J Incl Phenom Macrocycl Chem (2007) 57:545–552
DOI 10.1007/s10847-006-9247-2

ORIGINAL ARTICLE

The complexation efficiency

Thorsteinn Loftsson · Dagný Hreinsdóttir · Már Másson

Received: 15 May 2006 / Accepted: 20 October 2006 / Published online: 23 January 2007
© Springer Science+Business Media B.V. 2007

Abstract Studies have shown that cyclodextrins form both inclusion and non-inclusion complexes and that several different types of complexes can coexist in aqueous solutions. In addition, both cyclodextrins and cyclodextrin complexes are known to form aggregates and it is thought that these aggregates are able to solubilize drugs through micellar-type mechanism. Thus, stability constants determined from phase-solubility profiles are rarely true stability constants for of some specific drug/cyclodextrin complexes. A more precise method for evaluation of the solubilizing effects of cyclodextrins is to determine their complexation efficiency (CE). CE can be determined by measuring the solubility of a given drug at 2–3 cyclodextrin concentrations in pure water or a medium constituting the pharmaceutical formulation such as parenteral solution or aqueous eye drop formulation. Based on the CE value the drug:cyclodextrin ratio in the complexation medium can be determined as well as the increase in the formulation bulk in a solid dosage form. Determination of CE is a simple method for quick evaluating the solubilizing effects of different cyclodextrins and/or the effects of excipients on the solubilization. Here we report the CE of 43 different drugs with mainly 2-hydroxypropyl-β-cyclodextrin but also with randomly methylated β-cyclodextrin as well as few other cyclodextrins. Calculation of CE, drug:cyclodextrin molar ratio and the increase in the formulation bulk is discussed, as well as the influence of the intrinsic solubility and drug lipophilicity on the CE.

T. Loftsson (✉) · D. Hreinsdóttir · M. Másson
Faculty of Pharmacy, University of Iceland, Hofsvallagata 53, 107 Reykjavik, Iceland
e-mail: thorstlo@hi.is

Keywords Cyclodextrin · Complex · Solubility · Solubilization · Aggregation

Introduction

Until recently it has been believed that when a molecule forms a complex with cyclodextrin then some given lipophilic moiety of the molecule enters into the hydrophobic cyclodextrin cavity, i.e. that an inclusion complex is always formed. It has also been assumed that the aqueous complexation medium is an ideal solution where the individual complexes are independent of each other. The most common stoichiometry of drug/cyclodextrin complexes is 1:1, i.e. one drug molecule forms a complex with one cyclodextrin molecule, and the most common method for stoichiometric determination during formulation studies is the phase-solubility method [1–3]. However, studies by several different research groups have shown that cyclodextrins form both inclusion and non-inclusion complexes and that several different types of complexes can coexist in aqueous solutions. Furthermore, both cyclodextrins and cyclodextrin complexes are known to form aggregates and it is thought that these aggregates are able to solubilize drugs and other hydrophobic molecules through micellar-type mechanism [1, 4, 5]. In addition, common pharmaceutical excipients, such as polymers and buffer salts, can participate in the complex formation [6]. Thus, stability constants obtained from phase-solubility diagrams are apparent stability constants describing the combined effect of the various complex structures on the drug solubility.

To complicate matters further the apparent stability constant ($K_{1:1}$) of the apparent 1:1 drug/cyclodextrin

complex is determined from the slope and the intrinsic solubility (S_0) of the drug in the aqueous complexation medium. Theoretically the intercept (S_{int}) of the phase-solubility diagram should be identical to S_0 [2]. For poorly soluble drugs with aqueous solubility <0.1 mM, S_0 is in general much larger than S_{int} resulting in non-linearity of otherwise linear (A_L-type) phase-solubility diagram [7, 8]. This can lead to erroneous $K_{1:1}$-values. Thus, due to inaccuracy of the determined S_0 and S_{int} values the apparent stability constants are frequently very inaccurate and very sensitive to the composition of the aqueous complexation medium. A more accurate method for determination of the solubilizing efficiency of cyclodextrins is to determine their complexation efficiency (CE), i.e. the concentration ratio between cyclodextrin in a complex and free cyclodextrin. CE is calculated from the slope of the phase-solubility diagrams and is independent of both S_0 and S_{int}. The purpose of this study is to determine the CE of various drugs and cyclodextrins and show how the CE is used to determine the formulation bulk of solid dosage forms. Also, the relationship between the S_0 or the lipophilicity of the water-insoluble drug and its CE was investigated.

Experimental

Data collection

The drug solubility data was generated in our lab over the past 15 years during various drug preformulation studies. Many of the formulation studies resulted in publication but some have remained unpublished [8].

