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CYCLODEXTRIN INCLUSION COMPLEXES OF THE ANTIHYPERLIPIDEMIC DRUG CLOFIBRIC ACID

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The products of the inclusion of clofibric acid, an antihyperlipidemic, in β-CD, γ-CD, heptakis(2,6-di-O-methyl)-β-CD (DIMEB) and heptakis(2,3,6-tri-O-methyl)-β-CD (TRIMEB), were investigated by thermal analysis and single crystal X-ray diffraction. All complexes have 1:1 host-guest stoichiometry and contain varying amounts of water of crystallization. Thermogravimetric and differential scanning calorimetric traces indicated dehydration as the first thermal event. The TRIMEB complex was the most stable in that it displayed a fusion endotherm while the other complexes decomposed on heating. Single crystal X-ray diffraction revealed that both the β- and γ-cyclodextrin complexes crystallize with the host molecules arranged in channel-mode (space groups C2 and $P42_12$ respectively), but extensive disorder of the guest molecules prevented their modelling. The DIMEB and TRIMEB complexes are orthorhombic (space group $P2_12_12_1$), the former crystallizing in a novel packing arrangement. The clofibric acid molecule is partially disordered when included in DIMEB and is oriented with the chlorine atom at the host primary rim and the carboxylic acid group at the secondary rim. In contrast, the guest is ordered in the TRIMEB complex and it assumes the opposite orientation. Furthermore, inclusion of the guest carboxylic acid group within the TRIMEB cavity is mediated by bridging water molecules.

Методами термального анализа и диффракции рентгеновскими лучами единичных кристаллов изучены продукты включения клофибрилловой кислоты-антигиперлипидемика, в β-ЦД, γ-ЦД, гептакис(2,6-ди-О-метил)-β-ЦД (ДИМЕБ) и гептакис(2,3,6-три-О-метил)-β-ЦД (ТРИМЕБ). Все комплексы имеют 1:1 "гость-хозяин" стехиометрию и содержат разные количества кристаллизационной воды. Термогравиметрические и дифференциально сканированные колориметрические следы указывают, что дегидратация является первым следствием термального воздействия. В этом плане самым стабильным был ТРИМЕБ комплекс, проявляя фузию эндотерм, в то времия как другие комплексы разрушались при нагревании. Методом диффракции рентгеновскими лучами единичных кристаллов выявлено, что как β-, так и γ - циклодекстриновые комплексы кристаллизуются с молекулами "хозяина", располагаясь в виде канала (пространственные группы C2 и $P42_12$ соответственно), однако их моделирование предотвращается выраженным беспорядком молекул "гостя". Комплексы ДИМЕБ и ТРИМЕБ являются орторомбическими (пространственная группа $P2_12_12_1$), предыдущий кристаллизуясь в новом упакованном порядке. Молекула клофибрилловой кислоты частично нарушается, когда включается в ДИМЕБ, и с атомом хлора ориентируется в первичном кольце "хозяина", а группой карбоксиловой кислоты в вторичном кольце. В противоположность этому, в ТРИМЕБ комплексе, "гость" определяет и принимает противоположеную ориентацию. Кроме того, включение группы карбоксиловой кислоты "гостя" в полость ТРИМЕБ опосредовано мостиками молекул воды.

Թերմալ անալիզի և եզակի բյուրեղների ռենտգենյան ճառագայթների դեֆրակցիայի մեթոդներով ուսումնասիրվել են կլոֆիբրիլաթթվի հակահիպերլիպիդեմիկի, ներառման նյութերը β-ՑԴ-ի, γ-ՑԴ-ի, հեպտակիս (2,6-դի-Օ-մեթիլ)-β-ՑԴ (ԴԻՄԵԲ)-ի և հեպտակիս (2,3,6-տրի-Օ-մեթիլ)-β-ՑԴ (ՏՐԻՄԵԲ)-ի մեջ : Բոլոր համալիրները ունեն 1:1 «տեր-հյուր» ստեխիոմետրիա և պարունակում են բյուրեղացած ջրի տարբեր քանակներ: Թերմոգրավիմետրիկ և դիֆերենցիալ սկանող կոլորիմետրիկ հետքերը ցույց են տալիս, որ դեհիդրատացիան համարվում է թերմալ

ազդեցության հետևանքը: Այս դեպքում ամենակայունը եղել է ՏՐԻՄԵԲ համալիրը, ցուցաբերելով էնդոթերմի ֆուգիա, այն դեպքում երբ մյուս համալիրները քայքայվել են տաքացնելիս: Եզակի բյուրեղների ռենտգենյան ճառագայթների դեֆրակցիայի մեթոդով բացահայտվել է, որ ինչպես β-, այնպես էլ γ-ցիկլոդեքստրինային համալիրները բյուրեղանում են «տիրոջ» մոլեկուլների հետ, տեղավորվելով նեղուցի տեսքով (համապատասխանաբար C2 և P 42₁2 տարածական խմբերը), իսկ նրանց մոդելավորումը կանխվում է «հյուրի» մոլեկուլների լայնատարած անկարգավորվածությամբ: ԴԻՄԵԲ և ՏՐԻՄԵԲ համալիրները օրթոռոմբաձև են ($P2_12_12_1$ տարածական խումբը), նախապես բյուրեղանալով նոր փաթեթավորված տեսքով: Կլոֆիբրիլաթթուն մասնակիորեն քայքայվում է, երբ ներառվում է ԴԻՄԵԲ-ի մեջ և բոլոր ատոմով կողմնորոշվում է «տիրոջ» առաջնային օղակի, իսկ կարբօքսիլաթթվի խմբով երկրորդային օղակի նկատմամբ: Հակառակ դեպքում, ՏՐԻՄԵԲ համալիրում, «հյուրն» է որոշում և ընդունում է հակառակ կողմնորոշում: Բացի այդ «հյուրի» կարբօքսիլաթթվի խմբի ներառումը ՏՐԻՄԵԲ-ի խոռոչի մեջ կատարվում է ջրի մոլեկուլների կամրջակների միջոցով:

Introduction

The manifold advantages of inclusion of poorly soluble drug molecules in cyclodextrins (CDs) is well documented [1,2]. Our studies in this area have focused on the preparation of crystalline CD-drug complexes and their physicochemical characterization by thermal and X-ray diffraction methods. Together, these techniques provide unequivocal proof of the authenticity of CD inclusion complexes and yield detailed information on the mode of drug inclusion in the CD cavity [3]. Representative drugs whose CD complexes have been characterised in this laboratory include ibuprofen [4], naproxen [5], diclofenac sodium [6], acetaminophen [7] and (L)-menthol [8].

