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Interaction of Hydroxy Acids with β-Cyclodextrin

E. FENYVESI[1], M. VIKMON[1], J. SZEMAN[1], E. REDENTI[2], M. DELCANALE[2], P. VENTURA[2] and J. SZEJTLI[1]
[1]*Cyclolab Research and Development Laboratory Ltd., Budapest, 1117 Dombóvári út 5-7, Hungary*
[2]*Chiesi Farmaceutici S.p.A., Parma, Via Palermo 26/A, Italy*

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Abstract. The solubility of β-cyclodextrin (β-CD) was studied in aqueous solutions of various organic acids. The hydroxy acids, especially citric and tartaric acid were found to increase the solubility of β-CD, while some other carboxylic acids reduced it. From solubility data the apparent complex association constants were calculated.

Key words: β-cyclodextrin, citric acid, tartaric acid, malic acid, hydroxy acids, solubility

1. Introduction

Organic hydroxy acids, like citric and tartaric acid, are often used as pH adjuster to improve either the solubility or the stability of drugs complexed with cyclodextrins (CDs) [1]. Many effervescent formulations contain hydroxy acids, mostly citric or tartaric acid, to generate carbon dioxide gas from the hydrogencarbonate salts [2]. Not too much is known, however, about the interactions between the hydroxy acids and CDs, which can influence the properties (solubility, absorption) of the active ingredient of the formulation.

The complex formation of aliphatic organic acids and CDs was studied by the freezing point depression method [3]. Though the data have high error (the standard deviation is eventually higher than 50%), some relationships could be observed: the association constant for the interaction of α-CD with carboxylic acids seems to be an order of magnitude greater than those obtained for β- and γ-CD, except for hydroxy acids. While no complex formation could be detected between β- or γ-CD and acetic, formic or oxalic acid, hydroxy acids yielded well measurable association constant values with β-CD. The highest stability constant was found for the citric acid/β-CD complex.

The complexation equilibrium of citric acid with β-cyclodextrin was studied in aqueous solution by calorimetry [4]. The equilibrium association constant calculated from the calorimetric data turned out to be 16.4 M^{-1} at 25°C. The interaction between citric acid and β-CD was also investigated by ^{1}H NMR spectroscopy: a significant NOE enhancement of the methylene group signal of the acid was observed indicting that a real inclusion complex was formed (data not shown).

Drug/CD/hydroxy acid multicomponent systems have been extensively studied [5–8]. It was found that in the presence of a hydroxy acid as the third component the solubility of both the drug, and of the β-CD increased remarkably [9]. For instance, in an aqueous Terfenadine/β-CD/tartaric acid multicomponent system 160–200 mg/mL concentration of dissolved β-CD (corresponding to an approximate 10-fold increase) can be achieved, while in a β-CD/tartaric acid binary system at the same acid concentration (10 mg/mL) only 35 mg/mL β-CD is dissolved [10]. An even higher concentration (more than 500 mg/mL, 40–50 fold increase) was observed in the aqueous solution of the Ketoconazole/β-cyclodextrin/tartaric acid system [11]. The aim of the present work was to obtain more information on the influence of carboxylic acids on the solubility of β-CD.

2. Experimental

2.1. MATERIALS

β-Cyclodextrin was supplied by Wacker Chemie (Munich, Germany), the acids by Aldrich Co. (Steinheim, Germany)

2.2. SOLUBILITY MEASUREMENTS

An excess amount of β-CD (1000 mg, drying loss: 13%) was weighed into test tubes, and equilibrated with 5 mL of acid solutions for 2 days at $28 \pm 2^{\circ}$C. The concentration of acids was varied in the range of 0–0.75 mol/dm^3. The samples were then filtered on a glass filter (G4), and their β-CD content was determined by HPLC. (Apparatus: Beckman 114M Solvent Delivery Module, Waters Differential Refractometer R401, Hewlett-Packard 3396A Integrator, Column: Cyclodextrin Assay column 4.6 $\times$ 250 mm, particle size: 5 μm (Astec), mobile phase: distilled water, flow rate: 1.0 mL/min, sample size: 20 μL, retention time: 9.2 min) [12].

