Study of the Inclusion Complexes Formed Between Cetirizine and α-, β-, and γ-Cyclodextrin and Evaluation on Their Taste-Masking Properties

MLADEN STOJANOV, REINHARD WIMMER, KIM L. LARSEN

Department of Biotechnology, Chemistry and Environmental Engineering, Aalborg University, Aalborg 9000, Denmark

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ABSTRACT: Complexation properties of cetirizine dihydrochloride (cetirizine) with α-, β-, and γ-cyclodextrin (CD) were investigated by ultra violet (UV) and nuclear magnetic resonance (NMR) spectroscopies and isothermal titration calorimetry (ITC). The use of the continuous variation method, applied on UV and NMR data, demonstrated 1:1 complex stoichiometry for cetirizine–α-CD, cetirizine–β-CD, and cetirizine–γ-CD, respectively. NMR two-dimensional Rotational nuclear Overhauser Effect SpectroscopY experiments revealed that for α- and β-CD, the complexation takes place by including either the phenyl or chlorophenyl ring of the cetirizine into the CD cavity, whereas in the case of γ-CD, both rings can be included simultaneously. Association constants (K_a) determined by UV spectroscopy demonstrated that cetirizine forms more stable complex with β-CD ($K_a = 5641 \pm 358\,M^{-1}$) than α-CD ($K_a = 1434 \pm 60\,M^{-1}$). No information could be extracted from the UV spectroscopic analysis of cetirizine–γ-CD solutions. ITC results for association constant determination were in compliance with UV results and confirmed that the highest association constant was found for the cetirizine–β-CD complex ($2540 \pm 122\ M^{-1}$). The association constants from ITC measurements for cetirizine–γ-CD and cetirizine–α-CD complexes were found to be 1200 ± 50 and $800 \pm 22\,M^{-1}$, respectively. Taste-masking studies revealed that β-CD is the only native CD recommendable for oral pharmaceutical formulations. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:3177–3185, 2011

Keywords: cetirizine; cyclodextrins; complexation; structure; taste masking; NMR spectroscopy; UV/Vis spectroscopy; Calorimetry (ITC).

INTRODUCTION

Cetirizine is a second-generation antihistaminic drug with selective affinity to H_1 receptors. Its selectivity in the inhibition of the peripheral histamine H_1 receptors provides minimal antihistaminic adverse effects such as dry mouth and sedation.[1] Cetirizine dihydrochloride (cetirizine) is a relatively water-soluble drug with a very bitter taste, and its use in some oral pharmaceutical dosage forms such as syrups, chewing tablets, or gums may be limited by this property. In these cases, an appropriate taste-masking agent is needed in order to reduce or eliminate the unpleasant bitter taste.[2,3]

One approach to reduce the unpleasant bitter properties of the active pharmaceutical ingredients (APIs) is by inclusion complex formation with cyclodextrins (CDs).[4] First-generation or parent CDs such as α-, β-, and γ-CD are composed of six, seven, and eight α-(1,4)-linked glucosyl residues, respectively. The glucose units of the CDs form a cyclic structure with a hydrophilic outer surface and a less polar inner cavity. As a result of this, CDs are capable of accommodating various molecules or hydrophobic parts of the molecules inside their cavity, whereas more polar groups remain exposed to the bulk solution (water).[5] The ability of CDs for the formation of inclusion complexes with other molecules makes them potential solutions to several problems encountered in drug formulation. The complexes most often display altered physical, chemical, and biological properties compared with the uncomplexed active compound itself. This includes improved stability,

Correspondence to: Kim L. Larsen (Telephone: +45-9940-8521; E-mail: kll@bio.aau.dk)

