

Some comments on the Cyclodextrin solubilities

Abstract

The cyclodextrin (CD) solubilities in various solvent systems are discussed. The erroneous aqueous solubility-temperature equations have been substituted with simpler ones. The new equations calculate the CD solubilities in water more accurately. Re-calculation of the literature data of organic solvent-water mixtures from molar fractions to volume percentage of organic solvents resulted in a more user friendly data

Keywords: water-organic solvent mixtures, aqueous solubility equation, nonlinear curve fitting

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Cyclodextrins (CDs, cyclic, $\alpha(1\rightarrow4)$ linked oligosaccharides) have become important additives in various pharmaceutical, food, fragrance, and agricultural applications since their safety and biocompatibility issues clarified.¹⁻⁴ Both natural and derivatized CDs are used in various analytical methods, too. The macrocyclic structure, where the cavity is less hydrophilic than the hydroxyl rims, is suitable to form non covalent, host-guest complexes. Usually these complexes are called inclusion complexes. However it is also true that in numerous cases the real inclusion association can be found only in solid, crystalline state. In solution a dynamic equilibrium exists and the molecular interactions other than complexation also heavily influence the physicochemical properties of the system.

Among the most commonly used CDs the β CD has the lowest aqueous solubility. Despite the fact that α - and γ CD are considerably better soluble in water in many cases their complexes can precipitate in diluted solutions, too.⁵ The relatively rigid, truncated cone structure is suitable to form H-bonded associations of the natural CDs which considerably reduces the aqueous solubility. Reducing the ability of the CD self-associations, like derivatizations, the aqueous solubility can be increased. The complex formation can increase the solubility of the guest although many times it is forgotten that the host molecule solubility can also be changed.⁶ Addition of poorly complexing hydrotropic materials or shifting the pH to basic can also increase the CD solubility. The destruction of the circular hydrogen bond system at the secondary alcohol rim prevents the formation the CD associations which increases the CD solubility.

Another important factor is the water content of the natural CDs. In many times the users, particularly who is not familiar with the CDs, tend to forget that natural cyclodextrins, as they are from the suppliers, are rather CD-hydrates ($\approx 10\%$ (α/γ) or $\approx 14\%$ (β) water content). This affects the aqueous solubilities and often causes misunderstanding in literature data. Despite the availability of data in old publications they are difficult to compare and so the fast availability of the information is restricted. A further confusion is that the data range is not really wide and incomplete. Extrapolation of data is always risky, particularly when misleading or confused information is found in the literature. Calculation of CD solubilities in water by the equations 1-3, (from p.13 in Szejtli et al.³ and p.10 in Jin⁷) results in noticeable deviations as it is seen in Figure 1. The equations are derived from least-squares fits to experimental data of Jozwiakowski et al.⁹ according to Szejtli et al.³

$$\alpha\text{CD}c = (112.71 \pm 0.45) * e^{(-3530 \pm 31) * (1/T - 1/298.1)} \text{-----Equation 1}$$

$$\beta\text{CD}c = (18.3236 \pm 0.099) * e^{(-14137 \pm 31) * (1/T - 1/298.1)} \text{-----Equation 2}$$

$$\gamma\text{CD}c = (219.4 \pm 9.8) * e^{(-3187 \pm 320) * (1/T - 1/298.1)} \text{-----Equation 3}$$

Where c is the concentration in mg/ml of dried CDs and T is the temperature in Kelvin.³

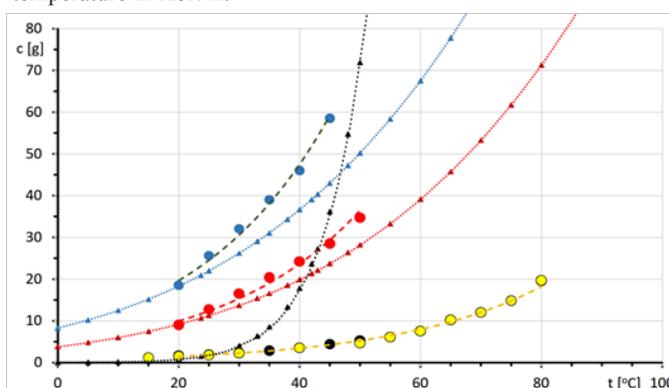


Figure 1 Temperature dependent solubilities of CDs in water, using the published^{3,17} equations (1-3)

Experimental values of α CD, β CD, γ CD are from³, and β CD is from⁸

The incorrect parameters are especially striking for β CD (Figure 1). Re-examining the literature^{3,8-12} and fitting new exponential curves using Microsoft Excel (2013) to the experimental data, a better estimation of the missing data is possible by the proposed Eqs. 4-6. But extrapolations should still be treated with due care, particularly when the estimated range is far from the values used in the parameter estimation.