3. Results and Discussion

Generally, when shifting the pH from neutral to acid values by adding inorganic acids to a β-CD/water system, no solubility enhancement of β-CD can be observed. Organic acids, however, may have an influence on the solubility. It was found that some hydroxy acids have a remarkable solubilizing capacity probably due to the H-bonds (Figure 1). The data obtained for citric acid are in good agreement with those published by Germain et al. [4].

The dicarboxylic acids without hydroxyl groups (malonic, succinic, maleic acids) have an opposite effect probably due to the precipitation of the β-CD-acid complex (Figure 2).

Only the hydroxy acids enhance the aqueous solubility of β-CD. A β-CD concentration as high as 200 mg/mL ($\sim$11 fold solubility enhancement) can be achieved in the presence of 144 mg/mL citric acid. The dissolved β-CD concentration can

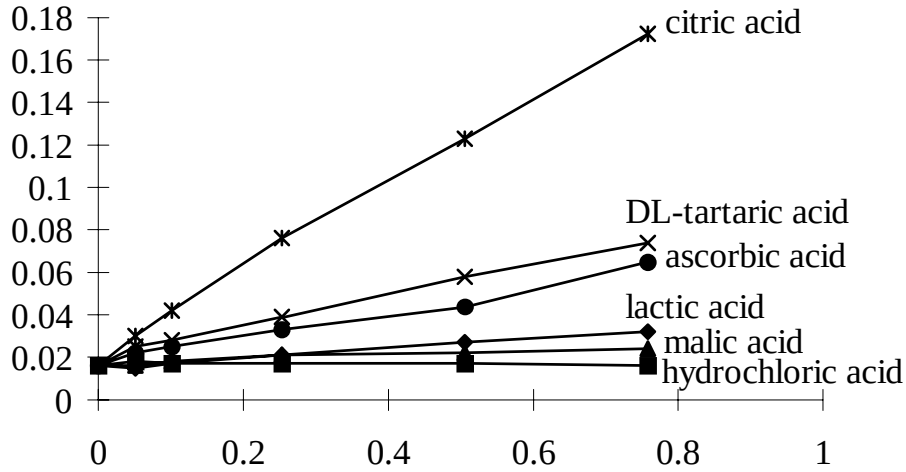

Figure 1. Solubility of β-CD in solutions of hydroxy acids and HCl as a function of the acid concentration.

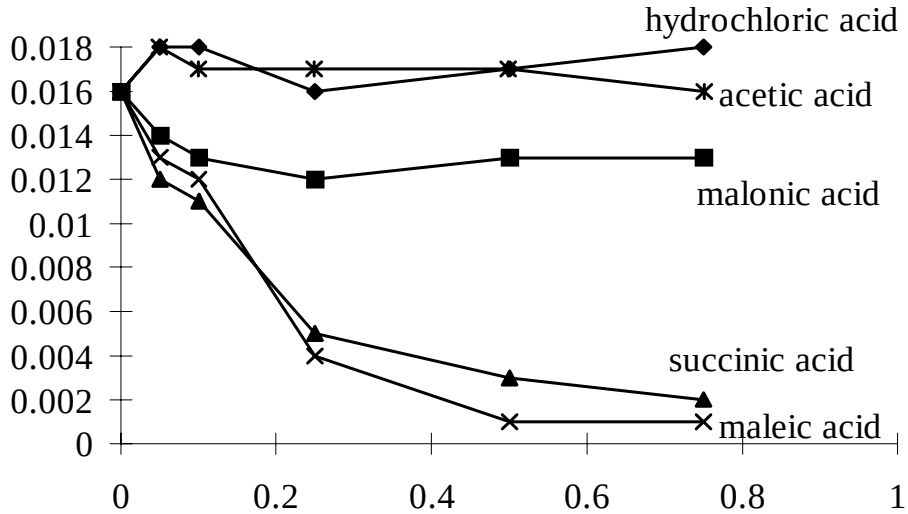

Figure 2. Solubility of β-CD in solutions of organic acids and HCl as a function of the acid concentration.

be enhanced up to 4–5 fold with (±)tartaric and (±)ascorbic acids, while (±)lactic and (±)malic acid have a slighter effect on the solubility of β-CD.