Here we report results obtained by thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), UV and infrared spectroscopy, and single crystal X-ray diffraction for the inclusion complexes of the antihyperlipidemic clofibric acid with β-CD, γ-CD, heptakis(2,6-di-O-methyl)-β-CD (DIMEB) and heptakis(2,3,6-tri-O-methyl)-β-CD (TRIMEB). The guest clofibric acid [2-(4-chlorophenoxy)-2-methyl propionic acid], shown in Figure 1, is known to reduce triglyceride and cholesterol concentration in the serum [9]. It is poorly soluble in aqueous media, rendering it a good candidate for solubilization by CDs. The selection of clofibric acid as a target for CD inclusion was also prompted by the fact that it is the active metabolite resulting from *in vivo* hydrolysis of its ethyl ester, clofibrate, for which studies of CD-inclusion have already been reported [10,11].

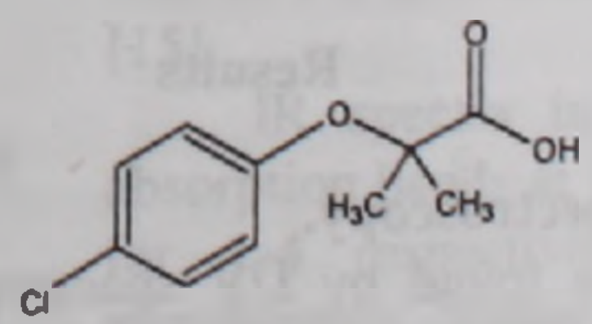

Figure 1. Chemical structure of clofibric acid.

A novel feature of the present study is the X-ray structural elucidation of four distinct crystalline CD complexes of the same drug molecule, revealing a variety of modes of inclusion ranging over extensive guest disorder in β-CD and γ-CD, partial order in DIMEB

and an ordered arrangement in TRIMEB. In the latter case, water molecules are shown to play a definitive role in the inclusion process.

Materials and Methods

Clofibric acid was purchased from Sigma Chemical Co. (Missouri, USA). The cyclodextrin host compounds β-CD, γ-CD, DIMEB and TRIMEB were supplied by Cyclolab (Budapest , Hungary).

The complexes of clofibric acid with β-CD and γ-CD were prepared by addition of the solid guest to hot saturated aqueous solutions of the CDs (host-guest ratio 1:1) with stirring for 12h at 65°C. Slow evaporation of filtered solutions yielded the crystalline complexes. Complexes with the methylated CDs were prepared by addition of clofibric acid to saturated aqueous solutions of the CDs (host-guest ratio 1:1) at 20°C, followed by incubation of the solutions at 50°C.

Thermal analysis was performed on a Perkin Elmer PC7 Series system with sample masses in the range 3-5 mg and a heating rate of 10°Cmin^{-1} under a nitrogen gas purge of flow rate 30cm^3 min^{-1}. For TGA, samples were placed in open aluminium pans while vented pans were used for DSC runs.

Complex stoichiometries were ascertained from a combination of TGA (yielding the water content) and UV spectrophotometry (host-guest ratio). For the latter, absorbance measurements were recorded on a Philips PU8700 UV/vis spectrophotometer in the range 200-400nm.

IR spectra were recorded on a Perkin Elmer 983 IR spectrometer with samples in the form of Nujol mulls.

To confirm phase transitions on heating, powder X-ray diffraction (PXRD) traces of the methylated CD complexes at different stages of heating were recorded photographically with samples in capillary tubes. The specimens were irradiated with Ni-filtered CuKα-radiation (λ = 1.5418Å).

Single crystals were examined for diffraction quality by X-ray photographic methods which also yielded unit cell and space group data. Intensity measurements were performed on a Nonius Kappa CCD diffractometer at 293(2)K with graphite-monochromated MoKα-radiation (λ = 0.71069Å) using a combination of φ- and ω-scans (0.5° for the DIMEB complex and 1° for each of the others). Detector to crystal distances were in the range 45-50mm and exposure times in the range 160-243s. Data-reduction was carried out with the program DENZO-SMN [12]. The structures of the β-CD, γ-CD and TRIMEB complexes were solved by isomorphous replacement using atomic coordinates of the rigid fragments of CD hosts from previous structure determinations [6,8]. The structure of the DIMEB complex was solved by the Patterson search method using program PATSEE [13]. Guest and water molecules were located from difference electron density maps. Full-matrix least-squares refinements based on F^2 with program SHELXL-93 [14] included mixed modes of isotropic and anisotropic thermal treatment and inclusion of H atoms in idealized positions. Least-squares weights of the form $w = 1/[\sigma^2(F_o)^2 + (aP)^2 + bP]$ were employed, with $P = [\max(F_o^2, 0) + 2F_c^2]/3$.

Results

Thermal analysis and spectroscopy.

All four complexes were found by UV spectrophotometry to have 1:1 host-guest stoichiometry. In Table 1, TG-DSC data are listed for the complexes whose compositions are as follows:

1 (host β-CD): $C_{42}H_{70}O_{35}\cdot C_{10}H_{11}O_3Cl\cdot 8.4H_2O$,
2 (host γ-CD): $C_{48}H_{80}O_{40}\cdot C_{10}H_{11}O_3Cl\cdot 15.5H_2O$,
3 (host DIMEB): $C_{56}H_{98}O_{35}\cdot C_{10}H_{11}O_3Cl\cdot 5.4H_2O$,
4 (host TRIMEB): $C_{63}H_{112}O_{35}\cdot C_{10}H_{11}O_3Cl\cdot 1.4H_2O$.

Table 1. TG-DSC data for the CD inclusion complexes of clofibric acid.