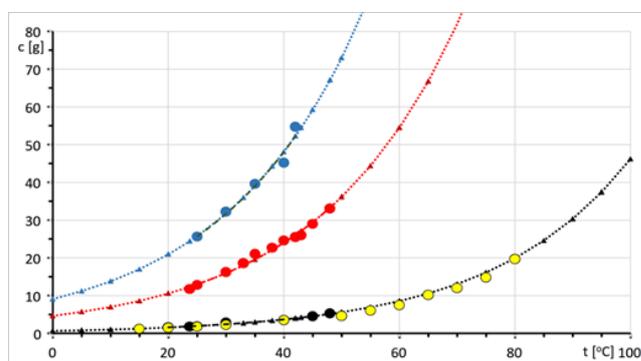


Figure 2 Temperature dependent solubilities of CDs in water, using the updated equations (4-6)

$$\alpha\text{CD}c = 4.68434 * e^{0.040894 * t} \text{R}2 = 0.9881 \text{-----Equation 4}$$

$$\beta\text{CD}c = 0.68894 * e^{0.042060 * t} \text{R}2 = 0.9769 \text{-----Equation 5}$$

$$\gamma\text{CD } c = 9.11294 * e^{0.041616 * t} \quad R^2 = 0.9817 \text{-----Equation 6}$$

Where c is the concentration of dried CDs in g/100ml water and t is the temperature in Celsius.

The correlation coefficients are good enough but not excellent what is the consequence of the relatively high experimental errors. Unfortunately, particularly at the higher temperatures, the extrapolated data of α - and γ CDs are noticeably overestimated and they are poorly acceptable. Owing to a wide temperature-range experimental data of β CD the solubility estimation of β CD is better but the values over the upper limit are also not reasonable. Using the CDs as is, in their commercial form, the calculated solubilities are slightly higher, i.e. at room temperature $\approx 14\text{g } \alpha\text{CD}$, $\approx 2.2\text{g } \beta\text{CD}$, and $\approx 28\text{g } \gamma\text{CD}$ is soluble in 100ml water.

To increase the solubility of natural CDs in aqueous systems, particularly when warming is not option water/organic solvent mixtures can also be used.⁹ Unfortunately many solvents, like EtOH,

2-PrOH, or DMSO are able to form complexes with CDs and not the CD but its complex solubility is measured. A further complication comes from the fact that the real composition of the solvent-water mixtures is not adequately determined. For the users g/100g or rather g/100ml solvent concentration is important, but in the literature¹² the solvent mixtures are usually presented as g/molar fractions of solvents. For the practical point of view this latter is less favorable Figure 3.

Except MeOH and DMSO, the solubility maxima are found in the 20-40 vol% range as it is seen in Figure 3. Additionally, in many cases the solvent mixtures are available in vol % despite that in the practice mixing of solvents by adding $V_1 + V_2$ is simpler than using volumetric flasks. Unfortunately, what are many times also forgotten, the volumes are not additives. The positive aspect is that despite volume change in mixing various organic solvents and water, usually this effect seems to be negligible considering the experimental error of the solubilities. The volumes of water to be added to the various organic solvents to reach the desired vol % are listed in Table 1.¹³⁻¹⁸

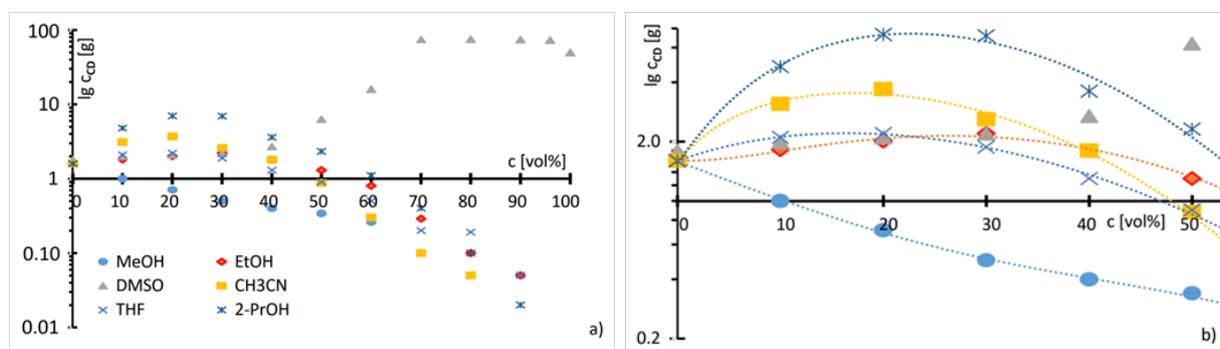


Figure 3 CD solubilities (g/100ml), in various water-organic solvent mixtures as the function of the organic solvent vol%

a. Full range

b. Around the maxima. Solubilities of CDs were re-calculated to vol% from the published data¹²

Table 1 Calculated approximate volumes of water to organic solvents to get the targeted vol% solutions.

