Infrared spectroscopic study of triacetyl-β-cyclodextrin and its inclusion complex with nicardipine

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Abstract. Infrared spectra of inclusion compounds of triacetyl-β-cyclodextrin with nicardipine hydrochloride were compared and analysed with those corresponding to their physical mixture and the pure compounds, respectively. Different O–H stretching vibrations, assigned to water molecules, were located in the Fourier Transform Infrared (FT IR) spectra of triacetyl-β-cyclodextrin, and its inclusion complex with nicardipine obtained by spray-drying (SD) method. Water molecules involved in various hydrogen bonds environments change their status during complexation process. Evidences are observed of the formation of the complex especially in the spectral regions of the amino and carbonyl stretching vibrations.

Keywords: FT IR spectra, self-deconvolution, inclusion complex, nicardipine, triacetyl-β-cyclodextrin

1. Introduction

Cyclodextrins (CDs) act as molecular hosts for a large variety of guest molecules, polar and non-polar ones. In order to increase their host qualities, derivatives of CDs were prepared, among them triacetyl-β-cyclodextrin (TA-β-CD). This molecule has a rigid cavity similar to the one of β-CD, but all the OH groups of β-CD are replaced by $OCOCH_3$ groups. It is interesting to make a comparative spectroscopic study concerning these two CDs. In the case of pure β-CD [1,2] both infrared and Raman spectra in the 4000–3000 cm^{-1} region were reported and analysed, whereas for β-CD complexes only the FT IR spectra of copper(II)-β-CD has been investigated [3] in this spectral region. FT IR, X-ray diffraction and thermal studies [4–6] were used in the structure investigation of different inclusion complexes in solid state. Some interesting studies were reported on the hydration and dehydration processes [2,7] and thermal stability of β-CD [8] or hydrophobically modified β-CD [9]. In order to clarify the nature of the bands that appear in the 4000–3000 cm^{-1} spectral region, infrared spectra at low temperature (liquid nitrogen and liquid helium) were reported [10]. From these experimental data, Fourier self-deconvolution and band fitting procedures, the number of the components in the 4000–3000 cm^{-1} spectral region was determined and an assignment of these O–H stretching bands appearing there was performed [1]. Until now, there are no publication, to our knowledge, on TA-β-CD and its inclusion complexes by FT IR
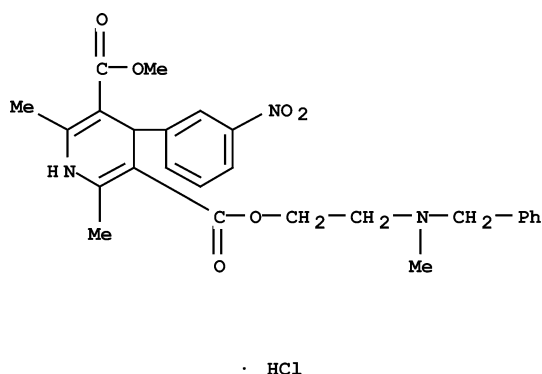

Fig. 1. Structural formula of nicardipine hydrochloride.

spectroscopy. This paper presents the results of an analysis applied to this case where its inclusion complex contains nicardipine hydrochloride (NIC), Fig. 1, a calcium channel-blocking agent used in the management of mild to moderate hypertension, angina pectoris and cerebral disease.

2. Experimental

Nicardipine hydrochloride from Effechem SRL (Milan, Italy) and TA-β-CD from Aldrich were used without further purification. Equimolar quantities of NIC and TA-β-CD were dissolved in ethanol : water (50 : 50). The resulting mixture was stirred for 24 h at room temperature and the obtained solution was subsequently spray-dried (LabPlant SD-05), under the following conditions: 50 m^3/h – air flow, 1.0 bar – atomising air pressure, 160°C – inlet temperature, 85°C – outlet temperature and 400 ml/h – flow rate of solution. The product was sieved through a 63–160 μm mesh. A physical mixture (PM) of NIC and TA-β-CD (1 : 1 molar ratio) was also prepared.

