MONITORING THE FORMATION OF THE CINNARIZINE:HYDROXYPROPYL-β-CYCLODEXTRIN INCLUSION COMPLEX IN SOLUTION BY SPECTROSCOPY NMR

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Abstract

Cinnarizine, a piperazine derivative with multiple pharmacological activities, was studied due to its poor aqueous solubility, which limits its clinical use. β-Cyclodextrin, an oligosaccharide composed of seven glucopyranose units linked by α-1,4-glycosidic bonds, serves as an effective host for hydrophobic molecules, making it suitable for improving cinnarizine solubility and bioavailability.

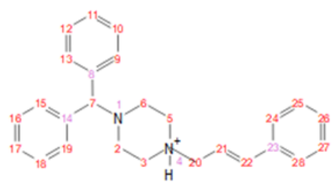

Figure 1. Structure of cinnarizine with proton numeration

The aim of this study was to investigate the complexation of cinnarizine with hydroxypropyl-β-cyclodextrin (HP-β-CD) using nuclear magnetic resonance (NMR) spectroscopy.

Chemical shift variations observed during titration of cinnarizine with HP-β-CD solutions indicated inclusion of the drug within the cyclodextrin cavity. The titration, performed up to a 1:2 molar ratio (CIN:HP-β-CD), revealed a systematic shift of the proton assigned to CIN H-7, suggesting an extended interaction in which one cinnarizine molecule may be partially included within two HP-β-CD cavities.

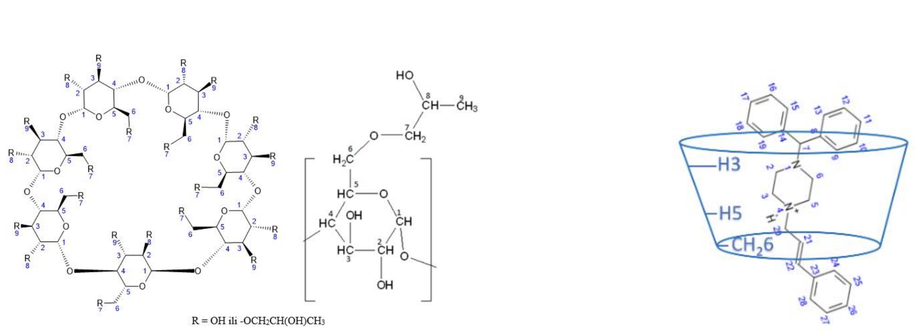

Figure 2. a) structure of HP-β-CD and b) shematic inclusion of CIN in β-CD

Sample preparations and NMR measurements

For sample preparation, 2.0 mg of cinnarizine was dissolved in 1 mL of deuterated hydrochloric acid (DCl, c = 1.0 mol dm^{-3}) and divided into two 500 µL aliquots. One aliquot served as a blank, while the other was titrated with a hydroxypropyl-β-cyclodextrin (HP-β-CD) solution prepared by dissolving 10.0 mg of HP-β-CD in 100 µL of DCl, c = 1.0 mol dm^{-3}, with ultrasonic assistance. Titration was performed in ten steps with 10 µL additions, and the procedure was repeated using DCl of lower acidity (c = 0.01 mol dm^{-3}).

All one-dimensional ^{1}H NMR spectra were recorded at 25 °C on a Bruker Avance AV600 spectrometer (600 MHz, 14 T) equipped with a broadband observe BBO probe and z-gradients. Standard Bruker pulse sequences were applied, and data were processed using the Bruker TopSpin software package.

Discussion and results

Cinnarizine, due to its asymmetric structure, can enter the hydroxypropyl-β-cyclodextrin (HP-β-CD) cavity in two possible orientations, with potential for partial inclusion or complexes of different stoichiometries. In this study, the interaction between cinnarizine and HP-β-CD was examined in solution using ^{1}H NMR spectroscopy to monitor chemical shift changes during titration.

It is important to note that the complex sample in study[10] was previously prepared by mechanochemical activation in the solid state and subsequently dissolved for NMR measurements. In the present investigation, the interaction between cinnarizine and hydroxypropyl-β-cyclodextrin was examined in solution, through titration and analysis of chemical shift changes in the ^{1}H NMR spectra, providing insight into the behavior of the system in the dissolved state.