Solubility determinations

The solubility of the drugs in water or aqueous cyclodextrin solutions was determined by a heating method [8, 9]. First, the stability of the drug in the aqueous complexation media was evaluated. Small amount of the drug to be tested was dissolved in aqueous cyclodextrin solution. The solution was then divided into four sealed vials that were heated in an autoclave for 0–3 heating cycles; each cycle consisted of heating to 121 °C for 20 min. The drug concentrations in the vials were then determined by a high-performance liquid chromatographic method (HPLC). If the drug degradation was less than 1% during one cycle then the heating method in an autoclave was applied. If the degradation was greater then heating in autoclave was replaced by heating in an ultrasonic bath for 1 h at 60–70 °C. The maximum allowable drug degradation during the solubility studies was under all circumstances 1%. The drug solubility was then determined as follows:

1. Specific amount of cyclodextrin was dissolved in water, aqueous buffer solution or the aqueous formulation vehicle.
2. An excess amount of the drug to be tested was added to the aqueous cyclodextrin solution.
3. The suspension formed was placed in a sealed container and heated in an autoclave (121 °C for 20 min) or sonicated in an ultrasonic bath (at e.g. 70 °C for 1 h). After cooling to ambient temperature the container was opened and a small amount of the solid drug added to the container to promote drug precipitation.
4. After equilibration at ambient temperature (22–23 °C) in a sealed container under constant agitation for 3–7 days, the suspension was filtered through a 0.45 μm membrane filter (discarding approx. the first third of the filtrate) and the solution analyzed by HPLC (after dilution with 70% aqueous methanol solution, if necessary). The time needed to reach equilibrium solubility was determined by analyzing samples of the equilibrating solution at different time points to establish constant drug solubility.

The CE was calculated from slope of the phase-solubility profiles where the molar cyclodextrin concentration is on the X-axis and the molar drug solubility on the Y-axis.

Theoretical background

The most common type of cyclodextrin complexes is the apparent 1:1 drug/cyclodextrin complex (D/CD) where one drug molecule (D) forms a complex with one cyclodextrin molecule (CD):

$$\mathrm{D} + \mathrm{CD} \overset{K_{1:1}}{\leftrightarrows} \mathrm{D/CD} \tag{1}$$

The value of the stability constant ($K_{1:1}$) is used to compare the affinity of drugs for different cyclodextrins or cyclodextrin derivatives. The total solubility of drug (S_t) in aqueous cyclodextrin solution will then be:

$$S_t = S_0 + \frac{K_{1:1} \cdot S_0}{1 + K_{1:1} \cdot S_0} \cdot [\mathrm{CD}]_t \tag{2}$$

where S_0 is the intrinsic solubility of the drug, i.e. the solubility when no cyclodextrin is present, and $[CD]_t$ is the total concentration of cyclodextrin in the aqueous medium. A plot of S_t versus $[CD]_t$, according to Eq. (2) (i.e. a phase-solubility profile), will give a straight line

with a slope ($K_{1:1}\cdot S_0/(1 + K_{1:1}\cdot S_0)$) less than unity and an intercept (S_{int}) equal to S_0. Then $K_{1:1}$ is calculated from the slope and S_0 according to Higuchi and Connors [2]:

$$K_{1:1} = \frac{\text{Slope}}{S_0(1 - \text{Slope})} \quad (3)$$

However, the $K_{1:1}$ value determined by Eq. (3) is strongly affected by the S_0 value which is usually very inaccurate for compounds with $S_0 < 0.1$ mg/ml [8].

It is well documented that both cyclodextrins and cyclodextrin complexes self-aggregate and that cyclodextrins are able to form non-inclusion complexes in addition to the well-known inclusion complexes (Table 1). In a recent publication Bonini et al. describe how β-cyclodextrin (βCD) aggregates in pure water to form differently shaped aggregates with a minimum hydrodynamic radius of about 90 nm at low βCD concentration that are in equilibrium with larger structures (i.e. disks and sheets) at higher βCD concentrations [10]. Previously Coleman et al. [11] had shown that the three natural cyclodextrins, αCD, βCD and γCD, exist as aggregates in solution bound together by a network of hydrogen bonds. The self-aggregation is partly concentration dependent, increasing with increasing cyclodextrin concentration. Furthermore, multi component ternary and quaternary cyclodextrin complexes have also been observed [6, 12, 13]. Thus, stability constants, such as $K_{1:1}$, obtained from phase-solubility diagrams are most frequently observed constants that are composed of a number of true stability constants for multiple types of coexisting water-soluble drug complexes in the aqueous complexation media. This coexistence of multiple types of complexes could also explain why the experimentally determined values of $K_{1:1}$ are highly sensitive to both the method applied and the composition of the medium [1]. A more reliable method for evaluation of cyclodextrins and their solubilizing potentials is to determine the CE, which is equal to the complex to free cyclodextrin concentration ratio and can be obtained from the slope of their phase-solubility profile [14]:

$$\text{CE} = S_0 \cdot K_{1:1} = \frac{[\text{D/CD}]}{[\text{CD}]} = \frac{\text{Slope}}{(1 - \text{Slope})} \quad (4)$$

