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MODELLING THE THERMAL BEHAVIOUR OF CARBOXYLIC ACID DERIVATIVES WITH CYLCODEXTRINS IN THE SOLID-STATE

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Abstract

The application of classical QSAR and molecular modelling to the inclusion complexation of natural and modified cyclodextrins (CDs) with carboxylic acid derivatives as guest molecules was examined. Information was available on the thermal behaviour, in the solid-state of benzoic acid (BA), salicylic acid (SA), and various substituted aminosalicylic acids (3-aminosalicylic acid, 3-ASA, 4-aminosalicylic acid, 4-ASA and 5-aminosalicylic acid, 5-ASA), as well as on the thermal behaviour of 1:1 molar ratio physical and kneaded mixtures of these acids with each of three different cyclodextrins, β-, (BCD) 2-hydroxypropyl-β-, (HPBCD) and γ-cyclodextrin (GCD). The thermal behaviour of the binary (1:1 stoichiometry) mixtures was modelled using stepwise multiple regression (SMR). Two models for the prediction of the percentage mass loss and enthalpy of dehydration of the physical mixtures were established with correlation coefficients (r) of 0.79 and 0.92, respectively. Decreased correlation in the thermal behaviour of kneaded mixtures indicated significant interaction and possible formation of inclusion complexes.

Keywords: carboxylic acid derivatives, cyclodextrins, stepwise multiple regression, thermal analysis

Introduction

Cyclodextrins (CDs) are natural or semi-synthetic macrocyclic oligosaccharides, comprised of α-*D*-glucopyranose molecules linked to form a cylindrical structure with α-cyclodextrin (ACD) containing six, β-cyclodextrin (BCD), seven and γ-cyclodextrin (GCD) eight linked molecules. In 2-hydroxypropyl-β-cyclodextrin (HPBCD), the structure of BCD is modified by the random incorporation of hydroxypropyl groups to a specified degree of substitution. The hydroxyl groups on the outside of the cyclodextrin cylinder form an exterior hydrophilic surface while the central cavity of the cylinder is relatively non-polar and thus hydrophobic. This hydrophobic cavity provides a favourable environment for accommodating a variety of hydrophobic organic and inorganic

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molecules, [1] called guests. Cyclodextrins are therefore capable of forming host/guest inclusion complexes with a variety of drug molecules. Inclusion of the guest may not only increase its solubility but also its stability, with the resulting inclusion complex exhibiting different physicochemical properties from both the cyclodextrin and the drug molecule. As a consequence, cyclodextrins have received much attention in the area of drug delivery because of their ability to improve the water solubility and thus the bioavailability of drug molecules.

Although the actual formation of an inclusion complex can only be confirmed after consideration of the results of several analytical approaches, such as phase solubility analysis, spectral methods and where possible, single-crystal X-ray structure determinations [2], thermal analysis (DSC and TG) is commonly used as a routine method for a rapid and reliable preliminary qualitative investigation. Indications of inclusion complexation are usually based on differences in thermal behaviour of the single components, binary physical mixtures and potential inclusion compounds, prepared according to standard procedures. Differences can be found in the water content, the onset temperatures of thermal degradation and the mass loss values at given temperatures. Generally, kneaded mixtures are expected to show greater changes in thermal behaviour than their corresponding physical mixtures. However, although the conditions used in preparing physical mixtures are very mild, the resulting behaviour of these mixtures may differ considerably from that predicted from the individual components. It is thus difficult to find examples of mixtures where little or no interaction has occurred. The kneading procedure however, can also produce changes in the crystallinity and water content of the CDs.

Despite the fact that thermal methods are considered to be very reliable and relatively fast, there is a need for more quantitative information and an ability to predict behaviour. The aim of this work was thus to correlate the structural characteristics of benzoic, salicylic, and aminosalicylic acid isomers as guest molecules and BCD, HPBCD and GCD as hosts, with the previously determined thermal behaviour of the physical and kneaded mixtures [3–5], using a stepwise regression method.

Materials and methods

The materials and methods used are described in more detail in [3–5].