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increased aqueous solubility and bioavailability, decreased side effects, and masking of unpleasant tastes.[6–14] The use of CDs for taste masking of bitter APIs has been a subject of many studies,[4] and CDs have been shown to be able to mask the taste of propantheline bromide, oxyphenonium bromide,[15,16] primaquine phosphate,[17] famotidine,[18] doxylamine,[19] thiamine,[20] nicotine.[21] The reduction in unwanted taste is a direct consequence of the CDs inclusion complex formation with the unpleasant tasting component. In addition, it has been speculated that interaction and blockage of the gatekeeper proteins of the taste buds by the CDs also adds to the taste-masking effect.[4] All these features of the CDs make them multifunctional excipients for drug formulation. Very little has been reported in literature on the complex formation between cetirizine and CDs. So far, only nuclear magnetic resonance (NMR) studies on cetirizine–β-CD complex[22] have been performed, and as we will substantiate in the discussion section, these results are in part inconclusive. A couple of patents describe pharmaceutical formulations of cetirizine containing CDs as agents for the reduction of the unpleasant bitter taste.[23,24] Szejtli and Szente[4] also discuss the taste-masking effect of β-CD in cetirizine–β-CD complexes. No detailed study of the inclusion complexes formed between CDs and cetirizine has been published. Here, we present a thorough characterization of the complexes formed between cetirizine and α-, β-, and γ-CDs in aqueous solution, providing detailed information on the thermodynamics, stoichiometry, and structure of the formed complexes. The taste-masking properties of α-, β-, and γ-CDs on cetirizine were examined. This study gives useful information for further development of different cetirizine pharmaceutical dosage forms.

In the present paper, an ultra violet (UV) spectroscopic study was applied for observing the changes in the spectral properties, determination of the stoichiometry, and the association constants of the complexes. NMR spectroscopy was used to examine the stoichiometry and structure of the complexes. The thermodynamics of the complex formation was described by enthalpy and entropy changes obtained from isothermal titration calorimetry (ITC) measurements. The gustatory sensory study was performed by healthy volunteers.

MATERIALS AND METHODS

Materials

Two batches of cetirizine were used. One batch of cetirizine dihydrochloride (certified content 100%) was obtained from Sigma–Aldrich (Steinheim, North Rhine-Westphalia, Germany) and another batch was obtained from Dr. Reddy's Laboratories Ltd. (Hyderabad, Andhra Pradesh India) with a certified content of 99.77%. α-, β-, and γ-CDs were purchased from Wacker Chemie (Burghausen, Bavaria, Germany). Deuterium oxide (D_2O, 99.9%), used for the NMR experiments, was purchased from Larodan Fine Chemicals, Malmö, Sweden.

UV Spectroscopic Studies

For all UV spectroscopy studies, a Shimadzu UV–visible spectrophotometer, model UV-1601, was used with 1 cm matched quartz cells and wavelength scanning speed of 370 nm/min. Cetirizine from Sigma–Aldrich was used for all UV spectroscopic studies. Stock solution of cetirizine was prepared by dissolving 100 mg of cetirizine in 100 mL demineralized water. From the stock solution, by further dilution with demineralized water, standards were prepared in the concentration range of 1–30 $\mu g\ mL^{-1}$. Absorption spectra were measured in the wavelength range between 200 and 250 nm. In the concentration range of 1–30 $\mu g\ mL^{-1}$, cetirizine obeyed Beer's law and the standard curve demonstrated very good linearity. Room temperature (21°C) was used for all UV studies.

Continuous Variation Method (Job's Plot) for UV Spectroscopic Determination of The Complex Stoichiometry

Continuous variation method[25] was used for complex stoichiometry determination. Stock solutions of 10 mM cetirizine, α-, β-, and γ-CDs, in demineralized water were prepared. From the stock solutions, a set of solutions of cetirizine with α-, β-, and γ-CDs were prepared to a constant volume. This was performed by adding various amounts of the respective CD solution to the cetirizine solution. Thus, molar fractions of cetirizine and CDs were varied continuously from zero to one with a rate of 0.1, maintaining a constant accumulative concentration (10 mM) of cetirizine and CDs.

The absorbance maximum of the samples was measured at 230 nm. By measuring the absorbance of samples containing cetirizine with (denoted A) and without CD (denoted A_0), the absorbance difference $\Delta A = A_0 - A$ could be determined. Complex stoichiometry was determined from the plot of the product ΔA [cetirizine] as function of ratio R = [cetirizine]/[cetirizine + CD].

UV Spectroscopic Determination of the Association Constant

Determination of the association constant (K_a) was carried out according to Connor's[26] mole ratio method. This was performed by the addition of various amounts of α-, β-, and γ-CDs, respectively, to a cetirizine solution resulting in cetirizine–CD solutions with constant concentration of cetirizine