Where [D/CD] is the concentration of dissolved complex, [CD] is the concentration of dissolved free cyclodextrin and Slope is the slope of the phase-solubility profile. The CE can be used to calculate the D:CD ratio, which can be correlated to the expected increase in formulation bulk:

$$\text{D:CD} = 1 : \left(1 + \frac{1}{\text{CE}}\right) \quad (5)$$

Results and discussion

Table 2 displays the CE for a number of drugs and a number of cyclodextrins although mainly for

Table 1 Some publication showing formation of cyclodextrin aggregates and/or non-inclusion complex formation

Title of the article	Ref.
Extended 2,5-diphenyloxazole-γ-cyclodextrin aggregates emitting 2,5-diphenyloxazole excimer fluorescence	[15]
^{2}H NMR study of the self-assembly of an azo dye-cyclomaltooctanose (γ-CD) complex	[16]
Phase transition pattern of 2,5-diphenyloxazole/γ-cyclodextrin (PPO/γ-CD) self-assembly aggregates	[17]
Inclusion compounds of psychotropic agents and cyclodextrins	[18]
Non-covalent association of cyclomaltooligosaccharides (cyclodextrins) with trans-β-carotene in water: evidence for the formation of large aggregates by light scattering and NMR spectroscopy	[19]
Self-association and cyclodextrin solubilization of drugs	[5]
Cyclodextrins and drug permeability through semi-permeable cellophane membranes	[20]
The aggregation of cyclodextrins as studied by photon correlation spectroscopy	[21]
Self-association and cyclodextrin solubilization of NSAIDs	[4]
On the specificity of cyclodextrin complexes detected by electrospray mass spectrometry	[22]
Study of inclusion complexes of acridine with β- and (2,6-di-*O*-methyl)-β-cyclodextrin by use of solubility diagrams and NMR spectroscopy	[23]
Influence of response factors on determining equilibrium association constants of non-covalent complexes by electrospray ionization mass spectrometry	[24]
Self-association of cyclodextrins and cyclodextrin complexes	[1]
Higher-order cyclodextrin complexes: the naphthalene system	[25]
Cyclodextrin solubilization of the antibacterial agents triclosan and triclocarban: formation of aggregates and higher-order complexes	[6]
Evaluation of cyclodextrin solubilization of drugs	[8]
Preparation of celecoxib-dimethyl-β-cyclodextrin inclusion complex: characterization and in vitro permeation study	[26]
Self-assembly of β-cyclodextrin in water. Part 1: cryo-TEM and dynamic and static light scattering	[10]