Materials

Three different cyclodextrins (BCD, HPBCD (DS 4.81) and GCD), were obtained from Wacker-Chemie, GmbH (Munich, Germany). Benzoic acid (BA) and salicylic acid (SA) were obtained from Unilab, Saarchem (Pty) Ltd. 3-, 4-, and 5-aminosalicylic acid (3-ASA, 4-ASA and 5-ASA) were obtained from Aldrich Chemical Co. Ltd (UK). The samples were used in the form supplied and their thermal behaviour is shown in Table 1.

Table 1 Thermal behaviour of the cyclodextrins used in this study [3-5]

	DSC			TG		
CDs	T_{onset}/°C	ΔH/ kJ (mol CD)$^{-1}$	T_{range}/°C	Mass loss/ %	ΔH/ kJ (mol H_2O)$^{-1}$	ΔH/ J (g CD)$^{-1}$
BCD	76	266	40–125	11.4	33.3	234
HPBCD	53	64	40–120	6.0	12.8	45
GCD	65	73	40–120	9.0	10.4	56

Preparation of the cyclodextrin mixtures

1:1 molar ratio physical mixtures were made [3–5] by mixing the calculated amounts of the dry powder 'host' (CD) and 'guest' compounds by shaking in a test-tube, avoiding grinding. Kneaded mixtures were prepared by weighing and transferring the components to a suitable container where they were kneaded with sufficient ethanol to make a paste. The mixtures were then placed in an oven at 40–50°C overnight to dry (water-free), followed by gentle grinding.

Equipment

Thermal analyses were carried out [3–5] on a PerkinElmer Series 7 TG and DSC. For the TG experiments, the sample masses were between 2 and 5 mg, in an open platinum pan, the atmosphere was flowing nitrogen and the heating rate used was 10 K min^{-1}. DSC experiments were carried out in standard aluminium pans with lids, but uncrimped, while calibration involved using the melting point and enthalpy of melting of indium. The DSC and TG curves recorded are described in [3–5].

Software

Statistica TM 5.5 (StatSoft) was used for building the QSAR and Molecular Modelling Pro 5.10 (ChemSW Inc) was used to calculate molecular descriptors from the drug structures. For each of the guest molecules, as well as the cyclodextrin molecules, 49 molecular descriptors were calculated (Table 2).

Stepwise regression

The general purpose of multiple regression is to quantify the relationship between several independent or predictor variables and a dependent variable. A multi-linear model can be represented as:

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \ldots + \beta_k x_k + \varepsilon \quad (1)$$

where k is the number of independent variables, $\beta_1 \ldots \beta_k$ are the regression coefficients and y is the dependent variable.

In this application, the thermal behaviour for each potential host/guest system has been calculated as a composite of a variety of molecular descriptors weighted by their re-

spective coefficients. Regression coefficients represent the independent contributions of each calculated molecular descriptor. In order to select the subset of descriptors that best explains the investigated thermal behaviour, stepwise regression has been used. Stepwise model-building techniques for regression with a single dependent variable involve identifying an initial model, repeatedly altering the model from the previous step by adding (forward stepwise) or removing (back stepwise) a predictor variable and terminating the search when stepping does not further improve the model.

The forward stepwise method used in this study employs a combination of the forward entry of the independent variables and backward removal of the insignificant variables.

The best single predictor, which is the most significant variable, was used for the initial linear regression step. Then descriptors were added one at a time, always adding the one that most improved the fit, until the fit was not significantly further improved. Once all the significant variables were determined, the regression equation was constructed.

Results and discussion

Formation of an inclusion complex between a guest molecule and a cyclodextrin depends on a variety of physicochemical parameters and requires a multivariate approach for its description. In the current study, the guest molecules were carboxylic acid derivatives and the hosts included cyclodextrins with different average cavity diameters: 6.2 Å (BCD) and 7.9 Å (GCD) and a cavity length of 8 Å. The change of the microenvironment from the hydration shell in aqueous solution to the more hydrophobic interior of the host cyclodextrin is responsible for the modification of the molecular properties of the guest. The inclusion capabilities of different cyclodextrins depend not only on the sizes of the cavities but also on the flexibilities of the CDs. A variety of non-covalent forces, such as van-der-Waals forces, hydrophobic interactions and other forces, are responsible for the formation of a stable complex.