Complex	Event (DSC)	Onset (t/°C)	Peak (t/°C)	% H_2O (TGA)
1	Endo A	48	66	10.1
	Endo B	104	110	
	Exo C	302	309	
2	Endo A	50	75	15.6
	Exo B	301	309	
3	Endo A	54	76	5.9
	Endo B	149	151	
	Endo C	201	207	
4	Endo A	30	45	1.5
	Endo B	129	132	
	Endo C	145	147	

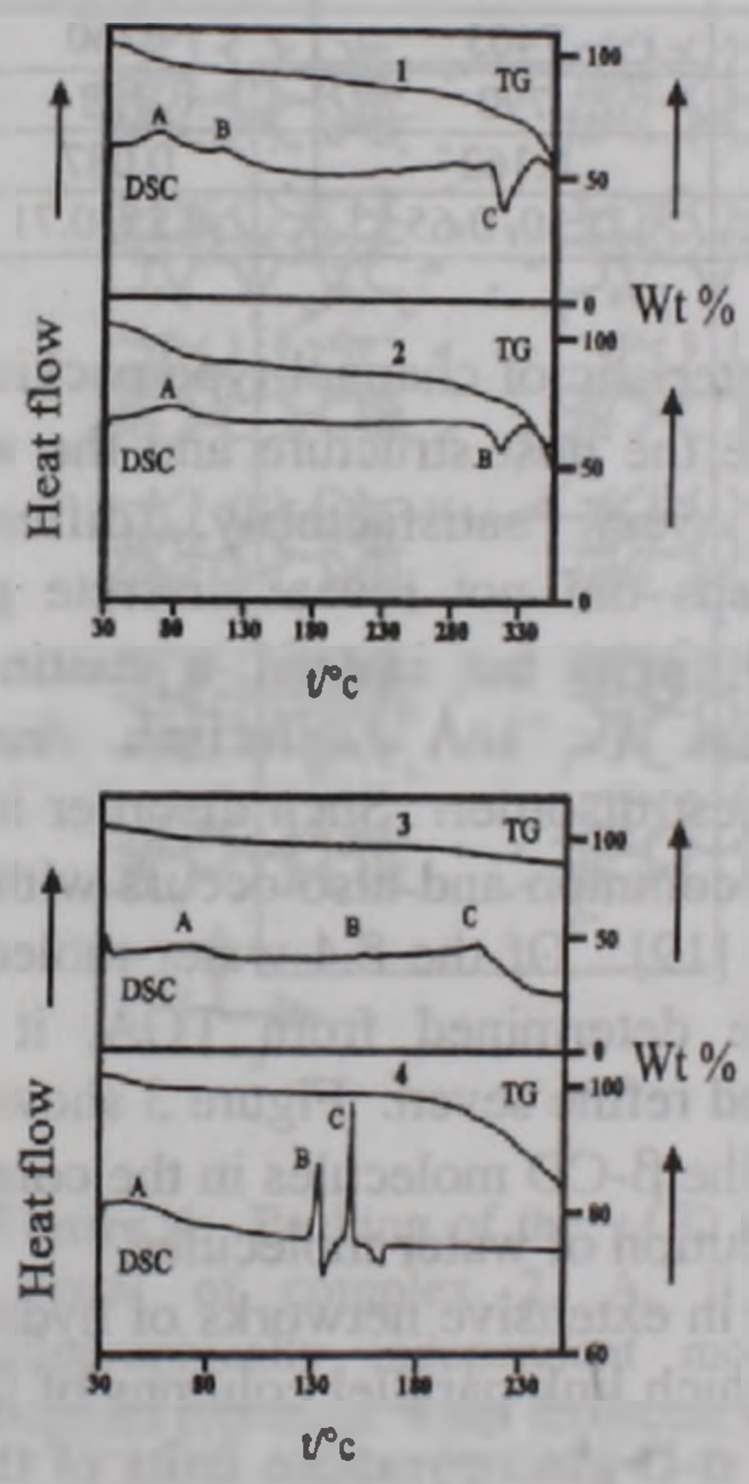

Figure 2. TG and DSC traces for CD complexes of clofibric acid.

Figure 2 shows the combined TG/DSC traces for the complexes. Those for complexes **1**, **2** and **4** were discussed elsewhere recently with an emphasis on dehydration aspects [15] and only a brief summary is therefore given here. For completeness, the traces for complex **3** are included in this report. Dehydration is a two-step process for the β-CD complex (endo A, endo B, Table 1) and one-step for the other complexes. The TG traces for **1** and **2** indicate gradual weight loss after dehydration and major decomposition (exothermic from DSC) following at around 300°C. In contrast, complexes of the methylated CDs, **3** and **4**, are thermally more stable, as indicated by the relatively small weight loss in TG following dehydration (endo A). Complex **3** undergoes a phase transition (endo B) followed by decomposition (endo C). The TRIMEB complex undergoes an endothermic phase transition (endo B) followed by exothermic recrystallization, and finally melting (endo C). The presence of a fusion endotherm with zero weight loss in TG is characteristic of TRIMEB complexes [15].

IR spectra in the carbonyl region yielded absorption bands at 1730, 1729, 1734 and 1726cm^{-1} for **1**-**4** respectively. These frequencies are significantly higher than the value of 1706cm^{-1} reported for pure clofibric acid, indicating stronger C=O bonds in the complexed materials. The magnitudes of the shifts in ν_{CO} are similar to those reported by Wei *et al.* for CD-tolbutamide complexes [16].

Single crystal X-ray analyses.

Crystallographic data for the complexes and details of structure refinements are listed in Table 2.

Table 2. Crystal Data and Structural Refinement Details for CD complexes of Clofibric Acid.

