FT-IR SPECTROSCOPY OF INCLUSION COMPLEXES
OF β-CYCLODEXTRIN WITH FENBUFEN AND IBUPROFEN*

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FT IR spectra for inclusion complexes of β-cyclodextrin with fenbufen and ibuprofen reveal the complexation process. The C=O stretching spectral region is used successfully to investigate this mechanism which implies strong restriction of the C=O group inside cyclodextrin cavity. The breaking of the hydrogen bonds plays an important role also.

Key words: infrared spectroscopy, inclusion complexes, cyclodextrins, antiinflammatories, fenbufen, and ibuprofen.

1. INTRODUCTION

Fenbufen (FEN, see Fig. 1) is an NSAID used in the treatment of rheumatic diseases and represents a weak acidic molecule with low solubility in water. Cyclodextrins (CDs), which are cyclic oligosaccharides and their hydrophilic derivatives are used for improving the solubility and dissolution rate of poorly water soluble NSAID.

Fig. 1. – Fenbufen molecule.


Few papers appeared as to be dedicated to the spectroscopic investigation of the inclusion complex (IC) of FEN with β-CD [1–3] or their photophysical and photochemical behaviour [4]. FEN is known to produce high incidence of skin rashes so the photo physical properties and their correlation with toxicity were recently investigated [5]. Due to its gastrointestinal irritation, FEN is prepared as an inclusion complex with β-CD and the drug release was studied by using it as suppository. In recent years the dermal route for drug administration was intensely studied [3], but no detailed vibrational analysis of IC was done.

Ibuprofen (IBU, see Fig. 2) is also a NSAID, being very slightly soluble in water, causing adverse reactions in oral administration [6].

Fig. 2. – Ibuprofen molecule.

The present work is aimed at characterising, by means of infrared spectroscopy, the structure of 1:1 β-cyclodextrin (β-CD) inclusion complexes with the non-steroidal anti-inflammatory drugs (NSAID) FEN and IBU, members of the propionic acid class. Two different methods of obtaining the inclusion complexes of these drugs were used: the co-precipitation and the freeze-drying (lyophylization) ones. The different solubility of these two drugs in water at identical pH conditions was also taken into account.

2. EXPERIMENTAL

The following methods were used in order to prepare the mentioned IC: co precipitation (co) and lyophylisation, i.e. freeze drying (fd) ones. Other method of IC preparation that was recently used [7, 8] is consisting on the enhancement of IBU dissolution via wet granulation with β-CD. Physical mixtures (pm) of FEN or IBU and β-CD (1:1 molar ratio) were prepared also.

FT IR spectra were obtained using the KBr pellet technique; they were collected with Bomem DA3 FT IR spectrometer, under vacuum in the 4000 to 400 cm⁻¹ spectral range with a resolution of 2 cm⁻¹. Good S/N ratios were obtained by co adding 250 interferograms.
3. RESULTS AND DISCUSSION

The infrared spectra of the complexes, Figs. 3 and 4, were analysed and compared with the spectra of the pure compounds and their physical mixtures, respectively. The differences, which appear in the 1800–1600 cm$^{-1}$ spectral region, were analysed in terms of the implication of different molecular groups of the guest and the host molecules in the inclusion process. A special attention was paid to the 4000–2500 cm$^{-1}$ region, where absorption bands of different O-H groups present in these supramolecular assemblies appear.

![Absorbance vs Wavenumber](image)

Fig. 3. – FT IR spectra (4000–2500 cm$^{-1}$) of FEN (_____), pm (------), co (.....), fd (.-.) and β-CD (.-.). 4000–2500 cm$^{-1}$

In this spectral region one identify, Figs 3 and 4, the ν(O-H) stretching vibrational modes belonging to different OH groups, primary, secondary and H-O-H ones, each giving typical absorption bands [9]. The effect of the guest molecules on the position and intensities of these bands depends also [10] on both
the size and the rearrangement of the guest within the host cavity. A frequency increase can be due to the weakening of the hydrogen bond in the heptameric host units. The hydrophobic molecules at the interface insert into the space between the hydrophobic chains of the β-CD and enhance the amphiphilic character of the CD [11]. In the 2800–3000 cm$^{-1}$ one see the C-H stretching bands, which are unchanged upon complexation.

1800–1600 cm$^{-1}$

The most influenced bands of the FEN and IBU upon complexation are the carbonyl group vibrations, see Figs. 5 and 6, respectively.

In the case of FEN two bands appear in this spectral region, one centred at 1711 cm$^{-1}$ (peak 1, the carboxyl carbonyl) and another one, a doublet (peak 2), centred on 1681 cm$^{-1}$, assigned to ketone carbonyl. The intensity of the peaks 1 and 2 are reduced drastically (more for peak 1 than for peak 2) and broaden considerably suggesting a stronger interaction between FEN and β-CD. One can explain the frequency shift of the ν(C=O) band by the restriction of the C=O group of FEN or IBU into the β-CD cavity. The drastic decrease of the intensity of these two bands tends to explain the inclusion of these groups into the CDs cavity. It has been recently established that FEN molecule is deeply included into the β-CD cavity, the C=O group has to be located in a hydrophobic microenvironment [1].
The assignment of the C=O stretching vibration of IBU was done by comparison with the ketoprofen [12, 13]. The C=O stretching vibration appears unchanged in IBU and pm (1723 cm\(^{-1}\)) spectra but is shifted to a higher frequency (1735.7 cm\(^{-1}\) with a shoulder at 1711.6 cm\(^{-1}\)) in co-precipitated and in lyophilised products and diminishes strongly in intensity as was recently observed [13]. This frequency shift might be due to the breakdown of intermolecular hydrogen bonding strengthened by ionic resonance, associated with IBU dimers and the establishment of weaker forces, already reported [8, 14] and the formation of a monomeric dispersion of drug as an interaction with the hydrophobic cavity of CDs. Whereas for co spectrum these two bands appear clearly, in the case of fd spectrum only a very broad band appears, suggesting an increase of the amorphous state, typical for lyophilised products, as X-ray diffraction [13] measurements demonstrate.
The complexation of IBU with β-CD leads to a considerably increase of their solubility in water and has a stabilising effect [15] on the pharmacologically active substance. In the case of FEN complexation with β-CD, the drug release was considerably promoted when used together with some ointment bases [2, 3].

4. CONCLUSIONS

The fundamental changes which appear in the FT IR spectra of IC complexes of FEN and IBU with β-CD are reflected mainly in the C=O stretching spectral region. These changes suggest similar basic complexation mechanism for both guest molecules included in the torus host cavity.

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