The first step in developing a quantitative structure activity relationship (QSAR) was the calculation of the molecular descriptors. Ninety-eight calculated structural features, including bulk properties, solubility parameters and topological descriptors, were generated for each guest (49 descriptors) and cyclodextrin molecule (49 descriptors) (Table 2). The molecular connectivity indices provide quantitative characterization of skeletal variation in a molecule. These descriptors are based on structural features in the molecular graphs, such as bonds, clusters and rings. Connectivity indices encode, in a particular manner, the structural information resident in a molecular skeleton. The connectivity index of the third order reflects patterns of adjutancy in skeletal branching. The size of the substituted benzenes is encoded in the third-order connectivity and it is sensitive to specific structural aspects, such as ring substitution and the correlated molar volume. The valence connectivity index on the other hand, accounts for the presence of hetero-atoms in the molecule, as well as double bonds.

Table 2 Calculated molecular descriptors

Bulk properties	Molecular mass, van-der-Waals volume, surface area, molecular volume [6], molar volume [7], density, molecular length, width and depth
Solubility parameters	Octanol-water partition coefficient (Fragment addition [8] and atom based Log *P* [9]), molar refractivity (MR), *Q* Log *P* [10], hydrogen bonding number, solubility parameter and 3D solubility parameters (dispersion, polarity and hydrogen bonding) (van Krevelen, and Hansen's methods), dipole moment [11], mean water of hydration [12], hydrophilic-lipophilic balance (molecular mass and volumetric HLB), hydrophilic surface area and % hydrophilic surface area, polar surface area [13], surface tension, water solubility [14] (log*W*–log water solubility, g L^{-1}, [ppm]), Log S_w (water solubility estimated from Log Kow [15]), Log Kow (log molar water solubility), Log molar olive oil - gas partition coefficient [16]
Topological descriptors	Randic connectivity indices [17] (Chi 0-Chi 4), valence connectivity indices [18] (Chi V1-Chi V4), Kier's topological shape indices [19] (Kappa 1–3), difference indices (0 –4), 3-D Wiener number [20]

The next step was to correlate the descriptor variables with the experimentally-determined thermal behaviour (Table 3) using a multiple-regression method. Because an equation containing an excessive number of independent variables can be too cumbersome to use and the model is likely to be over-fitted, we have used stepwise regression to refine the model.

Generally, as expected, the kneaded mixtures showed greater changes in thermal behaviour from that of the individual components than do the physical mixtures, but the changes in the physical mixtures are also significant. Correlations of the percentage mass loss and the measured enthalpy of dehydration with the molecular descriptors, used to describe the investigated carboxylic acid derivatives and the different cyclodextrin molecules (BCD, HPBCD and GCD), are as follows:

Physical mixtures

mass loss% = –10.74 –10.18 (G dipole moment) + 8.44 (G molecular length) –15.91 (G Chi 3) –3.83 (CD molecular depth) + 4.84 (G Valence Chi 0);

Multiple R= 0.81 (2)

ΔH dehydration =1082.63 –32.44 (CD's water of hydration) –43.99 (G molecular width) +124.51 (G Chi 3) –351.139 (G molecular density);

Multiple R= 0.92 (3)

Table 3 Summary of observed thermal behaviour of 1:1 molar ratio mixtures of benzoic, salicylic acid and aminosalicylic acid isomers with the cyclodextrins (*P* = physical mixture and *K*= kneaded mixtures) [3–5]

