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Synthesis and spectroscopy studies of the inclusion complex of 3-amino-5-methyl pyrazole with beta-cyclodextrin

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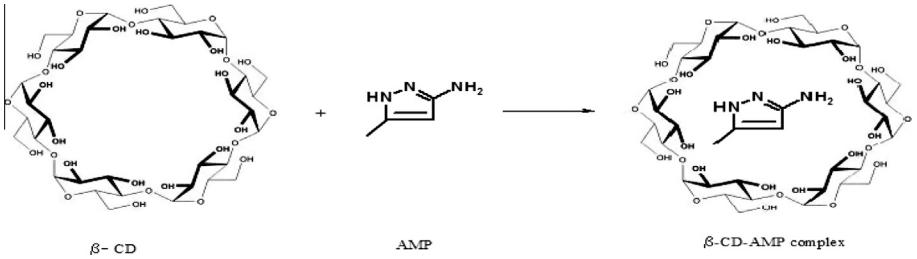
HIGHLIGHTS

- This paper attests that the complex between beta-CD and 3-amino-5-methyl pyrazole is new.
- AMP is a class of anti-inflammatory drug.
- Experimental data show that beta-CD interacts with and 3-amino-5-methyl pyrazole mainly via electrostatic force.
- Stoichiometry of the inclusion complex is 1:1.
- Binding constant is 1.1×10^4.

GRAPHICAL ABSTRACT



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ABSTRACT

Amino pyrazole belongs to anti-inflammatory class, and is characterized by a low solubility in water. (In order to increase its solubility in water, inclusion complex of amino pyrazole with β-CD was obtained.) The inclusion complex obtained between AMP and β-cyclodextrin, was characterized by FT-IR, ^{1}H NMR, ^{1}H–^{1}H NOESY, ^{13}C NMR, DEPT, XHCOR, spectra, through TG analysis, DTA, DSC and Scanning Electron Microscopy (SEM). The stoichiometry of inclusion complex is 1:1 (guest–host) and K stability is 1.1×10^4 M^{-1}.

Introduction

The biological and medicinal properties of 3-amino-5-methyl pyrazole have prompted enormous research aimed at developing synthetic routes to these heterocyclic compounds. The 3-amino-5-methyl pyrazole system represents an important heterocyclic template that has attracted considerable interest because of its long history of application in the pharmaceutical and agrochemical industries [1–4]. Besides, the importance of 3-aminopyrazole derivatives as biologically active agents, they are also useful synthons and building blocks for many heterocyclic products and can act as a binucleophile [5–9].

Cyclodextrins (CDs) are cyclic oligomers of six, seven or eight linked α – D-glucopyranose units, denoted α-, β- and γ-CDs, respectively. The CDs are well known to form inclusion complexes with a variety of organic compounds, among them, with drug substances [10–20]. This ability is based on the capability of the CDs to provide a hydrophobic cavity in aqueous solution for the hydrophobic guest molecule or moieties in the guest molecule.

Studies involving inclusion of active pharmaceutical substances into CDs are important due to the resulting improvement of aqueous solubility [21–23], stability of the guest molecule

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[24–26] and to the possibility of controlled drug release [26,27], which present many potential applications in drug formulations. CDs are capable of forming inclusion complexes with a wide variety of guest molecule by taking up a whole molecule, or some part of it, into the cavity. Molecular encapsulation may occur both in solid and in solution state. In solid state, guest molecules can be enclosed within the cavity or may be aggregated to the outside of the cyclodextrin molecule and in solution state; there is equilibrium between complexed and non-complexed guest molecules. Such molecular encapsulation will affect many of the physicochemical properties of drugs, such as their aqueous solubility and rate of dissolution Changes in the physicochemical properties provide methods to characterize whether guest molecules are really included in the cyclodextrin cavity. Among the various approaches, preparation of inclusion complexes with cyclodextrin has proven to be successful in enhancing the solubility of poorly water soluble molecules [28,29]. The preparation method used to obtain complex of pyrazole and cyclodextrin was the co-precipitation method, the kneading method and the ethanolic solution method. In this study, we have synthesized a novel inclusion complex of β-cyclodextrin and 3-amino-5-methyl pyrazole which was not reported elsewhere. The aim of the present work was to study the complexation of pyrazole with β-cyclodextrin, as a possibility of increasing the solubility of this active substance in water.

Experimental

Apparatus

Fourier transform infrared spectroscopy (FTIR) spectra of the samples were obtained in the range of 500–4000 cm^{-1} using Nicolet IR 200 FT-IR thermo-scientifique spectro-photometer with a resolution of 4 cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded with DMSO-d6 solvent containing TMS on a Bruker 300 spectrometer (^1H: 300 MHz, ^{13}C: 75.47 MHz). The chemical shifts (d) are reported in ppm relative to TMS (internal reference). For the ^1H NMR, the multiplicities of signals are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet.

