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COMMUNICATION

Study of the Binding in an Aqueous Medium of Inclusion Complexes of Several Cyclodextrins Involving Fenoprofen Calcium

David Díaz,* Carolina Marta Escobar Llanos, and María Josefa Bernad Bernad

Facultad de Química, Edificio B, Departamento de Química Inorgánica, Laboratorio 213, UNAM, Delegación Coyoacan, México

ABSTRACT

Interactions among fenoprofen calcium and α-, β-, γ- and hydroxypropyl-β-cyclode xtrins (HP-β-CD) were evaluated in aqueous solution by UV/vis and fluorescence direct spectroscopies and monodimensional (1D) ^{1}H-NMR. Different UV/vis and fluorescence emission spectra were obtained to study the apparent binding constants (K) to define the most appropriate cyclodextrin to form the inclusion complexes (IC). β-CD and HP-β-CD clearly fit the magnitude of stability constant data of the complexes to take into account the pharmaceutical technology interest.

INTRODUCTION

The principal application of anti-inflammatory agents is in the realm of rheumatic diseases, which are at times accompanied by gastrointestinal problems. These conditions may be even further complicated by drug therapy (1). Nonsteroidal anti-inflammatory drugs, for example fenoprofen calcium (fen), are slightly soluble in water and sometimes cause an adverse reaction to the stomach upon oral administration (2).

Cyclodextrins are well known for their ability to form inclusion complexes, conferring on guests new physicochemical properties (3), and to reduce gastric irritancy of some nonsteroidal anti-inflammatory drugs (3,4). Szejtli (3) established that only inclusion complexes with binding constants between 200 and 5000 M^{-1} can be used to improve the bioavailability of hydrophobic drugs (3).

The aim of this article is to obtain experimental information to study the interaction between fen and several cyclodextrins in aqueous medium and to propose a cyclo-

* To whom correspondence should be addressed.

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dextrin for a possible pharmaceutical formulation of this anti-inflammatory drug.

MATERIALS AND METHODS

Fenoprofen calcium dihydrate was purchased from Sigma Chemicals (St. Louis, MO). α-, γ-, and hydroxypropyl-β-cyclodextrins (HP-β-CDs; degree of substitution = 9) were a donation from Cerestar (Hammond, IL). β-CD was a donation from Arancia (Edo. Mex., México) and was purified by successive washings with different solvents and dried under a vacuum line. The buffer components Na_2HPO_4 and NaH_2PO_4 and D_2O (99.9% atom D) were supplied by Aldrich Chemical (Milwaukee, WI). NaCl, analytical reagent, was purchased from Mallinckrodt (Paris, KY).

Inclusion complexes were prepared in buffer solution of pH 7.5, Na_2HPO_4-NaH_2PO_4 (0.07895 M) with constant ionic strength of NaCl 0.1 M and with increasing cyclodextrin concentration (1×10^{-3} to 10^{-2} M) and constant concentration of fen (1×10^{-5} M).

Inclusion Complexes Study

The solutions were assayed by direct spectrophotometry (5,6). UV/vis diode array spectrophotometer (Hewlet Packard 8452A) was coupled to a Peltier Hewlet Packard 89090A system to control the temperature. For fluorescence, a Spex FluoroMax was coupled to a recirculating bath. Fluorescence emission spectra were obtained with a slit of 0.8 and $\lambda_{excitation} = 278$ nm.

The values of K were calculated by the isotherm binding according to the inverse Benesi—Hildebrand model (6).

Monodimensional (1D) ^{1}H-NMR studies were achieved in unbuffered D_2O at 25°C in a 300-MHz Varian Unity Plus. Spectra were collected with a 451-pulse (6.7 μsec) spectral width of 3229.5 Hz and 3.002 sec of acquisition time.

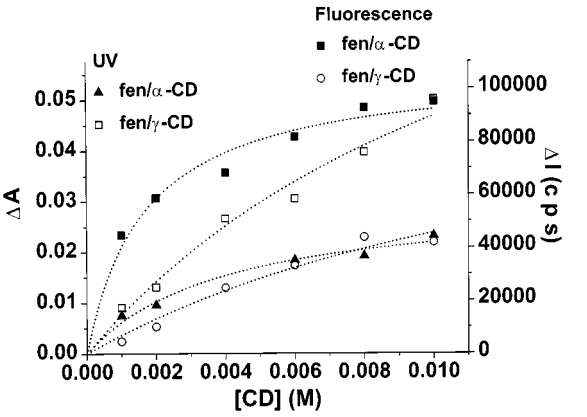

Figure 1. Hyperbolic dependence on cyclodextrin concentration for the complexes assayed by fluorescence (■, ○) and UV (▲, □).

RESULTS AND DISCUSSION

Inclusion complexes of fen with cyclodextrins in all cases show apparent 1:1 binding constants (Table 1) obtained from the inverse Benesi–Hildebrand model, whose representation is shown in Fig. 1. For each cyclodextrin, the K values obtained from absorption and emission data are in the same order. Similar behavior is common in the literature (7).