At higher acidity (c = 1.0 mol dm^{-3} DCl), no significant spectral changes were observed, indicating that the diprotonated form of cinnarizine was unstable within the cyclodextrin cavity.

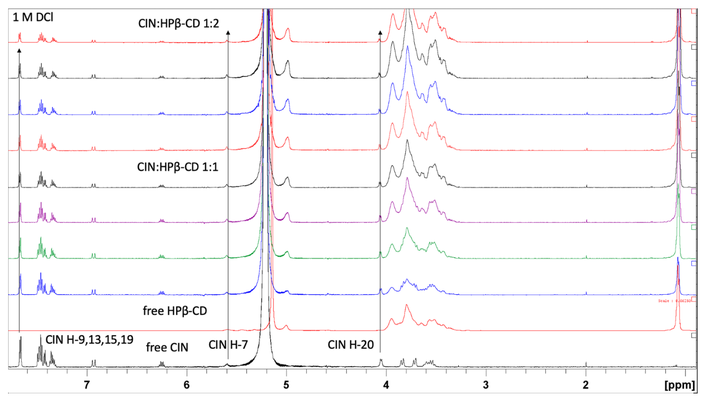

Figure 3. ^{1}H NMR spectra for monitoring the complexation of cinnarizine with hydroxypropyl-β-cyclodextrin solution in 100 µL of DCl, c = 1,00 mol dm^{-3}, at 25 °C

At lower acidity (c = 0.01 mol dm^{-3} DCl), clear downfield shifts, particularly for protons H-7 and H-9,13,15,19, confirmed the formation of an inclusion complex. The continuous change in chemical shifts up to a 1:2 cinnarizine:HP-β-CD molar ratio suggested that one cinnarizine molecule could interact with two HP-β-CD cavities, providing evidence of extended complexation in solution.

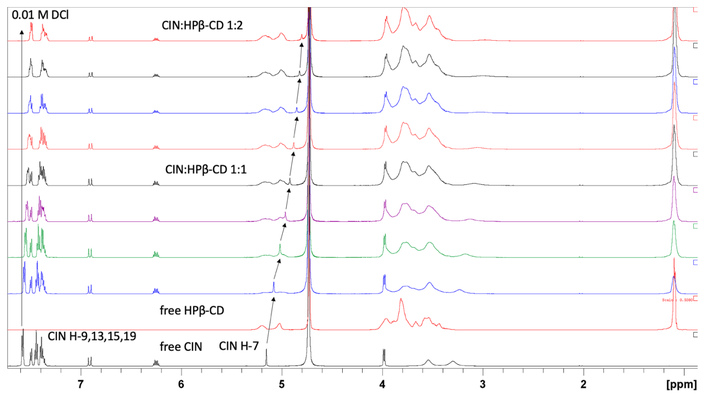

Figure 4. ^{1}H NMR spectra for monitoring the complexation of cinnarizine with hydroxypropyl-β-cyclodextrin solution in 100 µL of DCl, c = 0.01 mol dm^{-3}, at 25 °C

Conclusion

Titration of cinnarizine with hydroxypropyl-β-cyclodextrin (HP-β-CD) solutions was carried out at two DCl concentrations, c = 1.0 mol dm^{-3} and c = 0.01 mol dm^{-3}, to assess the effect of acidity on complex formation. At higher acidity, no significant chemical shift changes were observed, indicating that the diprotonated form of cinnarizine was unstable within the cyclodextrin cavity. At lower acidity, where both mono- and diprotonated species coexist, clear ^{1}H NMR spectral changes confirmed inclusion complex formation. Pronounced shifts, particularly for proton H-7 and aromatic protons H-9,13,15,19, supported this conclusion. The continuous shift of H-7 up to a 1:2 cinnarizine:HP-β-CD molar ratio suggested possible inclusion of one cinnarizine molecule into two HP-β-CD cavities. However, due to ^{1}H NMR limitations, the exact mode of inclusion requires further confirmation by complementary methods.

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