Table 2 Physicochemical properties, CE and formulation bulk of selected drugs

Drug[a]	MW (Dalton)	MP (°C)	log$K_{o/w}^{b}$	pK_a^c	Cyclodextrin[d]	pH[e]	S_0^f (mg/ml)	CE[g]	Dose[h] (mg)	Molar ratio[i]	Formulation bulk[j] (mg)
Acetazolamide (A)	222	260	–0.72	7.2	HPαCD	W	0.64	0.015	250	1:68	94,000
					HPβCD	W	0.64	0.197	250	1:6	9,700
					HPβCD	3.6	0.76	0.156	250	1:7	11,000
					HPβCD	6.4	1.4	0.128	250	1:9	14,000
					RMβCD	W	0.64	0.566	250	1:3	4,700
					HPγCD	W	0.64	0.021	250	1:49	86,000
Alfaxalone	333				HPβCD	W	0.05[k]	1.24	250	1:2	2,500
Alprazolam (B)	309	228	3.87	2.4	HPβCD	6	0.073	0.058	0.25	1:18	20
Benzoic acid (A)	122	122	1.87	4.2	HPβCD	W	2.4	2.343	4.5	2:3	80
Bupivacaine (B)	288	108	3.44	8.1	HPβCD	W	0.225	0.045	200	1:23	22,400
					HPβCD	3.7	0.14	0.161	200	1:7	7,040
					HPβCD	7.7	6.41	0.727	200	1:3	3,120
Calcipotriol	413	167			RMβCD	8	0	0.385	5	1:4	70
Carbamazepine (B)	236	191	2.25	7	HPβCD	W	0.3	0.548	100	1:3	1,900
					HPβCD	6.26	0.06	0.679	100	1:3	1,900
					RMβCD	W	0.3	0.476	100	1:3	1,800
Cholecalciferol	385	84	10.24		HPβCD	W	0.1	0.019	2.5	1:54	490
Clotrimazole	345	148	6.26		HPβCD	W	0.03	0.05	100	1:21	8,500
Cyclosporine A	1203	150	1		αCD	W	0.008	0.011	25	1.91	1,900
					HPαCD	W	0.008	0.004	25	1:250	6,400
					RMβCD	W	0.008	0.007	25	1:150	4,100
Dexamethasone	393	270	1.72		HPβCD	W	0.159	0.326	0.25	1:4	4
Dextromethorphan (B)	271	111	3.97	8.3	RMβCD	10	0.06	1.96	30	2:3	250
					SBEβCD	10.5	0.12	1.91	30	2:3	390
Diazepam (B)	285	133	2.7	3.3	HPβCD	3.6	0.5199	0.187	15	1:6	460
					HPβCD	7.7	0.1855	0.267	15	1:5	380
Diethylstilbestrol	268	171			HPβCD	5.4	0	2.824	1.5	3:4	10
Digoxin	781	240	0.5		HPβCD	4.4	0.99	0.435	0.05	1:3	0.3
Econazole	382	87			HPβCD	W	0.37	0.17	150	1:7	4,000
					HPβCD	3.1	0.157	0.208	150	1:6	3,500
Estradiol	272	176	3.94		HPβCD	W	0.078	0.322	0.5	1:4	10
					RMβCD	W	0.078	0.946	0.5	1:2	5
Ethoxyzolamide (A)	258	192	2.08	8.1	HPβCD	W	0.039	0.067	10	1:16	880
					HPβCD	3.5	0.1124	0.044	10	1.24	1,300
					HPβCD	7.6	0.0826	0.101	10	1:11	610
Finasteride	373	254	3.2		HPβCD	7	0.06	0.625	5	1:3	60
					SBEβCD	7	0.06	0.678	5	1:3	90
					RMβCD	6	0.05	0.708	5	1:3	60
Flunitrazepam (B)	313	170	1.91	1.8	HPβCD	W	0.004	0.01	1	1:100	450
					G1βCD	W	0.004	0.006	1	1:170	710
					MβCD	W	0.004	0.025	1	1:41	150
Fluoxetine HCl (A)	346	138	4.65	8.7	HPβCD	3.6	12.59	4.698	10	5:6	60
Hydrocortisone	363	214	1.62		HPβCD	W	0.418	1.164	5	1:2	40
					HPβCD	7.1	0.406	1.277	5	1:2	40
					HPβCD	5.3	0.721	1.318	5	1:2	40
					HPβCD	3.5	1.87	0.73	5	1:3	60
					RMβCD	W	0.418	1.896	5	2:3	30
Ketoconazole	531	150			HPβCD	W	0.01	1.34	200	1:2	1,300
Ketoprofen (A)	254	95	3	4.5	HPβCD	4	0.01	1.508	25	1:2	300
Lidocaine (B)	234	69	1.66	7.9	HPβCD	W	3.58	0.417	350	1:3	6,600
Methazolamide (A)	236	213	0.33	7.3	HPβCD	4.7	0.704	0.101	50	1:11	3,300
Methylparaben (A)	152	131	2	8.4	HPβCD	W	3.16	0.953	100	1:2	1,900
Miconazole (B)	416	182	6.25	6.7	HPethylβCD	W	0.089	0.087	1000	1:12	39,000
					HPβCD	W	0.089	0.105	1000	1:11	38,000
Omeprazole (A)	345	156	3.4	4	HPβCD	W	0.018	0.002	15	1:500	30,000
Oxazepam (B)	287	206	2.32	1.7	HPβCD	W	0.05	0.109	10	1:10	500
					RMβCD	W	0.05	0.163	10	1:7	330
Prazepam (B)	325	146	3.99	2.7	HPβCD	W	0.005	0.018	5	1:56	1,200
					G1βCD	W	0.005	0.019	5	1:54	1,100
					MβCD	W	0.005	0.028	5	1:37	680
					G2βC	W	0.005	0.016	5	1:63	1,400