Parameter	Complex 1	Complex 2	Complex 3	Complex 4
Host	β-CD	γ-CD	DIMEB	TRIMEB
Complex M/gmol^{-1}	1501.0	1791.0	1643.3	1669.4
Crystal system	Monoclinic	Tetragonal	Orthorhombic	Orthorhombic
Space group	C2	$P4_12$	$P2_12_12_1$	$P2_12_12_1$
a/Å	18.818(6)	23.647(9)	10.783(5)	11.601(3)
b/Å	24.476(8)	23.647(9)	15.338(6)	26.284(7)
c/Å	15.761(5)	23.064(9)	49.39(1)	28.882(6)
α/°	90	90	90	90
β/°	110.43(1)	90	90	90
γ/°	90	90	90	90
V/ Å^3	6803	12897	8167	8807
Z	4	6	4	4
Crystal size/mm	0.2 x 0.3 x 0.3	0.3 x 0.4 x 0.3	0.3 x 0.4 x 0.3	0.2 x 0.3 x 0.3
Refinement data	12828	11207	7492	41775
Unique data	12631	10960	7477	21770
Data with $I>2\sigma(I)$	9347	6590	7463	6760
L.S. parameters	546	634	790	758
R (on F)	0.121	0.101	0.162	0.087
Δρ min, max. /e Å^{-3}	-0.52, 1.05	-0.58, 0.64	-1.30, 0.65	-0.85, 0.71

The unit cell and space group data for **1** are characteristic of channel-type packing of dimeric units in β-CD complex crystals [17,18]. While the host structure and the water molecules refined very satisfactorily, difference electron density maps did not reveal discrete guest atoms in the β-CD cavity but instead, a continuous distribution of weak (< 1eÅ^{-3}) electron density, indicating severe guest disorder. Such disorder in the channel of β-CD is common and also occurs with e.g. the guest ibuprofen [19]. Of the 8.4 water molecules per β-CD molecule determined from TGA, it was possible to locate and refine seven. Figure 3 shows the channel packing of the β-CD molecules in the complex as well as the distribution of water molecules.

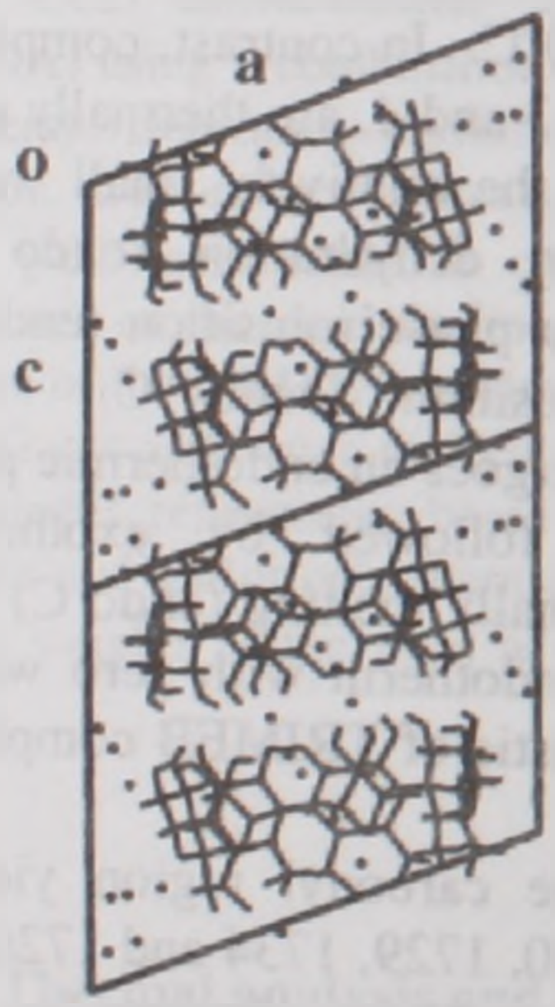

Figure 3. Packing of the β-CD molecules in the crystal of complex **1**. Small circles represent water molecule sites.

These engage in extensive networks of hydrogen bond interactions which link parallel columns of β-CD dimeric units. The α-D-glucopyranose units of the β-CD molecule adopt the usual $^4C_1$ chair conformation. One primary hydroxyl group is in a (-)-*gauche* conformation and the others are in a (+)-*gauche* conformation. The 'round' shape of the macrocycle is maintained by intramolecular $O3G_n\cdots O2G_{n+1}$ hydrogen bonds [17] with O···O distances in the range 2.75(1)-2.91(1)Å. Other standard geometrical data, with their observed ranges, include the glycosidic oxygen angles $C4G_n$-$O4G_n$-$C1G_{n+1}$ (117.9(4)-119.0(4)°), torsion angle index (113.5-125.5°), tilt angles (0.6(2)-8.0(2)°), heptagon radii (4.94(1)-5.22(1)Å) and $O4Gn\cdots O4G_{n+1}$ distances (4.32(1)-4.47(1)Å). The values of these parameters indicate that there are no unusual host distortions as a result of complexation with

clofibric acid. In this structural arrangement, the β-CD molecules form dimers with twofold crystallographic symmetry through multiple O-H···O hydrogen bonds across their secondary faces ($O3G_n$···$O3G_{8-n}$, 2.78(1)-2.92(1)Å). Each unit cell in Figure 3 shows such a dimer. On average each β-CD dimer accommodates two molecules of clofibric acid but guest disorder prevents description of the mode of inclusion. From the IR data, however, we conclude that the included clofibric acid molecules are unlikely to form carboxylic acid dimers through hydrogen bonding as they do in the pure solid drug.

Crystals of complex **2** have the tetragonal symmetry (Table 2) common to all γ-CD complexes [18]. The crystal packing is of the channel-type based on stacking of three γ-CD molecules in head-to-head, tail-to-tail and head-to-tail arrangements along the *c*-axis (Figure 4).