Acetic acid, hydrochloric acid and the potassium-sodium salt of tartaric acid have no effect on the solubility of β-CD. The latter finding enforces the hypothesis that hydrogen bonds play an important role in the solubilization.

The complex association constants calculated from the solubility data (assuming 1 : 1 stoichiometry) are listed in Table I. In the case of hydrochloric and acetic acid no complex formation can be detected (at the studied concentrations). With

Table I. Apparent complex stability constants between β-cyclodextrin and carboxylic acids calculated from the solubility data (K_{sol}), from calorimetric data (K_{cal} [4]), and from the freezing point measurements (K_{osm} [3])

Carboxylic acid	K_{sol} M^{-1}	K_{cal} M^{-1}	K_{osm} M^{-1}
Malic acid	1.4	No data	5.2 ± 0.0
Lactic acid	1.6	No data	No data
Ascorbic acid	3.7	No data	No data
Tartaric acid	4.1	No data	7.8 ± 2.3
Citric acid	12.8	16.4	50.5 ± 39.2

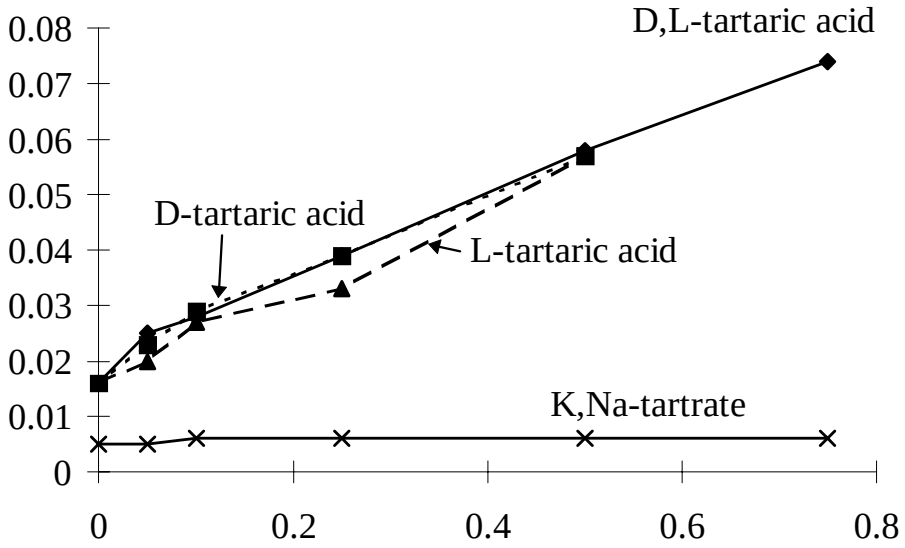

Figure 3. Solubility of β-CD in solutions of L-, D- and DL-tartaric acid and the potassium-sodium salt of tartaric acid as a function of the acid or salt concentration.

malonic, succinic and malic acid the association constant could not be calculated because of the negative slope of the solubility isotherms.

The data reported indicate that the solubilizing effect is probably related to the capability of the hydroxy groups to interact with the intra- and intermolecular hydrogen bond system of β-CD and strictly depends on their number and geometry. Since bicarboxylic acids are more effective than monoacids, it can be concluded that one of the carboxylic functions takes part as well, being the other group involved in the inclusion complex formation. In order to cast more light on the

mechanism, the pure enantiomers of tartaric acid were also used. It is well known, indeed, that CDs can interact with enantiomers giving rise to complexes with different physico-chemical properties (solubility, stability). No significant difference was observed, however, between the solubilizing effect of (+)-L and (−)-D-tartaric acid enantiomers, which was also very similar to the effect of the racemic mixture (Figure 3). The reason might be that the interaction between the enantiomers and β-CD does not fulfill the requirements for chiral recognition [13].

