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Determination of amantadine and rimantadine using a sensitive fluorescent probe

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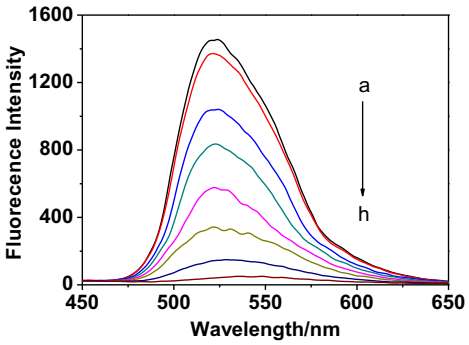
HIGHLIGHTS

- The analysis method is novel.
- A novel fluorescent probe method was used to determine the analyte.
- The method had higher sensitivity than all of reported analysis methods for amantadine and rimantadine.
- The interaction models of the complexes was established through theoretical calculations.
- The mechanisms of the competing reactions were studied using ^{1}H NMR.

GRAPHICAL ABSTRACT



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ABSTRACT

Amantadine hydrochloride (AMA) and rimantadine hydrochloride (RIM) are non-fluorescent in aqueous solutions. This property makes their determination through direct fluorescent method difficult. The competing reactions and the supramolecular interaction mechanisms between the two drugs and coptisine (COP) as they fight for occupancy of the cucurbit[7]uril (CB[7]) cavity, were studied using spectrofluorimetry, ^{1}H NMR, and molecular modeling calculations. Based on the significant quenching of the supramolecular complex fluorescence intensity, a fluorescent probe method of high sensitivity and selectivity was developed to determine AMA or RIM in their pharmaceutical dosage forms and in urine samples with good precision and accuracy. The linear range of the method was from 0.0040 to 1.0 μg mL^{-1} with a detection limit ranging from 0.0012 to 0.0013 μg mL^{-1}. This shows that the proposed method has promising potential for therapeutic monitoring and pharmacokinetics and for clinical application.

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Introduction

Cucurbit[*n*]uril (CB[*n*], *n* = 5–8, 10) is a macrocyclic compound consisting of *n* glycoluril units connected by 2*n* methylene bridges [1–3]. The symmetrical CB[*n*] hosts resemble a hollow barrel with hydrophobic cavities and restrictive polar portals lined with ureido carbonyl groups [2,3]. These characteristics enable CB[*n*] to form significant stable complexes with a variety of guest molecules in aqueous solution [4–7]. Various organic drugs and biologically relevant molecules have been encapsulated by CB[*n*] [7–13]. The formation of inclusion complexes often enhances or disturbs the photophysical and photochemical properties of the included guest molecules [14]. The cucurbit[7]uril (CB[7], Fig. 1) host has been of particular interest in recent years because of its superior solubility in aqueous solution compared with the other CB[*n*] members and its remarkable capability to form host-guest complexes with organic guest molecules [4–13]. An increasing number of papers

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on different CB[*n*] host-guest interactions with a wide range of compounds have been reported over the last few years [4–13]. However, little attention has been devoted to their fluorescent properties and potential analytical applications. Megyesi et al. discovered that the formation of an inclusion complex between CB[7] and berberine leads to improved fluorescence intensity [8]. Recently, Pozo and co-workers reported the 1:1 complex formation between carbendazim and CB[7], and a selective spectrofluorimetric method was devised to examine carbendazim in oranges [9]. In our laboratory, we studied the supramolecular interactions of CB[*n*]–isoquinoline alkaloid complex and its applications to the molecular recognition and determination of isoquinoline alkaloids and other drugs, owing to its excellent optical properties [10,11].

Coptisine (COP, Fig. 1) is a natural isoquinoline alkaloid [15]. Aqueous solution of COP exhibits weak native fluorescence. However, in the preliminary studies, the fluorescence of COP in aqueous solutions was observed to be greatly enhanced in the presence of CB[7] [10].

Amantadine hydrochloride (AMA, Fig. 1HH), an antiviral agent, can increase dopaminergic activity in the peripheral and central nervous systems. AMA has been clinically used against influenza type A virus infection to ameliorate its symptoms (when administered during the early stages of the infection) and to control herpes zoster [16]. Rimantadine hydrochloride (RIM, Fig. 1HH), which exhibits equal efficacy and fewer adverse reactions than AMA, has been clinically used for infection therapies caused by a broad range of RNA-containing viruses – the influenza A virus, in particular [17]. A number of assays have been reported for the determination of AMA and/or RIM in biological and pharmaceutical samples, including spectrophotometry [18–20], near-infrared spectroscopy [21,22], GC [23], HPLC [24–26], thin-layer chromatography [27], capillary electrophoresis [28,29], and potentiometry [30,31]. However, HPLC generally requires complicated and expensive equipment and labor-intensive sample preparation procedures. Some other methods are not sensitive enough.