The powder X-ray diffraction patterns (Fig. 1) were obtained by PHILIPS PW1729 diffractometer. The UV–visible spectrum was recorded in the range 200–400 nm with an UV JENWAY 6405 spectra photometer equipped with a Stoppard quartz cell with 1.0 cm optical path length.

DSC-TGA analysis was performed using TA DSC-TGA SDT-2960 instrument in flowing N_2 with an average heating rate of 5 °C/min, between room temperature and 450 °C.

The MES (Fig. 9) and DRX (Fig. 10) were performed using JEOL Scanning Electron Microscope JSM-6490LV equipped with SAMX Numeric DXP-X10P digital X-ray processor (for EDX analysis).

Reagents

β-Cyclodextrin and 3-amino-5-methyl pyrazole (AMP) obtained from Aldrich Chemical Co. Other chemical reagents of analytical reagent grade were used as commercial.

Synthesis of inclusion complex

0.5×10^{-3} mol (0.5675 g) of β-cyclodextrin was dissolved in 30 mL distilled water. Then 0.5×10^{-3} mol (0.0485 g) of AMP in EtOH (10 mL) solution was dropped into β-cyclodextrin (β-CD) aqueous solution with continuous stirring. The stirring operation was left for 72 h at room temperature after which it gave a solid product, inclusion complex of AMP and β-CD was obtained by filtration. The precipitate was washed with ether for three times in turn, respectively to clean the residual guest and host monomers. Then it was dried in vacuum oven at 40 °C for 48 h (yield = 80%).

Results and discussion

The inclusion complexes of β-CD have been successfully used to improve solubility, chemical stability and bioavailability of a number of poorly soluble compounds. Various known methods used for the formation of the inclusion complexes like co precipitation, neutralization, kneading, spray drying, freeze-drying, solvent evaporation, and ball-milling and sealed-heating in the laboratory have been widely reported [30]. In this study the inclusion complex was prepared by the co-precipitation method [31].

X-ray powder diffractometry

The formation of the inclusion complex was confirmed by X-ray diffractometry. Fig. 1, refers to the powder X-ray pattern of Powder X-ray diffraction patterns of (a): AMP-β-CD physical mixture AMP-β-CD; (b): complex; (c): AMP and (d): β-CD.

Powder X-ray diffractometry is a useful method for the detection of β-CD complexation in powder or microcrystalline states. The diffraction pattern of the complex is supposed to be clearly distinct from that of the superposition of each of the components if a true inclusion complex is formed. The XRD pattern of AMP showed intense, sharp peaks that prove the crystalline nature of the compound (Fig. 1c; see supplementary materials). AMP had strong crystalline peaks at 19.72°, 20.18°, 26.14° and several minor peaks. On the other hand the XRD pattern of inclusion complex did not exhibit the characteristic peaks of AMP and β-CD indicating the formation of a significant amount of AMP-β-CD complex. In the case of AMP and β-CD physical mixture with a molar ratio of 1:1, the diffraction pattern (Fig. 1a; see supplementary materials) was simply the superposition of the two patterns of the crystalline AMP and the β-CD. The sharp peaks of the pattern indicated the retention of the crystalline structure of AMP in the physical mixture.

UV–visible spectroscopy analysis

UV–visible spectroscopy is an important tool to study the complexation of AMP-β-CD. β-CD had no UV absorption. The obtained absorption spectra of AMP, β-CD and inclusion complex (AMP, β-CD) are presented in Fig. 2 (see supplementary materials). In the spectrum of AMP and inclusion complex, in EtOH solution with $C = 5 \times 10^{-5}$ mol l^{-1} (Fig. 2; see supplementary materials), one value of absorption was found for AMP: λ_{max} (nm) = 225.23; $A = 0.697$; $\log \varepsilon = 4.14$ and for Complex: λ_{max} (nm) = 223.36; $A = 0.807$; $\log \varepsilon = 4.20$.

FT-IR analysis

The complexation between AMP and β-CD was investigated by using FTIR. The FT-IR spectra of (AMP), AMP-β-CD, their physical mixture and the inclusion complex, were collected between 4000 and 500 cm^{-1} (Mild infrared region). FT-IR is a useful technique used to confirm the formation of an inclusion complex. The FT-IR spectra of β-CD, AMP and AMP-β-CD inclusion complex are presented in Fig. 3 (see supplementary materials). The FT-IR of β-CD (Fig. 3d; see supplementary materials) showed prominent absorption bands at 3200–3400 cm^{-1} (for O–H stretching vibrations). The presence of water in β-CD resulted in the presence of broad peak of OH, which masks the presence of NH and NH_2 in AMP. A few bands