Table 2 continued

Drug[a]	MW (Dalton)	MP (°C)	log$K^{b}_{o/w}$	pK^{c}_{a}	Cyclodextrin[d]	pH[e]	S^{f}_{0} (mg/ml)	CE[g]	Dose[h] (mg)	Molar ratio[i]	Formulation bulk[j] (mg)
Prednisolone	360	241	1.4		HPethylβCD	W	0.3376	1.526	5	2:3	30
					HPβCD	4	0.423	1.049	5	1:2	40
Pregnenolone	317	189	3.89		HPβCD	W	0.033	0.123	10	1:9	410
Progesterone	315	127	3.67		HPβCD	W	0.0006	0.315	40	1:4	750
					HPγCD	W	0.0006	0.219	40	1:6	1,200
Propofol (A)	178	19	3.57	11	RMβCD	W	0.16	2.205	10	2:3	120
					SBEβCD	W	0.16	4.105	10	4:5	130
					HPβCD	W	0.16	1.44	10	1:2	170
Retinol All-trans	300	62	7.62		HPβCD	W	0.044	0.007	0.25	1:150	180
Sulfamethoxazole (A)	253	167	0.48	5.6	HPethylβCD	W	0.402	0.543	400	1:3	6,700
					HPβCD	6.5	3.92	0.696	400	1:3	7,000
					HPβCD	W	0.402	0.561	400	1:3	7,000
Tamoxifen	372	97			HPβCD	6.4	0	0.004	10	1:250	9,400
Temazepam (B)	301	158	2.15	1.6	HPβCD	W	0.604	0.126	7.5	1:9	320
Terfenadine	472	148			HPβCD	7	0	0.294	60	1:4	770
Triamcinolone acetonide	435	293	0.96		HPβCD	W	0.114	0.241	1	1:5	15
Triazolam (B)	343	234	3.96	2.4	HPβCD	>3.5	0.03	0.017	0.25	1:60	60
Trimethoprim (B)	290	204	0.73	6.6	HPβCD	W	1.37	0.179	80	1:7	2,800

[a] Proton donor (A); proton acceptor (B)

[b] Calculated logarithm of the octanol/water partition coefficient, based on structure (www.syrres.com)

[c] pK_a values from literature [27]

[d] 2-Hydroxypropyl-α-cyclodextrin (HPαCD); 2-hydroxypropyl-β-cyclodextrin (HPβCD); randomly methylated β-cyclodextrin (RMβCD); 2-hydroxypropyl-γ-cyclodextrin (HPγCD); α-cyclodextrin (αCD); sulfobutylether β-cyclodextrin sodium salt (SBEβCD); glucosyl-β-cyclodextrin (G1βCD); 2-hydroxypropyl-ethyl-β-cyclodextrin (HPethylβCD); maltosyl-β-cyclodextrin (G2βCD); 2,3-dimethyl-β-cyclodextrin (MβCD)

[e] The pH of the complexation medium; unbuffered pure water (W)

[f] Drug solubility in the complexation medium when no cyclodextrin is present

[g] The CE calculated from the slope of a phase solubility diagram according to Eq. (4)

[h] Oral dosage, estimated values or literature values

[i] The drug:cyclodextrin molar ratio bases on the calculated CE according to Eq. (5)

[j] The formulation bulk of a solid dose containing the drug/cyclodextrin complex equivalent to the oral drug dose (see Eq. (6))

[k] From ref. [28]

2-hydroxypropyl-βCD (HPβCD) and randomly methylated βCD (RMβCD). The mean (±standard deviation (SD)) CE of HPβCD (degree of substitution 0.6) for 13 different drugs in Table 2 in pure water was determined to be 0.39 ± 0.47 indicating that on the average only about 1 out of every 3–4 HPβCD molecules in solution are forming a water-soluble complex with the poorly soluble drug, assuming 1:1 drug/HPβCD complex formation (i.e. that the D:CD ratio is on the average about 1:3.6). For six of the drugs in Table 2, the CE for both RMβCD (randomly methylated βCD, degree of substitution 1.8) and HPβCD (degree of substitution 0.6) was determined under identical conditions. For those six drugs the mean (±SD) value for CE in pure water at room temperature (22–23 °C) was 1.04 ± 0.75 for RMβCD (D:CD ratio is on the average about 1:2) but 0.63 ± 0.50 for HPβCD (D:CD ratio is on the average about 1:2.6). This confirms what a number of other studies have shown, that in aqueous solutions RMβCD is most often a better solubilizer than HPβCD.

Equation (6) shows the correlation between the increase in formulation bulk and molecular weights of the cyclodextrin (MW_{CD}) and the drug (MW_{Drug}), and the value of CE:

$$\text{Increase in Formulation bulk} = \frac{MW_{CD}}{MW_{Drug}} \times \left(1 + \frac{1}{CE}\right) \quad (6)$$

The new formulation bulk can be found by multiplying the number obtained from Eq. (6) with the drug dose. The MW of the natural βCD is 1,135 Dalton and the MW of the three most common βCD derivatives are 1,310 Dalton for RMβCD, 1,400 Dalton for

HPβCD and 2,163 Dalton for sulfobutylether β-cyclodextrin sodium salt (SBEβCD). Thus, based on Eq. (6) the βCD derivatives will result in 15–90% greater increase in the formulation bulk than the parent βCD, assuming that the CE will not be effected by the derivation of the βCD molecule.