β-CD and HP-β-CD show the largest stability in this complexation study (Table 1). The cyclodextrin internal diameter plays an important role in the inclusion process (3). Because of the small internal diameter of α-CD and the large internal diameter of γ-CD, fen fits better into β-CD and HP-β-CD due to the adequate size relationship between fen and their internal diameter cavities.

Table 1

Cyclodextrin	Apparent Binding Constants K (UV), M^{-1}	Apparent Binding Constants K (fluorescence), M^{-1}	Stoichiometry fen:CD
α-CD	253 ± 18	481 ± 49	1:1
β-CD	960 ± 94	1008 ± 146	1:1
γ-CD	52 ± 1.96	63 ± 0.51	1:1
HP-β-CD	705 ± 42	1197 ± 104	1:1

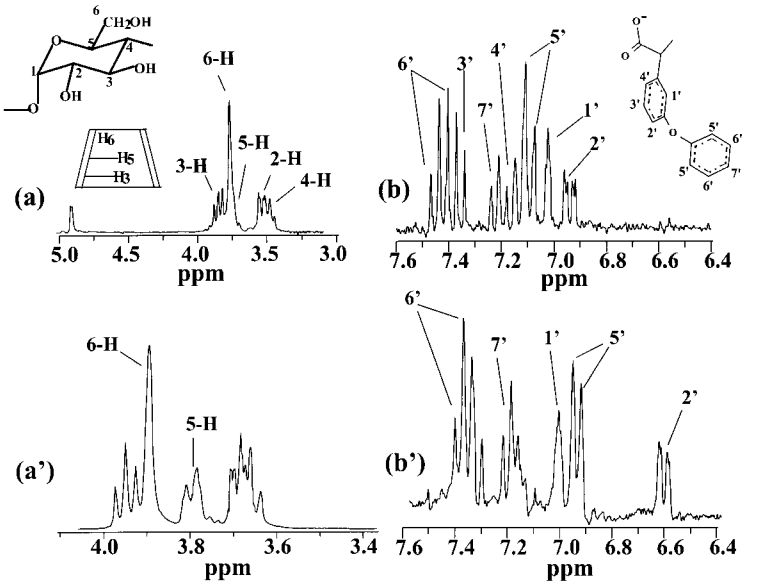

Figure 2. ^{1}H-NMR spectra in D_2O. (A) β-CD, (a') fen/β-CD, (b) fen, (b') fen/β-CD.

The effect of increasing concentration of cyclodextrins on the absorption and emission spectra of fen reveals hypochromic and batochromic and hyperchromic shifts, respectively. Both features are characteristic of inclusion complex formation (6). The cyclodextrin cavity behaves similarly with organic solvents, affording an apolar surrounding for the included chromophore and isolating the included section from the aqueous environment (8,9). Therefore, the fluorescence of the fen increases.

To confirm the interaction among fen and cyclodextrins, the spectral study was completed with 1D ^{1}H-NMR in D_2O. The ^{1}H-NMR spectrum of β-CD and of inclusion complex with fen are presented in Fig. 2. Bands corresponding to β-CD are represented in Fig. 2(a) and (a'). The shift corresponding to 5-proton signal, $\Delta\delta = 0.04$ ppm, reveals the formation of the inclusion complex with fen (10,11). The signals that correspond to external H, 2-H, and 4-H are hardly changed at all. The bands corresponding to fen aromatic section are also represented in Fig. 2(b) and (b'). The shifts in the benzenic ring bands support the fact that this section majority interacts with β-CD internal cavity.

Spectra of fen/α-CD and fen/γ-CD show a 5-H shift (0.03 ppm for α-CD and 0.08 ppm for γ-CD), and the signals corresponding to the external protons are changed, more in the case of fen/α-CD. The benzenic ring in the fen is involved in the inclusion process with γ-CD. Because of this larger γ-CD cavity, there will be too a large space between fen molecules and the section of the cavity that remains in contact, and then the interactions present will be weak. This fact may be proved by observing the K values in Table 1. Because of its size and of the presence of orthogonal glucose ring, α-CD shows steric blockage for the guest inclusion (3). Therefore, the section of benzenic ring of fen included will be smaller than in the other CDs.

CONCLUSIONS

The binding constants of these inclusion complexes majority depend on the size relationship between fen and CD cavity. The apparent 1:1 binding constant obtained from these systems indicate that β-CD and HP-β-CD are better than α-CD and γ-CD to form inclusion complexes with fen.

Considering the interval of binding constant values established by Szejtli (3), these systems with β-CD and HP-β-CD may improve the bioavailability of the fen.

^{1}H-NMR experiments verify the formation of inclusion complexes of fen with α-, β- and γ-cyclodextrin through benzenic ring.

These data are proof that make further investigations on anti-inflammatory drugs possible, taking into account the pharmaceutical technology interest that their complexes would represent.

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