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Study of α-, β- and γ-Cyclodextrin complexes with Cetirizine by UV Spectroscopy and Isothermal Titration Calorimetry

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ABSTRACT SUMMARY

Complex formation between the antihistaminic drug Cetirizine (CTZ) and α-, β- and γ-cyclodextrin (CD) was investigated by UV spectroscopy and Isothermal Titration Calorimetry (ITC). UV spectroscopy demonstrated that CTZ forms more stable complexes with β-CD (K_a=5641±358 M^{-1}) than α-CD (K_a=1434 ±60 M^{-1}). No information could be extracted from the UV spectroscopic analysis of CTZ γ-CD complex. ITC results for association constant determination were in compliance with UV results and confirmed that CTZ-β-CD has the highest association constant (2540 ± 122 M^{-1}). The association constants from ITC measurements for CTZ-γ-CD and CTZ-α-CD were found to be 1200±50 M^{-1} and 800 ±22 M^{-1}, respectively.

INTRODUCTION

Cyclodextrins are cyclic oligo saccharides that posses the ability to incorporate various molecules into their relatively apolar cavity. This property is caused by the unique structure of their molecule which posses outer hydrophilic surface and inner less polar cavity. Inclusion complex formation is favourized by incorporation of a guest molecule or an apolar part of a guest molecule into the CD cavity while more polar or charged group remains exposed to the bulk solution. The complexes often displays altered physicochemical properties compared to the guest molecule itself such as increased aqueous solubility, stability and bioavailability as well as reduced unpleasant tastes (Uekama, *et al.* 1998; Hedges, 1998).

Cetirizine is an antihistaminic drug with an unpleasant bitter taste which is a major drawback for its formulation in oral dosage forms such as chewable tablets, syrups or chewing gum. By complexation of Cetirizine with cyclodextrins, this negative effect could be decreased or diminished. Reduced bitter taste is a consequence of the formation of an inclusion complex with the bitter compound and the cyclodextrins interaction with and blockage of the gate-keeper proteins of the taste buds (Szejtli and Szente, 2005). The features of the cyclodextrins make them attractive for formulation of drugs where unwanted taste needs to be addressed.

The effects caused by inclusion complex formation of cyclodextrins with drug molecules in aqueous solution is closely related to the strength of the complexes formed and it is thus of high importance to have detailed information on the binding constants for the cyclodextrin-drug equilibrium. In this study UV spectroscopy and ITC are applied for determining which of the three native cyclodextrin is most suitable for inclusion complex formation and future formulation of different pharmaceutical forms of Cetirizine.

EXPERIMENTAL METHODS

Cetirizine dihydrochloride was obtained from Dr. Reddy's Laboratories Ltd. with certified content 99.77%, and it was kindly provided by Fertin Pharma, Vejle, Denmark. α-, β- and γ-CD were purchased from Wacker Chemie, Burghausen, Germany. Shimadzu UV-VIS spectrophotometer, model UV-1601 was used with 1 cm matched quartz cells.

UV spectroscopic determination of the association constant was carried out according Connor's mole ratio method (Connors, 1987). This was performed by addition of various amounts of α-, β-, and γ-CD, respectively, to CTZ solution with fixed concentration leading to CTZ-CD solutions with $3.25 \cdot 10^{-5}$ M CTZ and molar ratio of CTZ:CD from 1:1 to 1:100.

$$\Delta A = \frac{[CTZ]_t \cdot K_a \cdot \Delta\varepsilon_{11} \cdot [CD]}{1 + K_a \cdot [CD]} \qquad (1)$$

Equation (1) shows the binding isotherm used for modeling a 1:1 complex stoichiometry by non-linear regression from the plot of $\Delta A = f([CD]_t)$. In the isotherm (eq. 1), [CD] is related to the known total cyclodextrin concentration $[CD]_t$, since [CD] >>> [CTZ-CD] (Connors, 1987).

Calorimetric measurements were performed using a Microcal isothermal titration calorimeter (Microcal Inc., Northampton, MA). All experiments were conducted at 30 °C. The reaction cell (1.4095 ml) and the injection syringe were filled with aqueous solutions of 1 mM CTZ and 10 mM CD solution, respectively. Thirty portions, 10 μL each of the CD solution were injected into the CTZ solution with intervals of 250 sec and the heat change in the sample cell was recorded. First injection (1mL) was discarded to eliminate material diffusion from the syringe into the calorimetric cell. Calorimetric change in the sample cell was recorded and the data were processed in Origin 7 software (Microcal).