Figure 1 shows the CE as function of the octanol/water partition coefficient ($\log K_{o/w}$), the intrinsic solubility (S_0) in pure water, the melting point (MP) and the molecular weight (MW) of the drug. No linear correlation is between CE and any of these physicochemical properties. However, the figure shows that drugs possessing $\log K_{o/w}$ between 1 and 4 frequently show good CE with both HPβCD and RMβCD, and that drugs possessing $\log K_{o/w}$ greater than 4 are likely to have low CE with these same βCD derivatives (Fig. 1A). Equations (1) and (4) indicate that drugs possessing very low S_0 (i.e. low [D]) should in general have low CE and Fig. 1B appears to confirm that, since the highest CE is obtained with drugs possessing S_0 greater than about 0.01 mg/ml. The four most lipophilic drugs in Fig. 1A have $\log K_{o/w}$ greater than six and it could be assumed that these same four drugs would also have the lowest S_0 values. However, although their mean $\log K_{o/w}$ value is 7.6 (range 6.3–10) their mean S_0 value is 0.07 (range 0.03–0.1) mg/ml, or well above 0.01 mg/ml (Table 2). There is no obvious correlation between the CE and the MW or MP of the drug (Fig. 1C and D).

The CE can be estimated by determining the solubility of a given drug at two to three cyclodextrin concentrations in pure water or a medium constituting the pharmaceutical formulation such as parenteral solution or aqueous eye drop formulation. Based on the CE value the drug:cyclodextrin ratio can be determined in the complexation medium as well as the increase in the formulation bulk in a solid dosage form. Determination of the CE is a simple method for a quick evaluation of the solubilizing effects of different cyclodextrins and/or the effects of excipients on the solubilization.

The CE can be used asses the feasibility of using cyclodextrins in the formulation of drugs. For example, a reasonable upper limit for the maximum bulk of a cyclodextrin formulation, to be used in a solid oral dosage form, would be one gram. Analysis of the data in Table 2 (Fig. 2) shows that this target cannot be reached when the single oral dose of a drug is greater than 250 mg. In general, the formulation bulk will be less than one gram when the single oral dose is less than 50 mg and CE is greater than 0.1. This applies to only half of the more potent drugs possessing CE less than 0.1. Consequently, when cyclodextrin formulation for oral dosage forms is to be considered the drug has to be