The FT IR spectra were obtained using the KBr pellet technique, 0.8 mg of sample in 300 mg of KBr. They were collected with a Bomem DA3 FT IR spectrometer, working under a vacuum (pressure $\leqslant$ 133.3 Pa) to avoid IR absorption from atmospheric water. The effective apodized resolution was $s = 1.77$ cm^{-1} (RES = 2 and Hamming apodizing function). Good S/N ratios were obtained by coadding 250 interferograms. Different procedures for obtaining the Fourier self-deconvolution of the FT IR spectra have been proposed recently [11,12]. Our work was done with the so-called reference Fourier self-deconvolution procedure (RFSD) [12]. Second derivatives of the FT IR spectra and curve fitting were obtained with Thermo Galactic GRAMS/32 software.

3. Results and discussion

3.1. 4000–2000 cm^{-1}

This spectral region, where the OH stretching vibrations appear, presents an overlapping of primary and secondary OH group vibrations in β-CD, bonded intra- or inter-molecularly. Applying deconvolution techniques to the FT IR spectra of β-CD and based on the results obtained previously [1,3], it has been observed in this region that a superposition of the OH stretching vibrations corresponding to interstitial and intra-cavity water molecules occurs together with those assigned to the primary and secondary
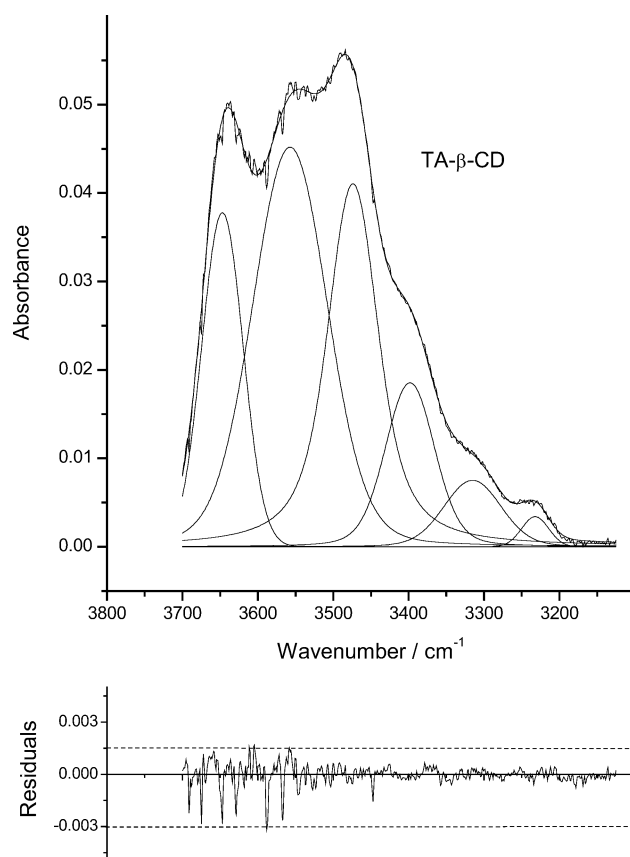
Fig. 2. O–H stretching region for TA-β-CD.

OH groups of the β-CD. In the case of TA-β-CD there are no primary and secondary OH groups, being replaced by $OCOCH_3$ groups, therefore the spectrum must reflect this change. Indeed, the FT IR spectra of TA-β-CD, see Fig. 2, of the inclusion complex (Fig. 3) and of the physical mixture (Fig. 4), do not contain the bands that correspond to primary and secondary OH groups [1,3]. It should be remarked the low absorbance values in this spectral region in the case of TA-β-CD, whereas for β-CD [1,3] the corresponding absorbance values are ten times higher for the same concentration in KBr pellet.