Mixture (1:1)	Acid/ mass%		Mass loss CD/ %	$\Delta H_{dehyd.}$/ kJ (mol CD)$^{-1}$	ΔH_{melt}/ kJ (mol acid)$^{-1}$
BA/BCD	9.7	P	12.0	234	14
		K	8.5	243	1
BA/HPBCD	7.9	P	6	158	0
		K	5	63	0
BA/GCD	8.6	P	10	74	20
		K	4	0	0
SA/BCD	10.8	P	12	281	9
		K	13	74	0
SA/HPBCD	8.9	P	12	19	0
		K	2	0	0
SA/GCD	9.6	P	14	123	2
		K	5	0	0
3-ASA/BCD	11.9	P	8.5	252	59
		K	2.0	0	69
3-ASA/HPBCD	9.8	P	5.0	100	5
		K	5.0	61	0
3-ASA/GCD	10.6	P	7.0	163	69
		K	3.0	65	10
4-ASA/BCD	11.9	P	5.5	184	32
		K	2.0	181	14
4-ASA/HPBCD	9.8	P	5.5	36	89
		K	1.0	0	0
4-ASA/GCD	10.6	P	5.0	69	0
		K	12.0	182	0
5-ASA/BCD	11.9	P	13.0	255	199
		K	12.0	199	122
5-ASA/HPBCD	9.8	P	13.5	72	0
		K	6.0	52	0
5-ASA/GCD	10.6	P	5.0	61	80
		K	6.0	120	67

Kneaded mixtures

mass loss% = –18.50 –9.63 (G dipole moment) + 6.01 (G molecular length) –21.66 (G Chi 3) –5.56 (CD molecular depth) + 9.52 (G Valence Chi 0);

Multiple R= 0.54 (4)

ΔH dehydration = 146.60 –18.40 (CD water of hydration) + 75.66 (G molecular width) –42.65 (G Chi 3) +12.13 (G molecular density);

Multiple R = 0.62, (5)

where Multiple R = coefficient of multiple correlation, G = guest molecule, CD = cyclodextrin molecule.

When comparing the predictions in % mass loss and ΔH dehydration (Table 4) for the complexes with the three cyclodextrins, the best values were found to be for the complexes with BCD (smallest average relative error). This is in close agreement with the fact that BCD possesses a 6–6.8 Å cavity, which is able to accommodate aromatic groups found in many drug molecules [21].

Of the various guests used with BCD as host, best predictions were achieved for the 3-ASA/BCD (physical mixture). Salicylic acid and benzoic acids were found to be unlikely to form a stable complex, due to the structure and polarity of the molecules. The dipole moment is a measure of the distribution and strength of partial charges in a molecule. Molecules with a mean distribution of the partial charge towards one side of the molecule will have a higher dipole moment than a molecule with a centralized mean charge distribution. The hydroxyl group in salicylic acid is in the *ortho*-position, which increases the polarity of the carboxylate group to a greater extent than if the hydroxyl group was in the *meta*- or *para*- positions, so the hydroxyl group would most probably be situated outside the cyclodextrin cavity [22–24]. The attachment of an amino group in position 3 of the benzene ring of salicylic acid will decrease this polarity, and hence, theoretically, should result in stronger complexation. The favourable predictions for 3-ASA with BCD could be due to the hydrophobic part (benzene) of the 3-ASA molecule being situated inside the cyclodextrin cavity while the hydroxyl-, carboxylate- and amino- groups are stabilized outside the cavity (Fig. 1).

Only the valence index and the guest molecular length have positive coefficients and should thus favour complexation. This suggests that the complex is stabilized by forming hydrogen bonding with the host's hydroxyl groups and emphasizes the importance of structural isomerism on molecular shape, length and dipole moment (longer molecules are preferred). As expected, phenolic OH and amino groups have an additional effect, and can further stabilize the complex by forming hydrogen bonds with the host's hydroxyl groups. The hydrogen bonding may contribute to a conformational change either in the cyclodextrin, the guest, or both, which results in a more stable complex [25]. However, the contribution by the phenolic OH moiety of the guests does not play a significant role. The hydroxyl group of the salicylate ion is in the *ortho*-position, which increases the polarity of the carboxylate group and

Table 4 Predictions of percentage mass losses and enthalpies of dehydration (ΔH) with the three cyclodextrins

