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Fluorimetric investigation of supramolecular system by modified β-cyclodextrin and its analytical application

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ABSTRACT

The supramolecular interaction of MAH-β-cyclodextrin (MAH-β-CD, a modified β-cyclodextrin carrying seven vinyl carboxylic acid groups) and meferamic acid (MF) has been studied by spectrofluorimetry. The results showed that MAH-β-CD reacted with MF to form a host–guest complex (MAH-β-CD–MF) with stoichiometry (1:1) and the inclusion constant ($K = 7.15 \times 10^2$ L/mol) was ascertained by the typical double reciprocal plots. From the phase-solubility diagram, an increase in the water solubility of the drug was observed and the apparent stability constant ($K_{1:1}$) was calculated to be 8.62×10^2 L/mol. Furthermore, the thermodynamic parameters (ΔG°, ΔH° and ΔS°) of MAH-β-CD–MF were obtained and the inclusion mechanism was also preliminarily discussed. In order to further confirm the experimental results, investigation on the molecular modeling was performed. On the basis of the significant enhancement of the fluorescence intensity of MF, a spectrofluorimetric method for MF determination in bulk aqueous solution in the presence of MAH-β-CD was developed. The linear range was 2.00×10^{-8}–9.00×10^{-5} mol/L and the detection limit was 3.36×10^{-9} mol/L. The proposed method was successfully applied to determine MF in tablets, serum and urine with the satisfactory result.

1. Introduction

β-Cyclodextrin (β-CD), the macrocyclic compound with seven D-glucopyranose units linked by α-1,4-glycosidic bonds, is well known to have a hollow truncated cone with a hydrophobic cavity and a hydrophilic wall, the narrow rim bearing primary hydroxyl groups and the wide rim secondary hydroxyl groups [1]. These properties enable β-CDs to encapsulate guest molecules which possess suitable polarity and dimension [2,3]. Drug molecules can indicate different properties through the formation of inclusion complexes with CDs, such as the enhancement of the solubility, stability, and bioavailability [4,5]. However, native β-cyclodextrin is very poorly soluble in water (1.85 g/100 mL, 25 °C) [6]. Cyclodextrins modified with hydrophilic substituents have enhanced solubilities in water compared to their native form [7]. While chemical modifications are often aimed at increasing the solubility of the cyclodextrin or of the inclusion complex, the presence of substituents may also contribute to the complexation of the host. In our previous study [8], a modified β-cyclodextrin carrying seven vinyl carboxylic acid groups (MAH-β-CD) with high solubility (36.8 g/100 mL H_2O) was successfully synthesized and studied as drug carriers. It exhibited good drug inclusion abilities.

Mefenamic acid {2-[(2,3-dimethylphenyl)amino]benzoic acid, MF; Fig. 1} is a non-steroidal anti-inflammatory drug with antipyretic and strong analgesic properties. MF is used for the treatment of joint disorders and various kinds of pain such as headache, dental pain, post-operative and post-partum pain. It has been widely applied in pharmaceutical field [9,10]. Nevertheless, the drug's direct application and determination is greatly restricted due to its low aqueous solubility. Therefore, it is quite meaningful theoretically and practically to improve the solubility of MF and determine MF in aqueous solution. To date, several methods, such as capillary electrophoresis, spectrophotometry and chromatography have been reported in the literatures for determination of MF and related mixtures [11–15]. Among these studies, there is no spectrofluorimetric way for MF determination in the presence of MAH-β-CD.

Fluorescence spectroscopy is a powerful tool to investigate the host–guest molecular systems with both high sensitivity and high selectivity [16]. The remarkable advantages of fluorescence analysis are that it is capable of measuring much lower concentrations than spectrophotometric analysis, and it is potentially more selective because both the excitation and emission wavelength can be varied. The sensitivity of the fluorescence detection of host–guest molecular interaction depends upon the electronic or steric changes of the chromophore being responsible for the fluorescence behaviour.

In this study, study on the supramolecular interaction of MAH-β-CD and MF was carried out by spectrofluorimetry. Phase

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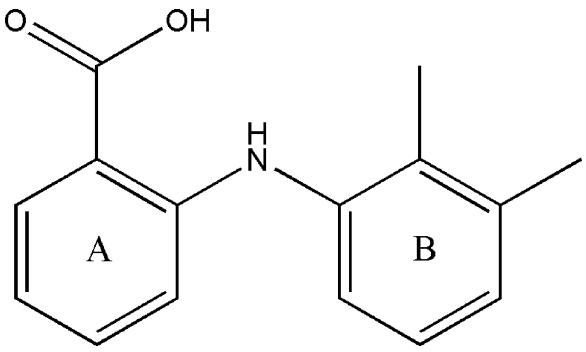

Fig. 1. The molecular structure of MF.

solubility studies were also performed. Moreover, the inclusion constant was calculated by the typical double reciprocal plots. In addition, the thermodynamic parameters (ΔG°, ΔH° and ΔS°) were obtained in the test and molecular modeling studies were also executed. In order to obtain the best measurement conditions and the maximum fluorescence intensity of MAH-β-CD–MF, a series of optimization conditions were investigated. On the base of which, a spectrofluorimetry was established to determine MF in tablets, serum and urine. The proposed method for MF determination is fairly simple and rapid, which is of significance for analytical determination.