Spectrofluorometry is considered as the most convenient analytical technique in pharmaceutical analysis, owing to its inherent simplicity, high sensitivity, and availability in most quality-controlled and clinical laboratories [18,32]. Considering that aqueous solutions of AMA and RIM have no native fluorescence, they cannot be directly determined through the normal fluorimetric method. Hence, the development of a fast, simple, and highly sensitive spectrofluorimetric method for the determination of AMA and RIM in aqueous solution is highly desirable.

Darwish et al. developed a fluorimetric method [33] for the determination of AMA based on the oxidation of the drug by cerium(IV) in the presence of perchloric acid with the assay detection limit of 0.021 μg mL^{-1}. Mahmoud et al. developed a spectrofluorimetric method [18] for the determination of AMA in capsules and in plasma. The method is based on the condensation of AMA with 1,2-naphthoquinone-4-sulphonate in an alkaline medium to form an orange-colored product. Its detection limit is 0.013 μg mL^{-1}. These methods have not been widely used because they are labor-intensive, they have poor reproducibility, and their sensitivity are not high enough.

In our study, the supramolecular fluorescent probe system is based on the competition between the guest molecules and the probe molecules for the hydrophobic cavity of CB[7]. Such competition results in optical property changes. In the absence of appropriate guest species, the probe molecules partially reside in the hydrophobic cavity of the CB[7] and form stable inclusion complexes. However, the presence of organic analytes leads to the decomplexation of the probe molecules and to a concomitant decrease in fluorescence intensity. To our knowledge, the use of COP as fluorescent probe for the determination of AMA and RIM has not yet been reported. The proposed method in the current study is fast, simple, and highly-sensitive. The detection limits for AMA and RIM are 0.0012 and 0.0013 μg mL^{-1}, respectively, making the proposed method more sensitive than any other method reported in the literature [18–31,33]. The proposed procedure was tested for the determination of drugs in their pharmaceutical dosage forms and in urine samples.

Experimental

Apparatus

Fluorescence spectra and intensity measurements were obtained using a Hitachi F-4500 spectrofluorimeter equipped with a 150 W xenon lamp (Japan). The slit widths of both excitation and emission monochromators were set to 5 nm. The fluorescence spectra were recorded at a scan rate of 1200 nm min^{-1}. All measurements were performed using a standard 10 mm path-length quartz cell at 25.0 °C ± 0.5 °C. The pH values were measured using a pHS-3 TC digital precision pH meter (Shanghai, China). ^{1}H NMR spectra were obtained using a Bruker AV-600 MHz spectrometer (Switzerland) in CD_3OD-D_2O (1:4, v/v).

Reagents and chemicals

AMA, RIM, and COP were obtained from the Chinese National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China) without further treatment. CB[7] was prepared and characterized according to reported procedure [3]. Amantadine hydrochloride (AMA) and rimantadine hydrochloride (RIM) were dissolved in double-distilled water to prepare stock standard solutions of 100 μg mL^{-1}. Coptisine (COP) was dissolved in 10 mL methanol then diluted with double-distilled water to prepare stock solutions with final concentration of 1.00 mM. A cucurbit[7]uril (CB[7]) stock solution of 1.00 mM was prepared by dissolving CB[7] in double-distilled water. Stock standard solutions were stable for several weeks at room temperature. Standard working solutions were prepared by diluting the stock standard solutions with double-distilled water before use. All other chemicals were of analytical reagent grade, and double-distilled water was used throughout the procedure.

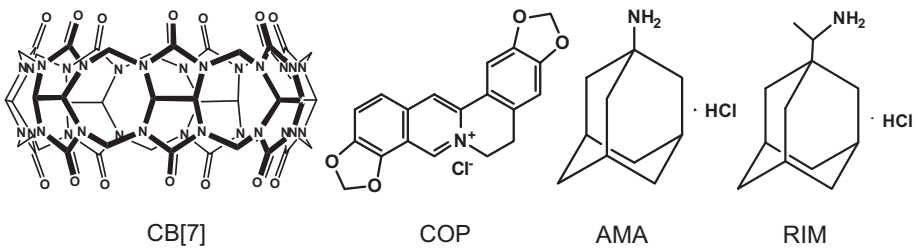

Fig. 1. The structures of CB[7], COP, AMA, and RIM.

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