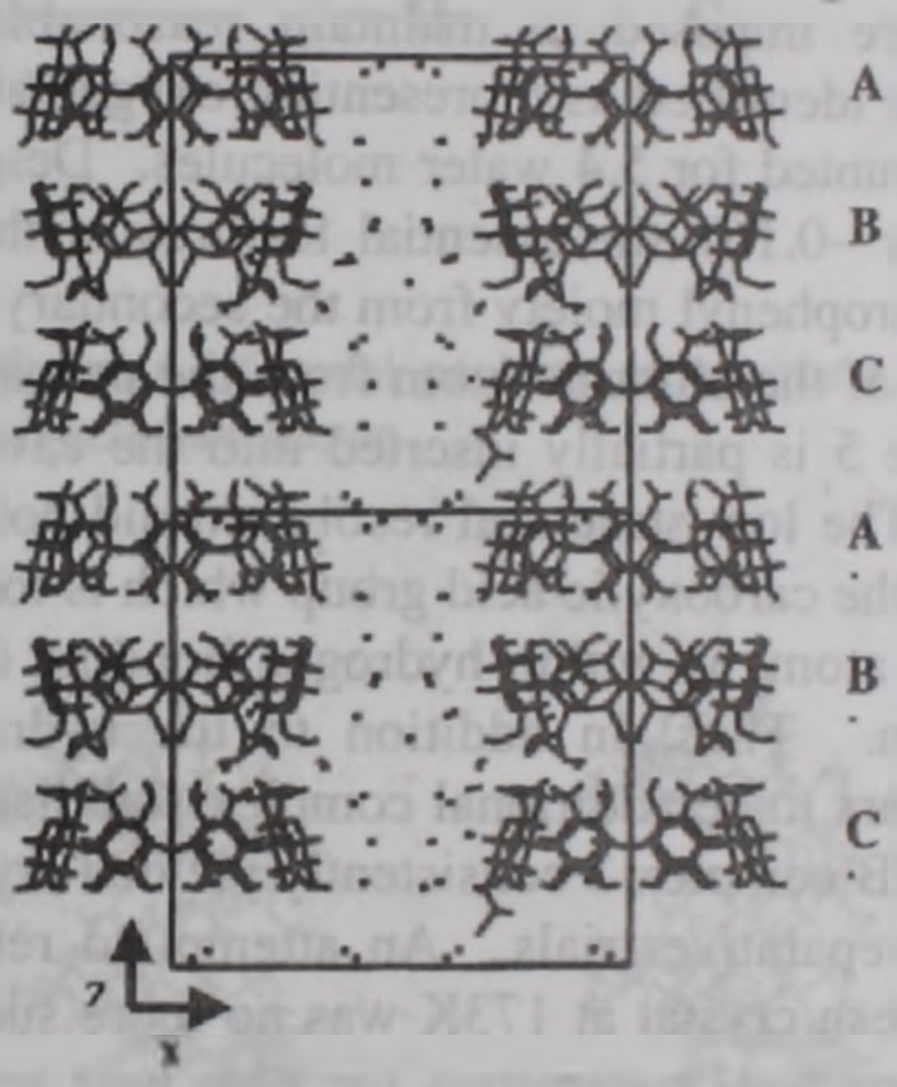

Figure 4. Packing of the γ-CD molecules in the crystal of complex **2**. A, B, C denote crystallographically independent molecules and small circles represent water molecule sites.

A fourfold crystallographic axis runs through the centre of the γ-CD channel. Consequently, unless the included guest molecule has inherent fourfold symmetry, it will be disordered within the channel. While refinement of the host molecule and several water molecules of complex **2** proceeded satisfactorily, the guest clofibric acid molecule was only evident as a distribution of very weak electron density, analogous to the situation for the β-CD complex **1**. Of the 15.5 water molecules per γ-CD molecule expected from TGA measurements, only 6.3 discrete water molecules were accounted for in the final model, the remainder being disordered over a large number of sites. Most of the molecules located were outside the γ-CD cavity. The α-D-glucopyranose rings of the three independent γ-CD molecules are in the $^4C_1$ chair conformation. As for β-CD, the 'round' shape of the γ-CD macrocycle is maintained by intramolecular $O3G_n$···$O2G_{n+1}$ hydrogen bonds (range 2.77(1)-2.89(1)Å). Other parameters and their ranges include the glycosidic bond angles (115.0(4)-116.7(4)°), tilt angles (5.8(2)-15.6(3)°), the octagon radii (5.82(1)-5.90(1)Å) and $O4G_n$···$O4G_{n+1}$ distances (4.49(1)-4.50(1)Å). As for the β-CD complex **1**, the crystallographic and UV data prove that an inclusion complex forms between clofibric acid and γ-CD. The guest disorder in the case of this host results primarily from the high symmetry requirements of the space group and is exacerbated by the larger diameter of the γ-CD channel. We recently reported a study of the kinetics of dehydration of complexes **1** and **2** [15]. This showed that the process is diffusion-controlled, with activation energies significantly lower than those for the respective parent CD hydrates.

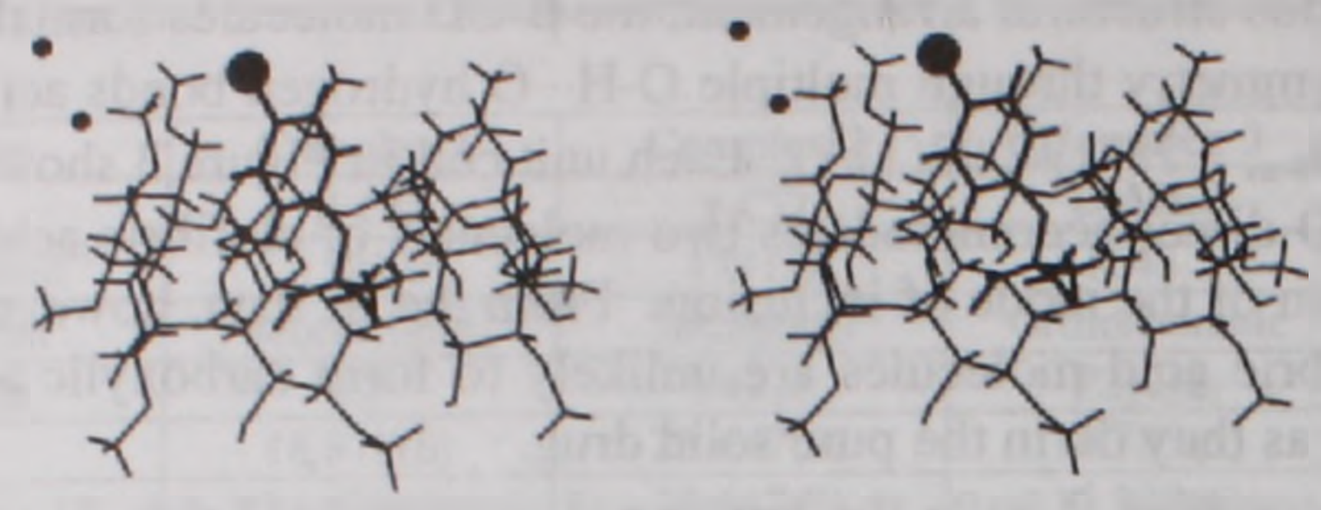

Figure 5. Stereoview of complex **3**. Water molecules are represented by small circles and the guest chlorine atom by a large circle.