2. Experimental

2.1. Chemicals and reagents

β-CD (Shanghai Chemical Corp.) was purified by two recrystallizations in water, followed by vacuum drying at the temperature of 60 °C. MAH-β-CD was synthesized according to our previous work [8] and its stock solution (1.0×10^{-2} mol/L) was freshly prepared with water. MF (Wuhan Yuancheng Technology Development Co., Ltd.) was recrystallized once from ethanol and the standard stock solution (1.0×10^{-4} mol/L) was prepared in ethanol. DMF (Shanghai Chemical Corp.) was purified by desiccation with activated molecular sieve and decompression distillation. Mefenamic acid tablets (Mudanjiang Lingtai Pharmaceutical Co., Ltd., China) were purchased. Other chemicals used were of analytical reagent grade without further purification. The doubly distilled water was used throughout this work.

2.2. Instruments and apparatus

All fluorescence measurements were performed with RF-5301PC spectrofluorimeter (Shimadzu, Japan). The pH measurements were made with a pHS-3C digital pH meter (Shanghai Leici, China) with a combined glass–calomel electrode.

2.3. Experiment procedure

2.3.1. Spectrofluorimetric determination of MF

Into a 10 mL color comparison tube, solutions were added in the following order: 1.0 mL (1.0×10^{-4} mol/L) of MF, 1.0 mL (pH 7.9) of H_3BO_3–KCl–NaOH buffer solution and an appropriate amount of 1.0×10^{-2} mol/L MAH-β-CD. The mixture was diluted to the mark with water and ultrasonically oscillated for 20 min at room temperature. The fluorescence intensity of MAH-β-CD–MF was measured at $\lambda_{ex}/\lambda_{em}$ = 367 nm/428 nm, $slit_{ex/em}$ = 5/10 nm.

2.3.2. Phase solubility studies

Phase solubility investigations were carried out in aqueous medium according to Higuchi and Connors's method [17]. The excessive guests of MF were added to 10.0 mL of aqueous solutions containing different concentrations of MAH-β-CD (0, 2, 4, 6, 8 and 10 mmol/L), respectively. All solutions containing MF were stirred for more than 24 h at room temperature. After equilibrium was reached, a volume of the upper liquids were withdrawn and filtered through a 0.45 μm hydrophilic membrane filter. The concentrations of MF in the filtrate were determined by spectrofluorimeter.

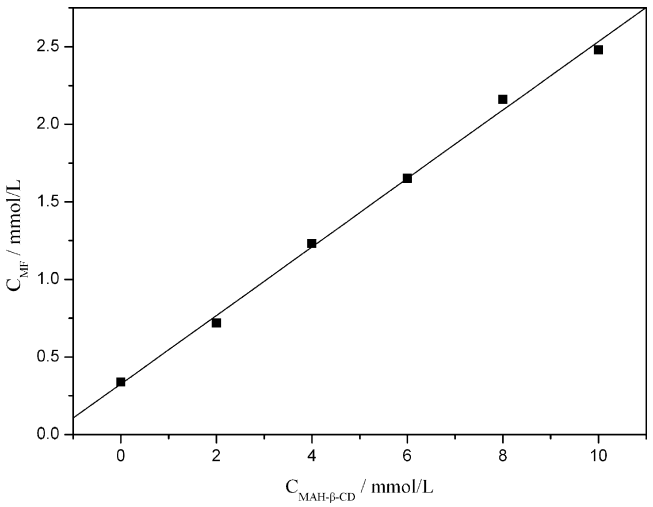

Fig. 2. Phase-solubility diagram for the MAH-β-CD/MF system.

2.3.3. Spectrofluorimetric determination of stoichiometry and inclusion constant

1.0 mL of 1.0×10^{-4} mol/L MF and 1.0 mL pH 7.9 H_3BO_3–KCl–NaOH buffer solution were added to a colorimetric tube, then the varied amounts of MAH-β-CD (0.0, 1.0, 2.0, 3.0, 4.0 and 5.0 mL of 1.0×10^{-2} mol/L) were added sequentially. The mixture was diluted to 10.0 mL with water and ultrasonically oscillated for 20 min at room temperature. The fluorescence spectra were performed. The stoichiometry and inclusion constant of MAH-β-CD–MF were gained from the double-reciprocal plots [18].

2.3.4. Calibration graph of MF

The standard calibration curve method was used in the quantitative determination of trace amount of MF in tablets, serum and urine. An aliquot of solutions containing 0.0–1.0×10^{-3} mol/L of MF were added in colorimetric tube, respectively, then, 1.0 mL (pH 7.9) of H_3BO_3–KCl–NaOH buffer solution and 5.0 mL of 1.0×10^{-2} mol/L MAH-β-CD were added sequentially. The mixed solution was diluted to 10 mL with water and oscillated ultrasonically for 20 min. The fluorescence intensities at 428 nm were measured.

3. Results and discussion

3.1. Phase solubility studies

The phase-solubility technique has been attracted extensive attentions on the solubility of some drugs in the presence of β-CD derivatives [19,20]. Fig. 2 exhibits the phase-solubility diagrams of MF in MAH-β-CD solutions. It could be observed that the solubility of MF increased linearly with increasing concentration of MAH-β-CD. When $C_{MAH-\beta-CD} = 1.0 \times 10^{-2}$ mol/L, the solubility of MAH-β-CD/MF enhanced nearly three times. According to the model proposed by Higuchi and Connors [17], this diagram is consistent with A_L type, which could indicate the formation of water-soluble inclusion complex. Moreover, the complexing agent (MAH-β-CD) is present in first-order degree with respect to MF