinity of αCD[20] for water compared to βCD,[23] it is more important that 1 mol βCD·12H_2O loses 5.4 mol of water at ball milling, while αCD·6H_2O loses only 1.5 mol (Table 4). Thus, the release of a large amount of water, which occurs at ball milling of the γCD·19H_2O and βCD·12H_2O hydrates, gives the significant competition of water with the IMC and decreases the IMC inclusion degree.

Table 4. Inclusion degree and thermal parameters for indomethacin (IMC) ball-milled in equimolar mixtures with dried native cyclodextrins and their hydrates.

Initial host	Inclusion product		
	Hydration, mol per mol CD	IMC inclusion degree	ΔH_f, J/g (T_m, °C) [a]
αCD [b]	2.4 [c]	100%	-
αCD·6H_2O	4.5	100%	-
βCD [b]	2.8 [c]	100%	-
βCD·12H_2O	6.6	70%	27.5 (147) [d]
γCD [b]	3.6 [c]	100%	-
γCD·6H_2O	5.9	100%	-
γCD·19H_2O	8.2	35%	59.6 (151) [d]
physical mixture of milled γCD and crystalline IMC		0%	103 (161) [d]

[a] Fusion enthalpy of unincluded IMC per gram of IMC in the mixture;
[b] Initial CD hydration is less than 1 mol/mol;
[c] The hydration increase is due to water sorption from the air at the sample transfer after the ball milling.
[d] Pure γ-polymorph of IMC has the melting point T_m = 160 °C, for α-polymorph T_m = 153 °C.[45]

A high inclusion degree of IMC by anhydrous amorphous CDs (Table 4) shows that this method requires much lower hydration for inclusion of large hydrophobic guests compared to crystalline CDs.[5,6,21] Such decrease of hydration threshold by host amorphization is similar to activation of guest inclusion by CDs with hydration,[5,6] Table 1–2, or water-mimic component.[23,44] Amorphous state of initial CD and its complex decreases the total number of phases and therefore increases the number of freedom degrees according to Gibbs phase rule. A similar effect was found for hydration of amorphous native CDs,[46] where instead of sigmoidal hydration isotherms with a threshold humidity for water sorption the linear hydration isotherms are observed.

Conclusions

The results of the present work give an intricate picture of competing and activating roles of water in solid-solid and vapor-solid inclusion of medical drug indomethacin and volatile organic compounds, respectively, by native cyclodextrins, which can be useful for the development of drug encapsulation technologies with these receptors of biological origin.

The specific feature of γCD, as well as of other native CDs, is a phase transition upon inclusion of water or volatile organic guests by a solid host in binary host-guest systems. This phase transition makes the hydration effect on inclusion properties of cyclodextrins hardly predictable giving a decrease or increase of inclusion threshold by guest thermodynamic activity. Thus, the CD hydration can activate or prevent the guest inclusion depending on the guest and host molecular structure.

In this work, a ratio between the competing and activating roles of water for three native CDs is compared with their hydration Gibbs energies and the structural features of their hydrates. In solid βCD, hydration does not increase the volume of crystalline cells, which correlates with the lower affinity of water for this CD. This may explain the observed ability of βCD hydrates to include hydrophobic molecules by the presence of relatively "high-energy" water, which energy should decrease upon guest inclusion. For αCD and γCD, their higher affinity for water estimated by hydration Gibbs energies allows hydration to increase the volume of crystal cells. As a result, the ratio between the activating and competing roles of water for these CDs becomes very specific and significantly depends on the guest structure. For γCD, this ratio is mostly shifted towards the competitive role compared to βCD and αCD.

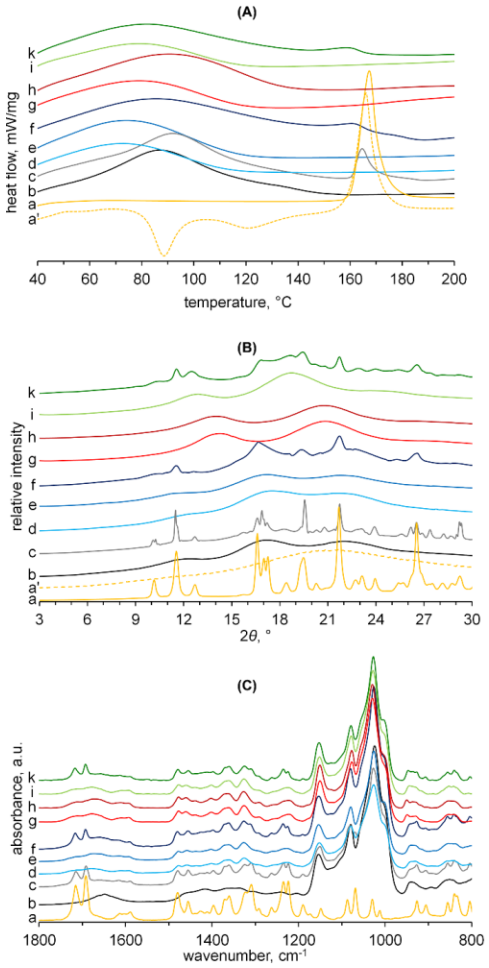

Figure 7. Data of (A) DSC, (B) PXRD and (C) FTIR spectroscopy for (a) crystalline and (a') amorphous indomethacin, (b) ball milled γCD·6H_2O, (c) equimolar physical mixture of ball milled γCD·6H_2O and crystalline indomethacin, and for products of indomethacin ball milling with (d) dried γCD, (e) γCD·6H_2O, (f) γCD·19H_2O, (g) dried αCD, (h) αCD·6H_2O, (i) dried βCD and (k) βCD·12H_2O.

The competing role of water in guest inclusion by cyclodextrin hydrates correlates with the size exclusion effect observed for dry γCD and other native CDs. This effect is caused with a limited space for guest inclusion in the CD crystalline matrix. Likewise, this limitation enables the observed solid-phase exchange of dichloromethane for other volatile organic guests in their inclusion compounds with γCD.

In the analysis of the observed water competition with a solid guest such as indomethacin for inclusion in native CDs, the additional factor – amorphization of components in the mixing procedure – should be taken in consideration. Its influence on the guest inclusion is the same as that of the third component forming a common three-component phase with the host and initial guest. Thus, amorphization of guest-CD mixture may decrease the amount of water needed for inclusion activation. The opposing effect is caused by partial CD dehydration through mechanical treatment of 'solid guest + CD hydrate' mixture observed for saturated γCD and βCD hydrates. This dehydration is a factor of water-guest competition.

The observed competing role of water indicates a lower efficiency of such methods of drug encapsulation as mixing with cyclodextrins in pastes and slurries when used in the presence of water added above a certain threshold level.

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