4. Conclusions

Hydroxy acids such as citric, tartaric and ascorbic acid used at high concentration strongly enhance the aqueous solubility of β-CD at room temperature. For instance, 200 mg/mL β-CD can be dissolved in citric acid solution at 140 mg/mL concentration. The solubilizing power of tartaric and ascorbic acid is still considerable, while that of lactic and malic acids is much weaker.

The effect probably relies on the capability of the hydroxy acid groups to modify the intra- and intermolecular hydrogen-bond system of β-CD [14]. As far as multicomponent complexes are concerned, much lower hydroxy acid concentration is needed to attain similar high solubility of β-CD [15, 16]. This indicates that other driving forces cooperate in the solubilizing enhancement effect.

References

1. Y. Kanayama and A. Myao (Fuji Seiyaku Kogyo Kk.): Jpn. Kokai Tokkyo Koho, JP 07267863 (1995); *Chem. Abstr.* **124**, 15512 (1995).
2. T. J. Grattan: (SmithKline Beecham PLC): PCT Int. Appl., WO 9504528 (1995); *Chem. Abstr.* **122**, 222879 (1995).
3. M. Suzuki, K. Ito, C. Fushimi and T. Kondo: *Chem. Pharm. Bull.* **41**(5), 942 (1993).
4. P. Germain, M. Bilal and C. de Brauer: *Thermochim. Acta* **259**, 187 (1995).
5. E. Redenti, G. Amari, M. Zanol, G. Fronza, A. Selva, M. Mor and P. Ventura: *Book of Abstracts of the 9th Int. Symp. on Cyclodextrins*, Santiago de Compostela, May 31–June 3, 1998.
6. E. Redenti, G. Amori, G. Fronza; M. Zanol, P. Ventura, J. Szejtli and M. Vikmon: *Proceedings of 7th International Symposium on Cyclodextrins*, Tokyo, 410 (1994).
7. E. Redenti, A. Selva, A. Pasini, P. Ventura and B. Casetta: *Proceedings of 7th International Symposium on Cyclodextrins*, Tokyo, 184 (1994).
8. A. Selva, E. Redenti, M. Pasini, P. Ventura and B. Casetta: *J. Mass Spectrometry* **30**, 219 (1995).
9. P. Chiesi, P. Ventura, M. Pasini, J. Szejtli, M. Vikmon, and E. Redenti: PCT Int. Appl. WO 9416733 (1994).
10. M. Vikmon, J. Szeman, J. Szejtli, M. Pasini, E. Redenti and P. Ventura: *Proceedings of 7th Int. Symp. on Cyclodextrins*, Tokyo, 480 (1994).
11. A. Gerlóczy, J. Szeman, K. Csabai, I. Kolbe, L. Jicsinszky, D. Acerbi, P. Ventura, E. Redenti and J. Szejtli: *Proceedings of 8th Int. Symp. on Cyclodextrins*, Budapest, Kluwer Academic Publishers, Doordrecht, 515 (1994).
12. Astec technical guide to the Cyclodextrin Assay column.
13. D. W. Armstrong, T. J. Ward, R. D. Armstrong and T. E. Beesley: *Science* **232**, 1132 (1986).
14. Á. Buvári and L. Barcza: *J. Incl. Phenom.* **7**, 379 (1989).

15. J. Szeman, M. Vikmon, J. Szejtli, M. Pasini and P. Ventura: *Proceedings of 7th Int. Symp. on Cyclodextrins*, Tokyo, 266 (1994).
16. K. Csabai, M. Vikmon, J. Szejtli, M. Pasini and P. Ventura: *Proc. of the 7th Cyclodextrin Symposium*, Tokyo, 1994, Buisness Cent. Acad. Sci. Japan., (Osa, T. ed.) p. 476.