Nevertheless, some very weak bands appear above 3400 cm^{-1}, Fig. 2. They should be assigned to O–H stretching vibrations of water molecules involved in different hydrogen bonding schemes [1,3]. By applying Fourier self-deconvolution techniques [12] and second derivative computations the wavenumber of the maxima for the band components have been evaluated. Curve fitting procedures with Voigt functions were applied to the experimental profiles based on these wavenumber values. Relative integrated intensities of the band components, I_{rel}, were calculated as the ratios of each integrated intensity *vs.* the sum of the component intensities, Table 1 and Figs 2–5. Relevant changes of intensity were observed for the components at ∼3480 and ∼3420 cm^{-1} for PM and SD, Table 1 and Figs 3 and 4. The significant decrease of intensity for the component at ∼3480 cm^{-1} and the increase for the component at ∼3420 cm^{-1} on complexation suggest a change of the number of water molecules involved in the hydrogen bond scheme. A redistribution of the water molecules among the different hydrogen bonds sites could take place. As dehydration of β-CD affects the water molecules included in its cavity to a
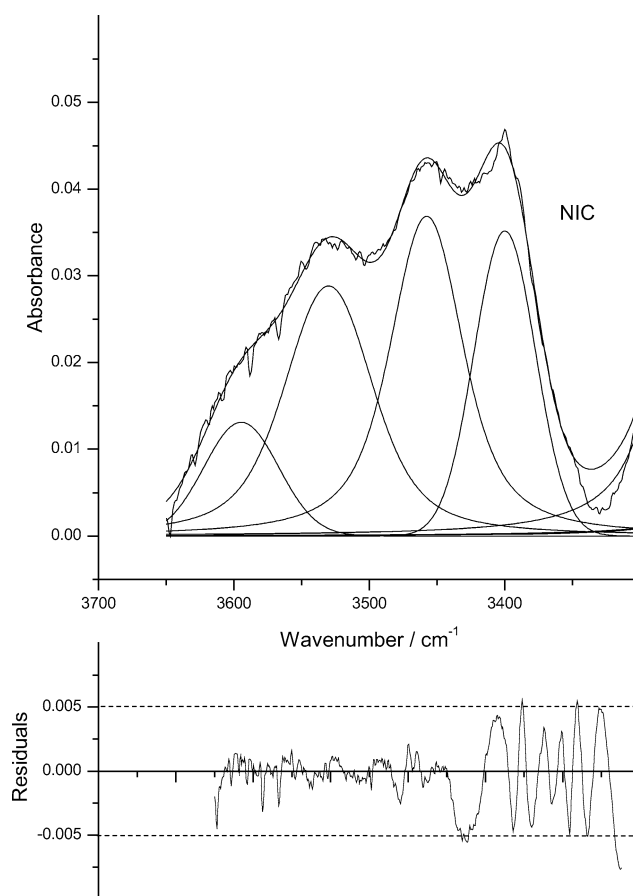
Fig. 3. O–H stretching region for NIC.

larger extent than the interstitial ones [13], it would be inferred that during the complexation process the drug enters into the TA-β-CD torus-shaped cavity and the water molecules from the inside of the torus change their hydrogen bonding environment.

An assignment of the bands that are changed upon complexation process is done and a possible explanation for these spectral changes is given. As concerning the functional groups of the NIC, one can observe, see Fig. 6, a medium intensity band at 3253 cm^{-1}, probably assigned to N–H stretching vibration [14–16] and a strong doublet band at 3182 and 3199 cm^{-1}, assigned to C–H stretching vibration. These bands are also observed in the spectrum of the physical mixture but in the case of the spray drying compound (SD), their intensities diminish considerably, specially the one located at 3253 cm^{-1}, the other two weakens and broadens clearly. On going to lower frequencies, the structured bands of NIC in the 2700–2300 cm^{-1} range are probably due to (NH–N) stretching bands. This structure of bands is also observed in the spectrum of PM but it is quite difficult to be observed in the spectrum of SD, a possible explanation being the breaking of these intermolecular links.