Vol%	Solvent V(ml)	MeOH	EtOH	2-PrOH	ACN	THF	DMSO
0	0	100	100	100	100	100	100
≈ 10	10	91	91	92	91	91	90
≈ 20	20	82	82	82	81	81	81
≈ 30	30	72	73	74	72	72	71
≈ 40	40	63	64	64	62	62	62
≈ 50	50	53	54	54	52	52	52
≈ 60	60	44	44	43	42	42	43
≈ 70	70	34	34	33	32	32	33
≈ 80	80	23	23	22	21	22	20
≈ 90	90	12	12	13	11	10	11
100	100	0	0	0	0	0	0

*Calculated from the literature densities of organic solvents¹³⁻¹⁸

Acknowledgments

None.

Conflicts of interest

The author declares that are no conflicts of interest.

References

1. Fourmentin S, Crini G, Lichtfouse E, et al. Cyclodextrin Fundamentals, Reactivity Analysis. New York: Springer International Publishing; 2018.
2. Fourmentin S, Crini G, Lichtfouse E. Cyclodextrin Applications Medicine, Food, Environment Liquid Crystals. New York: Springer International Publishing, 2018.
3. Szejtli J, Osa T, Lehn JM, et al. Aqueous Solubility Behavior of Three Cyclodextrins. 1st ed. New York: Pergamon; 1996.
4. Bilensoy E. Cyclodextrins in Pharmaceuticals, Cosmetics, and Biomedicine: Current and Future Industrial Applications. New Jersey: John Wiley & Sons, Inc; 2011.
5. Szente L, Szejtli J, Kis GL. Spontaneous opalescence of aqueous gamma-cyclodextrin solutions: complex formation or self-aggregation? *J Pharm Sci.* 1998;87(6):778–781.
6. Saokham P, Muankaew C, Jansook P, et al. Solubility of Cyclodextrins and Drug/Cyclodextrin Complexes. *Molecules.* 2018;23(5):1161.
7. Jin ZY. Cyclodextrin Chemistry Preparation Application, World Scientific, 2013.
8. Szejtli J. Cyclodextrins Their Inclusion Complexes. Budapest: Akademiai Kiado; 1982.
9. Jozwiakowski MJ, Connors KA. Aqueous Solubility Behavior of Three Cyclodextrins. *Carbohydr Res.* 1985;143:51–59.
10. Wiedenhoff N, Lammers JNJJ. Properties of cyclodextrins: Part II. Preparation of a stable β -cyclodextrin hydrate and determination of its water content and enthalpy of solution in water from 15–30°. *Carbohydr Res.* 1968;7(1):1–6.
11. Wiedenhoff N, Lammers JNJJ. Properties of cyclodextrins: Part I. Solubility measurements. *Carbohydr Res.* 1967;4(4):318–325.
12. Chatjigakis AK, Donze C, Coleman AW, et al. Solubility behavior of β -cyclodextrin in water/cosolvent mixtures. *Anal Chem.* 1992;64(14):1632–1634.
13. <http://www.handymath.com/cgi-bin/methanol%20ble3.cgi?submit=Entry>
14. <https://wissen.science-and-fun.de/chemistry/chemistry/density-tables/ethanol-water-mixtures/>
15. <https://www.gaylordchemical.com/literature/dmsso-physical-properties/>
16. Lebo RB. Properties of Mixtures of Isopropyl Alcohol and Water. *J Am Chem Soc.* 1921;43(5):1005–1011.
17. Nikitin AM, Lyubartsev AP. New six-site acetonitrile model for simulations of liquid acetonitrile and its aqueous mixtures. *J Comput Chem.* 2007;28(12):2020–2026.
18. Kiyohara O, D'Arcy PJ, Benson GC. Thermal expansivities of water + tetrahydrofuran mixtures at 298.15 K. *Can J Chem.* 1978;56(22):2803–2807.