Figure 5 is a stereoview of the complex **3**. Considerable difficulty was encountered during the refinement of this structure due to generally low electron densities observed for the guest atoms in the DIMEB cavity. In particular, the carboxylic acid group was poorly defined and extensive distance restraints were imposed to maintain reasonable guest geometry. In addition only two peaks could be identified as representing oxygen atoms of water molecules, whereas the TG analysis accounted for 5.4 water molecules. Despite the relatively poor quality of the analysis (R-factor ~0.16), the essential features of the guest inclusion are clear, namely insertion of the chlorophenyl moiety from the secondary side of the host DIMEB and the significant protrusion of the chlorine atom from the primary side. As detailed below, the chlorine atom in Figure 5 is partially inserted into the cavity of a DIMEB molecule directly above that shown. The low structural resolution did not permit distinction between the C=O and C-O bonds of the carboxylic acid group which is located at the host secondary rim, but one of the oxygen atoms is within hydrogen bonding distance (2.84(2)Å) of a host glycosidic oxygen atom. Thus, in addition to the hydrophobic interactions between host and guest, there appears to be additional complex stabilisation by direct host-guest hydrogen bonding. The DIMEB complex **3** consistently yielded crystals of mediocre diffraction quality despite several preparative trials. An attempt to refine the structure with intensity data collected from a fresh crystal at 173K was no more successful than the present one. The low precision of structural parameters for both host and guest preclude detailed discussion of molecular parameters.

An important feature of complex **3** is that the crystal packing arrangement (Figure 6) is a novel one for DIMEB complexes. Generally, DIMEB complexes crystallize in the space group $P2_12_12_1$ with typical unit cell dimensions a ~ 14.8, b ~18.9, c ~ 28.8Å and the representative X-ray powder pattern for this isostructural series has been reported [18]. Complex **3** crystallizes in the same space group but with different cell constants, one of them being ~10.8Å (Table 2), which is the approximate height of the complex molecule in the orientation shown in Figure 5. The result is that the DIMEB cavities are strictly aligned along the crystal x-direction, as shown in Figure 7 for three translated molecules. It is evident that successive guest molecules are virtually in contact in head-to-tail mode (e.g. the shortest intermolecular guest Cl···C(methyl) distance is only 3.51Å). This was confirmed by inspection of space-filling diagrams which show the head-to-tail contact of the molecular surfaces. In this novel packing arrangement, the guests thus form a 'continuum' along the channel axis. In contrast, in the other known packing arrangement of DIMEB complexes, the axes of the macrocycles are offset from one another, producing a decidedly non-linear 'channel'.

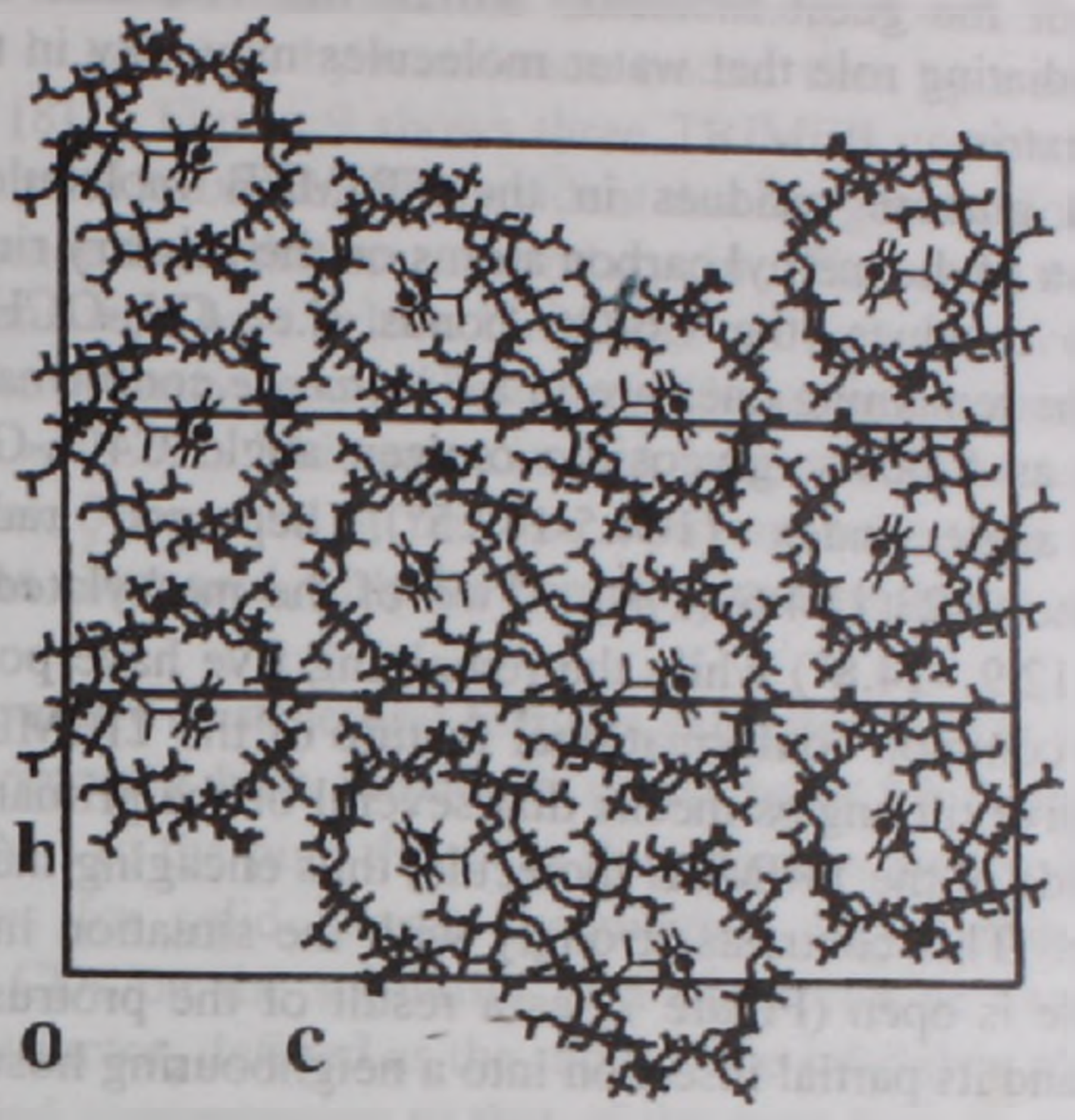

Figure 6. Crystal packing arrangement in complex **3** shown in projection down the *a*-axis. Three unit cells are shown.