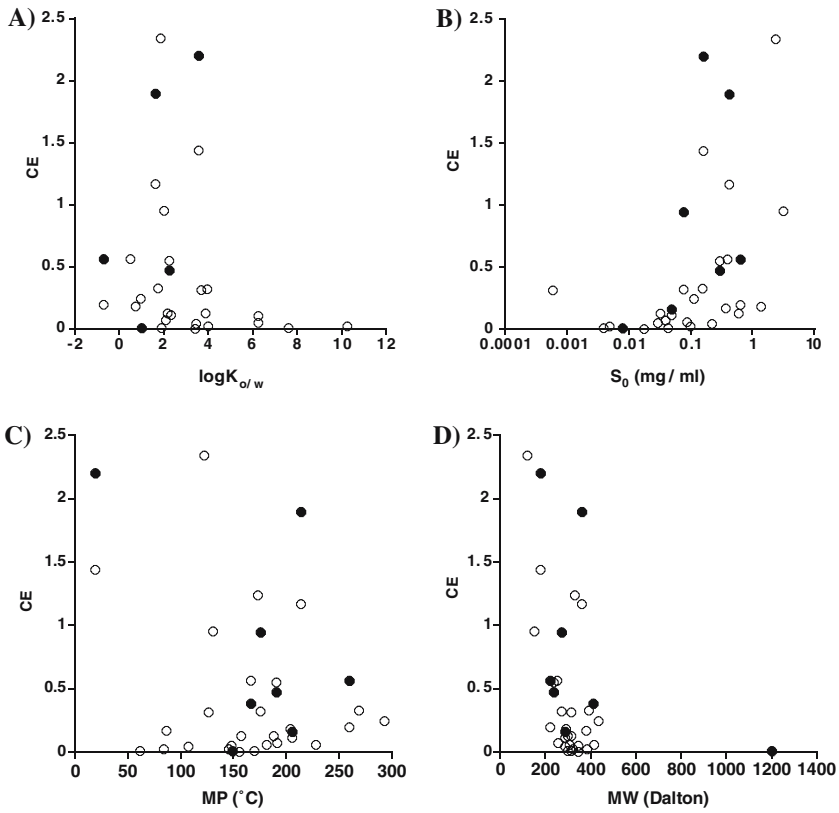

Fig. 1 The CE as a function of (**A**) the logarithm of the *n*-octanol/water partition coefficient ($\log K_{o/w}$), (**B**) logarithm of the intrinsic solubility (S_0) in pure water, (**C**) the melting point (MP) in °C, and (**D**) the molecular weight (MW) in Dalton. HPβCD (○) and RMβCD (●)

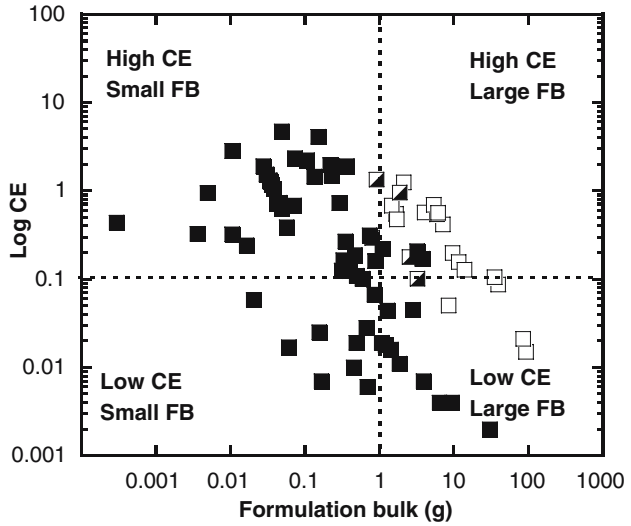

Fig. 2 The CE as a function of formulation bulk for drugs with a single oral dose of ≥250 mg (□), between ≥50 and <250 mg (▲) or <50 mg (■). Based on the data presented in Table 1

relatively potent and preferably it's CE has to be greater than 0.1. For other types of drug formulations, such as eye drops or infusion solutions, more stringent or relaxed conditions for potency and CE can be defined.

Acknowledgement This work was supported by a grant from the University of Iceland Research Fund.