	$\Delta H_{dehyd.}$			Mass loss CD / %		
	Experimental value	Predicted value	Relative error/%	Experimental value	Predicted value	Relative error/%
3-ASA/BCD	252	274.4	8.9	8.5	8.1	4.9
4-ASA/BCD	184	199.1	8.2	5.5	6.6	19.7
5-ASA/BCD	255	232.0	9.0	13	11.8	9.6
BA/BCD	234	258.0	10.3	12	10.6	11.8
SA/BCD	281	243.7	13.3	12	13.9	16.0
	Average relative error		9.9			12.4
3-ASA/HPBCD	100	112.2	12.2	5	6.1	22.6
4-ASA/HPBCD	36	36.9	2.4	5.5	4.6	15.8
5-ASA/HPBCD	72	69.9	3.0	13.5	9.8	27.4
SA/HPBCD	19	81.5	329.2	12	12.0	0.3
BA/HPBCD	158	95.9	39.3	6	8.6	43.8
	Average relative error		77.2			22.0
3-ASA/GCD	163	128.4	21.2	7	6.3	10.2
4-ASA/GCD	69	53.1	23.1	5	4.8	4.3
5-ASA/GCD	61	86.1	41.1	5	10.0	99.0
BA/GCD	74	112.1	51.5	10	8.8	12.2
SA/GCD	123	97.8	20.5	14	12.1	13.4
	Average relative error		31.5			27.8

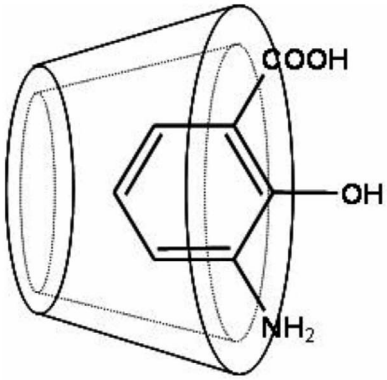

Fig 1. Schematic diagram of a 3-ASA molecule in the BCD cavity

thereby makes it more hydrophilic than if the hydroxyl group was placed in *meta*- or *para*- position. The hydroxyl group is most probably situated on the rim of the cavity as suggested by Lee and Lin [22].

The coefficient of correlation between selected descriptors and the percentage mass loss for the physical mixtures was 0.81. For the kneaded mixture, correlation was lower (0.54) and is evidence of inclusion and significant interaction between the host and guest molecules.

Cyclodextrins are generally marketed as hydrates. BCD (water content 14.9%) used in the study was the undecahydrate. A neutron diffraction study of the undecahydrate showed that, out of the 11 water molecules, 8 are distributed in the cavity of the cyclodextrin [26]. When small molecules (water) are included into the cavity, CD molecules form cage-like structures by closing both openings of each cyclic unit with an adjacent CD molecule, thereby entrapping the guest in the CD cavity. When water is eliminated from the cavity of the cyclodextrin by inclusion of a less-polar guest, a decrease in the energy occurs. This results from a decrease in the surface contact between the solvent and the cyclodextrin cavity, as well as between the solvent and the guest molecule. Furthermore, water inside the cyclodextrin cavity cannot achieve its normal tetrahedral hydrogen bonding capacity and it is therefore often referred to as 'high energy' water. One of the main driving forces for complexation is thus proposed to be the release of this “high energy” water from the cyclodextrin cavity followed by the formation of the full complement of hydrogen bonds with the surrounding water [27].

Apolar–apolar association between the more hydrophobic guest molecules and the cavity results in a decrease of the cyclodextrin ring strain and a more stable lower-energy state [28].

The enthalpy of dehydration is, as expected, correlated to the loss of water from the CD in the mixtures. Water of hydration was calculated by McGowan’s fragment constant addition [29]. In this procedure the amount of hydrated water is associated with the specific functional groups and molecular fragments are summed to give the

total amount of hydrated water for the molecule. The enthalpy of dehydration was negatively correlated with the molecular density of the guest molecule. Since density is inversely related to molecular size, the enthalpy of dehydration will increase with an increase in molecular volume of the guest. It decreases with molecular width, depending on the size and position of substituents, attributed to the destabilization of a complex due to steric hindrance. The correlation coefficient between ΔH dehydration and selected descriptors for the physical mixtures was 0.92. For the kneaded mixture, the correlation was lower (0.62) indicating an extensive interaction between the guest molecule and CDs, or that the water has been displaced from the CD cavity during the kneading process by the kneading solvent (ethanol).