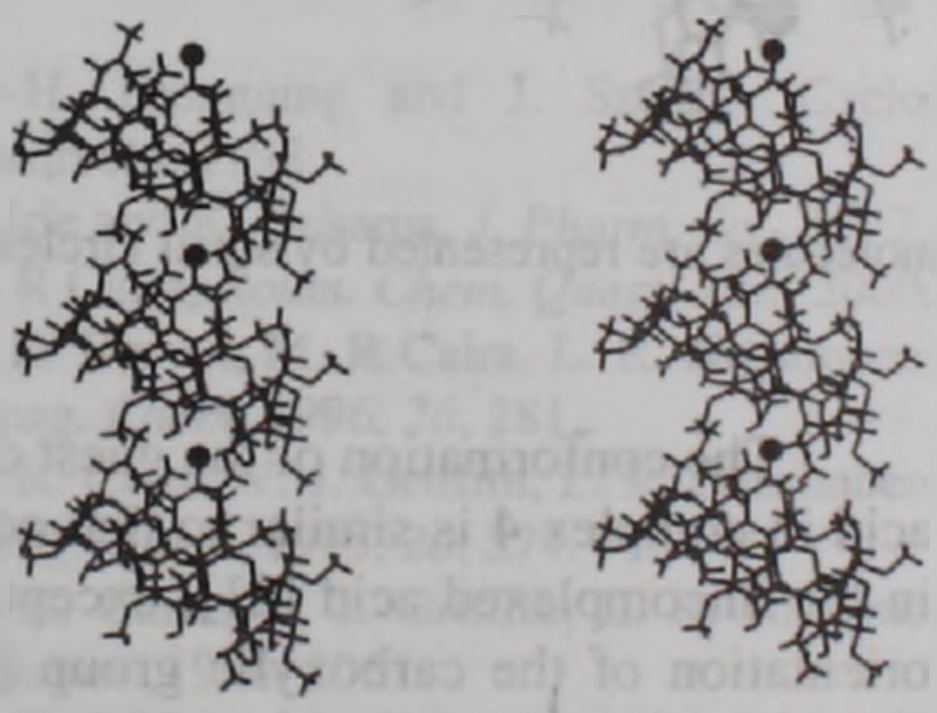

Figure 7. Stereoview showing three molecules of complex **3** related by translation along the *a*-axis (vertical).

The structure of **4**, the TRIMEB complex of clofibric acid. is illustrated in the stereoview of Figure 8. Of the four complexes analysed. this one yielded the best resolution of the guest molecule as well as the water molecules of crystallization. The orientation of the guest in the TRIMEB cavity is opposite to that observed in the DIMEB complex **3**. The chlorophenyl residue partially protrudes from the secondary side of the TRIMEB cavity while the carboxylic acid moiety is located inside the cavity and is linked to the host primary side via hydrogen bonding through bridging water molecules. Refinement of the water molecule site-occupancy factors yielded values of 0.89 and 0.51, the total corresponding to the stoichiometric value of $1.4H_2O$ observed in TGA. Figure 8 shows that one water molecule is hydrogen bonded to the carbonyl O atom of the guest while the other is hydrogen bonded to the guest hydroxyl group. Each water molecule is in turn hydrogen bonded to a member of a disordered pair comprising a DIMEB primary oxygen atom. The four O···O distances for these hydrogen bonds are in the range 2.53(1)-2.76(1)Å, indicating that strong attractive interactions are responsible for anchoring the

hydrophilic portion of the guest molecule within the TRIMEB cavity. This is a rare illustration of the mediating role that water molecules may play in the inclusion of a guest molecule in a cyclodextrin.

All methylated glucose residues in the TRIMEB molecule adopt the usual $^4C_1$ conformation with four of the methyl carbon atoms on the primary rim being disordered over two sites. For two residues, the C6-O6 bonds (i.e. CH_2-OCH_3) have a (+)-*gauche* conformation while the remaining ones are in a (-)-*gauche* conformation. Other parameters and their ranges are as follows: glycosidic oxygen angle $C4G_n$-$O4G_n$-$C1G_{n+1}$ (114.8(5)-118.8(3)°), torsion angle index (104.5-142.5°), heptagon radii (4.60(1)-5.41(1)Å), $O4G_n\cdots O4G_{n+1}$ distance (4.23(1)-4.62(1)Å). Two of the methylated glucose residues have negative tilt angles (-12.9, -14.8°) while the remaining five have positive tilt angles (range 9.9-42.4°) which is a common conformational feature of the TRIMEB molecule [20]. The predominance of positive tilt angles means that several of the primary methoxy groups tend to close the primary side of the TRIMEB molecule, thus encaging the guest within the bowl-like TRIMEB surface. This contrasts strongly with the situation in complex **3**, where the 'lid' of the macrocycle is open (Figure 7) as a result of the protrusion of the bulky guest chlorophenyl residue and its partial insertion into a neighbouring host cavity.