RESULTS AND DISCUSSION

The CTZ-γ-CD complex did not cause any measurable change in the absorption spectra of CTZ and thus only the

complex formation of CTZ with α- and β-CD could be studied using UV spectroscopy. Association constants K_a for α- and β-CD were found to be 1434±60 M^{-1} and 5641±358 M^{-1}, respectively (Figure 1 and 4).

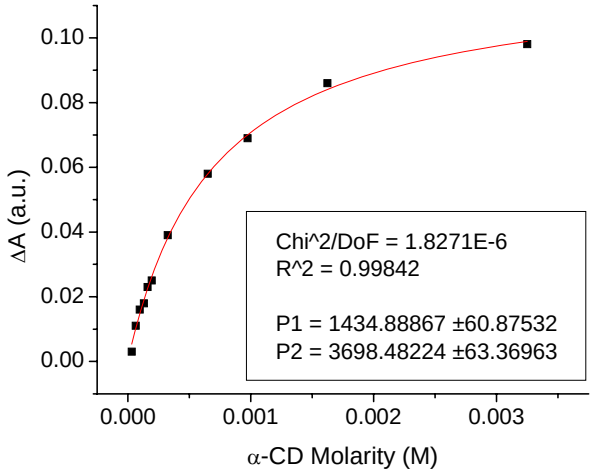

Figure 1. Mol ratio titration plot for Cetirizine-α-CD complex (CTZ $3.25 \cdot 10^{-5}$ M). Black dots represent the experimental data and the red line describes the theoretical function with the fitted data.

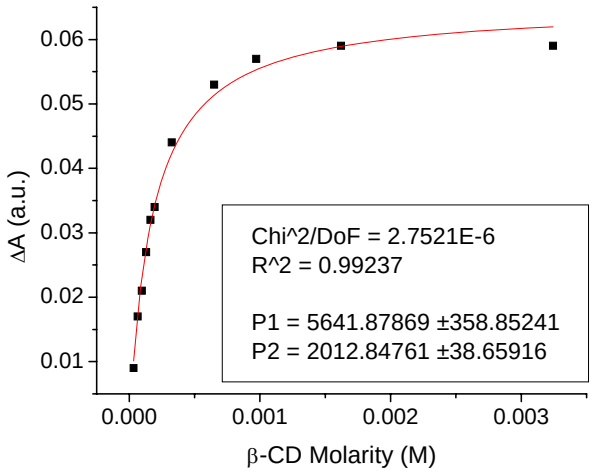

Figure 2. Mol ratio titration plot for Cetirizine-β-CD complex (CTZ $3.25 \cdot 10^{-5}$ M). Black dots represent the experimental data and the red line describes the theoretical function with the fitted data.

Fitting of the ITC titration data by non-linear regression analysis was applied using Origin 7 software (Microcal) with applying one sites model. The results from the fitting procedure are shown in Table 1:

Table 1. Thermodynamic parameters and the association constant of α-, β- and γ-CD inclusion complexes with CTZ determined by ITC.

Complex	ΔH° (kJ · mol^{-1})	ΔS° (kJ · mol^{-1})	K_a (M^{-1})
CTZ-α -CD	-5514±72.12	-4.9	800±22.6
CTZ-β -CD	-4733±65.42	-0.0323	2540±122
CTZ-γ -CD	-723.7±11.93	11.7	1200±49.9

CONCLUSION

Both UV and ITC results shows that CTZ forms more stable complex with β-CD than α- and γ-CD. The association constant for CTZ-β-CD complex were 5641±358 M^{-1} and 2540±122 M^{-1} obtained by UV and ITC, respectively, and are very close to literature reported values (3292 M^{-1} and 3587 M^{-1} determined by a competition method with crystal violet and methyl orange, respectively, Fanara *et al.* 2002).

REFERENCES

1. Connors, K. A. (1987). *Binding Constants*, John Wiley & Sons, Canada.
2. Hedges, A. R. (1998) Industrial applications of cyclodextrins. *Chemical Reviews*, **98**, 2035-2044.
3. Szejtli, J. and Szente, L. (2005). Elimination of bitter, disgusting tastes of drugs and foods by cyclodextrins. *European Journal of Pharmaceuticals and Biopharmaceuticals*, **61** (3), 115-125.
4. Uekama, K., Hirayama, F. and Irie, T. (1998). Cyclodextrin drug carrier systems. *Chemical Reviews*, **98**, 2045-2076.

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