References

1. Loftsson, T., Másson, M., Brewster, E.M.: Self-association of cyclodextrins and cyclodextrin complexes. J. Pharm. Sci. **93**, 1091–1099 (2004).
2. Higuchi, T., Connors, A.K.: Phase-solubility techniques. Adv. Anal. Chem. Instrum. **4**, 117–212 (1965).
3. Loftsson, T., Jarho, P., Másson, M., Järvinen, T.: Cyclodextrins in drug delivery. Expert Opin. Drug Deliv. **2**, 335–351 (2005).
4. Magnusdottir, A., Másson, M., Loftsson, T.: Self association and cyclodextrin solubilization of NSAIDs. J. Incl. Phenom. Macroc. Chem. **44**, 213–218 (2002).
5. Loftsson, T., Magnúsdóttir, A., Másson, M., Sigurjónsdóttir, J.F.: Self-association and cyclodextrin solubilization of drugs. J. Pharm. Sci. **91**, 2307–2316 (2002).
6. Duan , M., Zhao, N., Össurardóttir, Í.B., Thorsteinsson, T., Loftsson, T.: Cyclodextrin solubilization of the antibacterial agents triclosan and triclocarban: formation of aggregates and higher-order complexes. Int. J. Pharm. **297**, 213–222 (2005).
7. Loftsson, T., Brewster, E.M., Másson, M.: Role of cyclodextrins in improving oral drug delivery. Am. J. Drug Deliv. **2**, 261–275 (2004).
8. Loftsson, T., Hreinsdóttir, D., Másson, M.: Evaluation of cyclodextrin solubilization of drugs. Int. J. Pharm. **302**, 18–28 (2005).
9. Loftsson, T., Hreinsdóttir, D.: Determination of aqueous solubility by heating and equilibration: a technical note. AAPS PharmSciTech. **7**(1), www.aapspharmscitech.org (2006).
10. Bonini, M., Rossi, S., Karlsson, G., Almgren, M., Lo Nostro, P., Baglioni, P.: Self-assembly of β-cyclodextrin in water. Part 1: Cryo-TEM and dynamic and static light scattering. Langmuir **22**, 1478–1484 (2006).
11. Coleman, W.A., Nicolis, I., Keller, N., Dalbiez, P.J.: Aggregation of cyclodextrins: an explanation of the abnormal solubility of β-cyclodextrin. J. Incl. Phenom. Macroc. Chem. **13**, 139–143 (1992).
12. Loftsson, T., Másson, M.: The effects of water-soluble polymers on cyclodextrins and cyclodextrin solubilization of drugs. J. Drug Del. Sci. Tech. **14**, 35–43 (2004).
13. Yamakawa, T., Nishimura, S.: Liquid formulation of a novel non-fluorinated topical quinolone, T-3912, utilizing the synergic solubilizing effect of the combined use of magnesium ions and hydroxypropyl-β-cyclodextrin. J. Control. Rel. **86**, 101–113 (2003).
14. Loftsson, T., Másson, M., Sigurjónsdóttir, J.F.: Methods to enhance the complexation efficiency of cyclodextrins. S.T.P. Pharma Sci. **9**, 237–242 (1999).
15. Agbaria, A.R., Gill, D.: Extended 2,5-diphenyloxazole-gamma-cyclodextrin aggregates emitting 2,5 diphenyloxazole excimer fluorescence. J. Phys. Chem. **92**, 1052–1055 (1988).
16. Suzuki, M., Tsutsui, M., Ohmori, H.: ^{2}H NMR study of the self-assembly of an azo dye-cyclomaltooctanose (γ-cyclodextrin) complex. Carbohydr. Res. **264**, 223–230 (1994).
17. Agnew, A.K., McCarley, D.T., Agbaria, A.R., Warner, M.I.: Phase transition pattern of 2,5-diphenyloxazole/g-cyclodextrin (PPO/g-CD) self-assembly aggregates. J. Photochem. Photobiol. A Chem. **91**, 205–210 (1995).
18. Andronati, A.S., Shapiro, E.Y., Yakubovskaya, N.L., Gorbatyuk, Y.V., Andronati S.K., Krasnoschekaya, P.S.: Inclusion compounds of psychotropic agents and cyclodextrins. J. Incl. Phenom. Macroc. Chem. **24**, 175–186 (1996).
19. Mele, A., Mendichi, R., Selva, A.: Non-covalent associations of cyclomaltooligosaccharides (cyclodextrins) with *trans*-β-carotene in water: evidence for the formation of large aggregates by light scattering and NMR spectroscopy. Carbohydr. Res. **310**, 261–267 (1998).
20. Loftsson, T., Másson, M., Sigurdsson, H.H.: Cyclodextrins and drug permeability through semi-permeable cellophane membranes. Int. J. Pharm. **232**, 35–43 (2002).
21. González-Gaitano, G., Rodríguez, P., Isasi, R.J., Fuentes, M., Tardajos, G., Sánchez, M.: The aggregation of cyclodextrins as studied by photon correlation spectroscopy. J. Incl. Phenom. Macrocycl. Chem. **44**, 101–105 (2002).
22. Gabelica, V., Galic, N., De Pauw, E.: On the specificity of cyclodextrin complexes detected by electrospray mass spectrometry. J. Am. Soc. Mass Spectrom. **13**, 946–953 (2002).
23. Correia, I., Bezzenine, N., Ronzani, N., Platzer, N., Beloeil, J.-C., Doan, B.-T.: Study of inclusion complexes of acridine with β- and (2,6-di-*O*-methyl)-β-cyclodextrin by use of solubility diagrams and NMR spectroscopy. J. Phys. Org. Chem. **15**, 647–659 (2002).
24. Gabelica, V., Galic, N., Rosu, F., Houssier, C., De Pauw, E.: Influence of response factors on determining equilibrium association constants of non-covalent complexes by electrospray ionization mass spectrometry. J. Mass Spectrom. **38**, 491–501 (2003).
25. Sau, S., Solanki, B., Orprecio, R., van Stam, J., Evans, H.C.: Higher-order cyclodextrin complexes: the naphtha-

lene system. J. Incl. Phenom. Macroc. Chem. **48**, 173–180 (2004).
26. Ventura, A.C., Giannone, I., Paolino, D., Pistarà, V., Corsaro, A., Puglisi, G.: Preparation of celecoxib-dimethyl-β-cyclodextrin inclusion complex: characterization and in vitro permeation study. Eur. J. Med. Chem. **40**, 624–631 (2005).
27. Moffat, C.A., Osselton, D.M., Widdop, B. (eds.): 3rd ed. Clarke's Analysis of drugs and poisons. Vol. 2. Pharmaceutical Press, London (2004).
28. Peeters, J., Neeskens, P., Adriaensen, J., Brewster, M.: Alfaxalone: effect of temperature on complexation with 2-hydroxypropyl-β-cyclodextrin. J. Incl. Phenom. Macroc. Chem. **44**, 75–77 (2002).