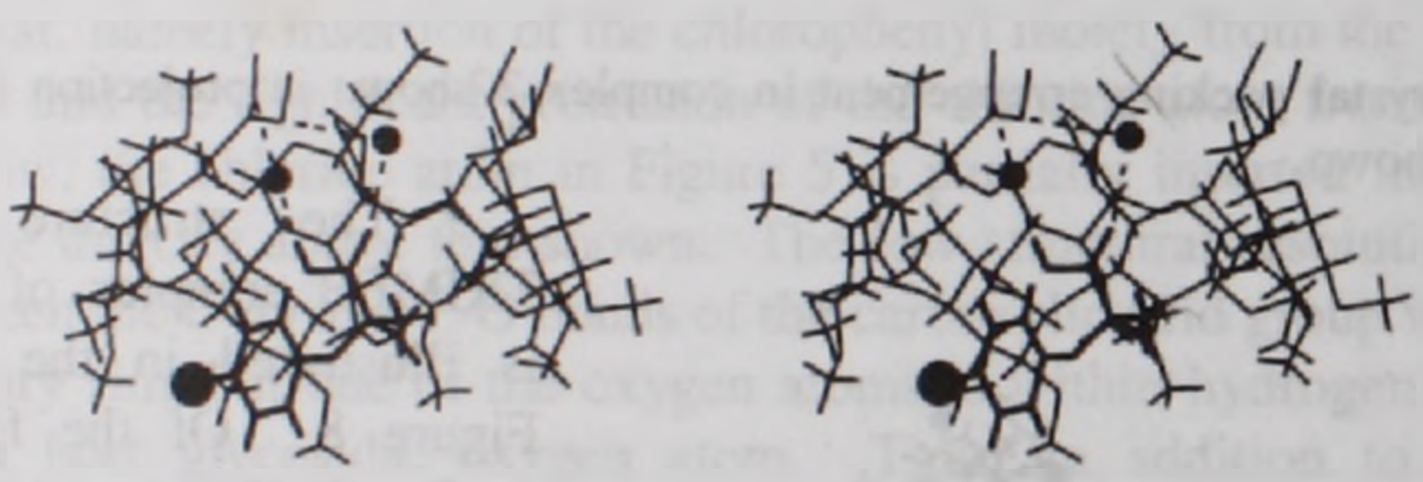

Figure 8. Stereoview of complex **4**. Water molecules are represented by small circles and the guest chlorine atom by a large circle.

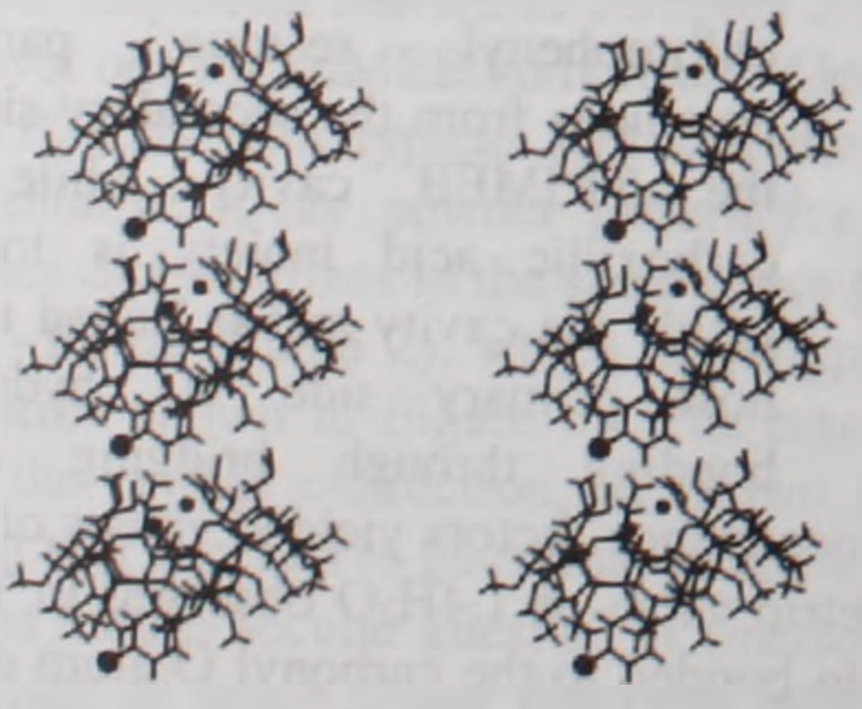

Figure 9. Stereoview showing three molecules of complex **4** related by translation along the *a*-axis (vertical).

The conformation of the guest clofibric acid in complex **4** is similar to that occurring in the uncomplexed acid [21], except for the orientation of the carboxylic group [O-C-C-O(hydroxyl) torsion angles 28.5(9) and -35.9(2)° respectively]. The high precision of the analysis permitted a distinction between the carboxylic C-O and C=O bonds (1.30(1), 1.17(1)Å respectively). The C=O distance is significantly shorter than the value of 1.231(6)Å reported for this bond in the uncomplexed clofibric acid molecule, a result consistent with the IR data which showed that complexation is accompanied by an increase in ν_{CO}. This complex is isostructural with the (L)-menthol complex of TRIMEB [8] whose packing arrangement is uncommon for

TRIMEB complexes. Details were reported earlier where it was shown that molecules in this arrangement pack in columns by translation (rather than by a screw-axis, which is the more common motif) [8]. Figure 9 shows three TRIMEB complex molecules related by translation along the crystal *a*-axis and it is evident that the guest chlorine atom and a portion of the phenyl ring protrude from the host secondary rim. However, they do not penetrate the primary side of the translated host below, but rather act as a spacer between the secondary face of one host and the primary face of the other. The complex units thus pack head-to-tail with a periodicity of a = 11.6Å. This value is ~1Å longer than the corresponding parameter of the DIMEB complex **3** because of the less efficient 'cage-type' inclusion by TRIMEB molecules (Figure 9) as compared with the complete encapsulation of the guest by DIMEB molecules (Figure 7).

Apart from the variety of structural features exhibited by this series of complexes, the characterization data reported here provide a sound basis for further development of the complexes as alternatives to the pure drug. In this regard, only the β- and γ-CD complexes are realistic candidates for solid dosage formulation, for reasons of safety and cost.[22] Finally, the effect of CDs on the solubility of a guest can be expressed in terms of the solubility enhancement factor, defined as the ratio of the solubility of the drug in an aqueous CD solution of specified concentration to that of the pure drug in water [1]. In the case of clofibric acid, the solubility enhancement factors at 25°C were found to be 1.4 and 2.1 for β- and γ-CD respectively [23].

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