Determination of the interaction pattern of Cetirizine with -, - and -Cyclodextrin by NMR spectroscopy

Stojanov, Mladen; Larsen, Kim Lambertsen; Wimmer, Reinhard

Published in:
36th Annual Meeting & Exposition of the Controlled Release Society, Transactions

Publication date:
2009

Document Version
Publisher's PDF, also known as Version of record

Determination of the interaction pattern of Cetirizine with α-, β- and γ-Cyclodextrin by NMR spectroscopy

M. Stojanov, K. L. Larsen, and R. Wimmer

Department of Biotechnology, Chemistry and Environmental Engineering, Aalborg University, Aalborg, 9000 Denmark
mladen@bio.aau.dk

ABSTRACT SUMMARY

^{1}H-NMR, COSY (Correlation Spectroscopy) and ROESY (Rotational nuclear Overhauser Effect Spectroscopy) experiments were applied in determination of the interaction of Cetirizine complexes with α-, β- and γ-cyclodextrin. ROESY experiment revealed inclusion complex formation by penetration of the Cetirizine aromatic rings into the cyclodextrin cavity. Cetirizine forms complexes with cyclodextrins from both the narrower and wider rim of cyclodextrin molecule.

INTRODUCTION

Cetirizine is second generation antihistaminic with selective affinity to H_1 receptors. It is water soluble component with very bitter taste, and formulation of some oral pharmaceutical dosage forms like syrups, chewing tablets or chewing gums may be accompanied by an unpleasant bitter taste. In these cases an appropriate taste masking agent needs to be added in order to reduce or eliminate the unpleasant bitter taste. One approach to reduce the unpleasant bitter properties of pharmaceutical active components is complexation with cyclodextrins (CD's). The glucose units of the cyclodextrins form a cyclic structure with hydrophilic outer surface and inner less polar cavity. As result of this CD's exhibit property for incorporation of various molecules inside the cavity. The ability of the CD's for formation of inclusion complexes with other molecules makes them a potential solution to the problem. Inclusion complex formation between a drug and cyclodextrins produces complexes with highly altered physical, chemical and biological properties compared to the drug molecule itself including increased stability, aqueous solubility and bioavailability. Decreased local irritation and reduction of unpleasant taste may also be achieved (Uekama, *et al.* 1998; Hedges, 1998; Szejtli and Szente, 2005).

EXPERIMENTAL METHODS

Two batches of Cetirizine dihydrochloride (CTZ) were used. The first batch of Cetirizine was obtained from Sigma-Aldrich with certified content 100%, and the second batch from Dr. Reddy's Laboratories Ltd. with certified content 99.77%, both kindly provided by Fertin Pharma, Vejle, Denmark. α-, β- and γ-CD were purchased from Wacker Chemie, Burghausen, Germany.

All NMR experiments were carried out at 20 ^{o}C on a BRUKER DRX600 NMR spectrometer, equipped with a TXI (H/C/N) probe and operating at field strength of 14.1 T.

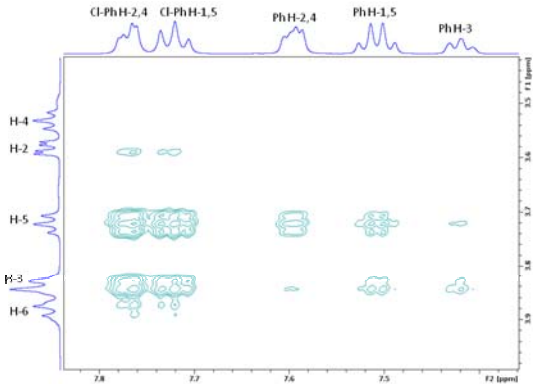
The property of change in observed ($\Delta\delta_{obs}$) chemical shift of cyclodextrin and the guest molecule protons is used for determination of the complex structure. When the guest molecule is incorporated into the cyclodextrin cavity the H-3 and H-5 protons of the cyclodextrins are by far most affected by the intermolecular interactions with the guest protons. This is based on the expectation that inclusion complex formation of the guest with cyclodextrin will alter the chemical shift of CD's H-3 and H-5 protons, since they are oriented towards the cyclodextrin cavity; while H-2, H-4 and H-6 are located on the outer surface of the cyclodextrin toroid and therefore they will be less affected (Yamamoto and Inoue, 1998; Schneider, H. J. et al. 1998).

^{1}H NMR, COSY and ROESY experiments were performed in D_2O. For all NMR analyses, CTZ from the second batch was used except for the ROESY experiment with γ-CD, which was performed with CTZ from the first batch.