Szente [30] has formulated some of the questions, which need to be answered concerning the nature of the interactions of the mixtures of potential guests with host CDs. These include determining whether the guest actually enters the CD cavity and how much of the guest remains outside the cavity. An additional aspect, seen in the present study, is the fate of water molecules already hosted within the CD cavity when the CD is mixed with another potential guest substance. Various possibilities for interaction exist. The guest can replace all the water and this expelled water can be lost from the mixture during, or soon after, the mixing process. This would be clearly shown by both disappearance of the dehydration endotherm from the DSC curves of the mixtures and the absent, or decreased, initial mass loss in the TG curves.

The next possibility would be that all, or most, of the water expelled from the CD cavities remains, although more loosely-bound, in the mixture and is released on heating with a similar mass-loss to that for the individual CD, but a decreased enthalpy of dehydration. Alternatively, some of the water molecules may share the CD cavity with the guest molecule, G, forming a type of hydrate, $G{\cdot}n\mathrm{H_2O}$, stabilised within the cavity and behaving differently from the pure guest, G.

Another possibility is that the guest molecules may only enter the cavity during the heating programme when the water molecules are expelled. Because dissociation of host-guest complexes will be endothermic and the formation of host-guest complexes could be close to thermally neutral, an apparent disappearance of, or marked decrease in the size of, the dehydration endotherm for the host CD could be observed.

Quantitative correlations between chemical structure and melting point are generally not found. Most of the DSC curves for kneaded mixtures [3–5], where the two components are in the stoichiometric ratio of interaction or there is an excess of the host CD, show the disappearance of the melting peak of the crystalline guest, while the curves for physical mixtures generally show an endothermic effect at a temperature corresponding to the melting point of the crystalline guest candidate.

Conclusions

Results from this study indicate that all the carboxylic acid derivatives studied appear to interact with all three of the cyclodextrins used, in particular after kneading with the kneading solvent (ethanol). There are differences in the behaviour of different isomers and also differences in the behaviour of individual cyclodextrins.

Group-contribution models for the estimation of the thermodynamic behavior of the complexation of the carboxylic acid derivatives with natural and cyclodextrin derivatives, respectively, were established. The models proposed in this work provide a basis on which to the evaluate inclusion complexation with cyclodextrins and to predict the complexation properties of guest molecules for which the experimental determination is difficult.

A variety of intermolecular interactions and solvation effects were proposed to explain the stability of the inclusion complexes formed. Hydrophobic desolvation and van-der-Waals interactions are among the most significant driving forces for CD complexation, besides hydrogen bonding between polar groups of the substrate and the OH groups of the macrocycles. In addition, release of water of hydration from the CD cavity and consequently release of conformational strain energy possessed by the uncomplexed CD, and molecular shape and size of guest are key driving forces in inclusion complexation.

The most important molecular properties of the guest proved to be the molecular length, connectivity index of the third order and the number of hydrogen bond acceptors.

The equation obtained by the stepwise regression method suggests that the percentage mass loss depends on the host/guest complementarity, measured by the host molecular length, structural features or shape (connectivity index 3), the presence of phenolic and amino groups and the cavity depth of the cyclodextrin.

The importance of individual contributions to the complexation process can be related to the value of the respective regression coefficients. Positive signs of regression coefficients indicate that those groups should enhance the complexation ability.

The orientation and alignment of the guest molecule in the CD cavity is crucial. The key factor is steric shape and depends on the relative size of the cyclodextrin cavity to the size of the guest molecule or certain key functional groups within the guest. Longer and less bulky molecules will fit better within the CD cavity. The major driving forces are hydrophobic/lipophilic interactions represented by the guest dipole moment [31] as an approximate [32] measure of van-der-Waals hydrophobic interactions [33, 34]. These forces are usually weak for all kind of interactions, but are likely to be numerous in the cyclodextrin cavity and therefore have to be taken into consideration [35].

The percentage mass loss depends directly on the guest molecular length. The longer the guest molecule and the smaller the cavity size of the cyclodextrin, the greater is the percentage mass loss. It is negatively correlated with the guest molecule polarity and molecular bulkiness (steric factor) but directly correlated to ring substitution with polar amino and hydroxyl groups (valence index 0).

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