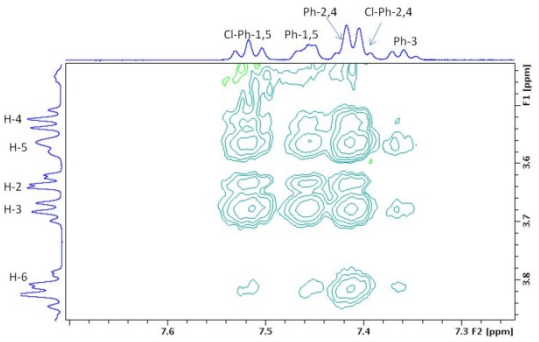
RESULTS AND DISCUSSION

Figure 1a) shows a 2D ROESY spectrum of α-CD with CTZ. Cross peaks from CD signals to the chlorophenyl ring protons had a higher intensity compared to the cross peaks to the phenyl ring protons. This observation shows that binding of the chlorophenyl ring is stronger and that the inclusion of the chlorophenyl ring into the cyclodextrin cavity is preferable over inclusion of the phenyl ring. For both CTZ-α- and β-CD we noticed low-intensity cross peaks between the cyclodextrin H-6 protons and aromatic CTZ protons (Figure 1a and b). These peaks are probably due to interaction of cyclodextrin H-6 protons with non-penetrating phenyl or chlorophenyl ring on the outer side of the cyclodextrin molecule, when CTZ enters from the narrower rim of the cyclodextrin cavity (Figure 2). Poor separation of CD's H-3 and H-6 peaks for CTZ-γ-CD prevents discrimination of these two interaction sites. In CTZ-γ-CD, the absence of cross peaks between CTZ H-3 phenyl ring proton and CD H-5 proton is probably due to a deeper penetration of the phenyl ring into the cyclodextrin cavity when the CTZ enters from the wider part of γ-CD molecule. This is possible due to larger cavity of γ-CD and might also allow partial incorporation of the other ring. Again strong intensity of cross peeks between the chlorophenyl ring of CTZ and γ-CD's H-3 and H-5 protons suggest that the

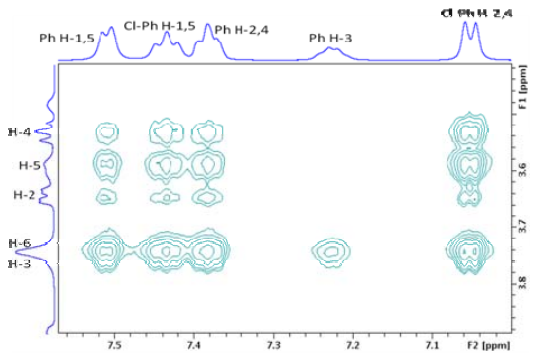
chlorophenyl ring is preferably incorporated into the γ-CD cavity.



a)



b)



c)

Figure 1. Partial contour plot of two-dimensional ROESY spectrum of solutions containing: a) 30 mM CTZ and 70 mM α-cyclodextrin, b) 4 mM CTZ and 6 mM β-cyclodextrin and c) 40 mM CTZ and 20 mM γ-cyclodextrin

CONCLUSION

2D NMR spectroscopic studies revealed two possible cyclodextrin binding sites in the CTZ structure, the phenyl and chlorophenyl rings. Previous NMR and UV spectroscopic studies for determination of the complex stoichiometry demonstrated 1:1 complex ratio between CTZ and cyclodextrin molecules. This indicates that both aromatic rings cannot be occupied at the same time and complexation is formed by incorporation of only one aromatic ring into the cyclodextrin cavity. This could be either the phenyl or chlorophenyl ring. Steric hindrance does not allow the chlorophenyl and phenyl ring to be occupied simultaneously. Furthermore, 2D NMR reveals is that the aromatic rings from CTZ molecule could enter from both the narrower and the wide rim into the cyclodextrin cavity (Figure 2).

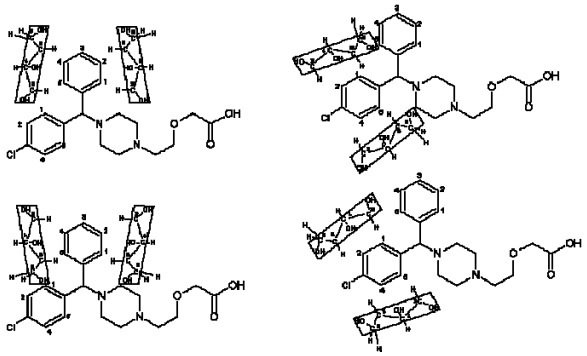


Figure 2. Possible structures of CTZ α-, β- and γ-CD complexes.

REFERENCES

1. Uekama, K., Hirayama, F. and Irie, T. (1998). Cyclodextrin drug carrier systems. *Chemical Reviews*, **98**, 2045-2076.
2. 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.
3. Hedges, A. R. (1998) Industrial applications of cyclodextrins. *Chemical Reviews*, **98**, 2035-2044.
4. Yamamoto, Y. and Inoue, Y. (1998). NMR studies of cyclodextrin inclusion complex. *Journal of Carbohydrate Chemistry*, **8** (1), 29-46.
5. Schneider, H. J. *et al.* (1998). NMR Studies of Cyclodextrins and Cyclodextrin Complexes. *Chemical Reviews*, **98** (5) 1755-1785.