3.2. 2000–700 cm^{-1}

Comparing the spectra of NIC and TA-β-CD in this spectral region, see Fig. 7, a strong band of NIC may be observed at 1707 cm^{-1} with a shoulder at 1704 cm^{-1}, both due to the $\nu_{C=O}$ vibration of the ester
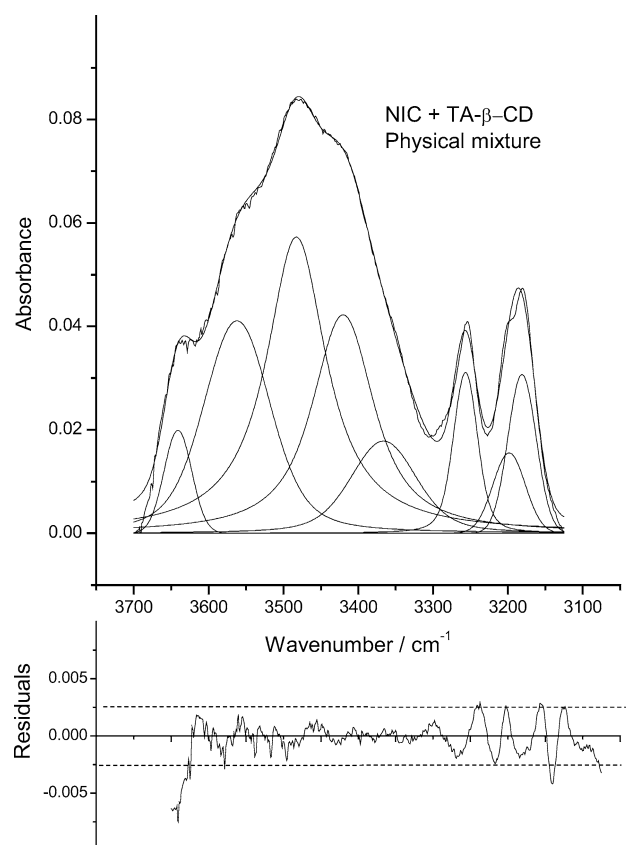
Fig. 4. FT IR spectrum of the physical mixture NIC + TA-β-CD, 1 : 1 molar.

groups. However, a strong band is observed in the TA-β-CD spectrum at 1757 cm^{-1}, but in this case due to $\nu_{C=O}$ vibration of the acetyl group.

In the spectrum of PM both bands are observed, whereas in the SD spectrum the $\nu_{C=O}$ band of the ester groups of NIC is shifted to lower frequencies (1701 cm^{-1}), diminished in intensity and broadened. Similar effects were observed and explained previously [17] for the HP-β-CD complex of NIC (NIC-HP-β-CD), suggesting the formation of hydrogen bonds between the carbonyl groups of NIC and the hydroxyl groups of the host cavity during inclusion phenomena. These observations are in full agreement with other authors [18] who reported that when a carbonyl group is joined to a hydroxyl by hydrogen bonds, the stretching band is shifted to lower frequencies due to the weakening of the carbonyl radical double bond. In this case, hydrogen bonds may be formed with water molecules present in the cavity. That is, a weakening of the double bond in the carbonyl group appears.

Phenyl group vibration (ring carbon–carbon stretching) appears at 1623 cm^{-1} in the spectrum of NIC, but it diminishes considerably of intensity in the spectrum of SD.

About the NO$_2$ group vibrations, see Fig. 8, their bands are located at 1536 cm^{-1}, ν_{as}(NO$_2$), and 1354 cm^{-1}, ν_{s}(NO$_2$), respectively. The band at 1494 cm^{-1} is probably due to the phenyl stretching vibration. Upon complexation the ν_{as}(NO$_2$) band is shifted to lower frequencies, 1530 cm^{-1}, and the ν_{s}(NO$_2$) is shifted to 1350 cm^{-1}, whereas the phenyl band of SD ($\sim$1490 cm^{-1}) is less affected by this process.

Table 1

Spectral treatment of the 3800–3100 cm^{-1} region: wavenumber of the band maxima obtained by spectral deconvolution, their corresponding relative integrated intensities (I_{rel}) and absorbances (A_{max}) evaluated by curve fitting

|							
			NIC + TA-β-CD, physical mixture				
ν/cm^{-1}	3640	3562	3482	3420	3366		
A_{max}	0.020	0.041	0.057	0.042	0.017		
I_{rel}	0.043	0.233	0.360	0.262	0.102		
			NIC + TA-β-CD, spray drying				
ν/cm^{-1}	3638	3559	3477	3419	3368	3266	3201
A_{max}	0.027	0.058	0.048	0.047	0.026	0.019	0.013
I_{rel}	0.064	0.290	0.224	0.305	0.116		
			TA-β-CD				
ν/cm^{-1}	3646	3557	3473	3398	3315	3232	
A_{max}	0.0377	0.0451	0.041	0.0185	0.007	0.0034	
I_{rel}	0.169	0.390	0.283	0.109	0.050		
			NIC				
ν/cm^{-1}	3594	3530	3457	3399			
A_{max}	0.0131	0.0288	0.0368	0.0351			
I_{rel}	0.103	0.314	0.353	0.230			
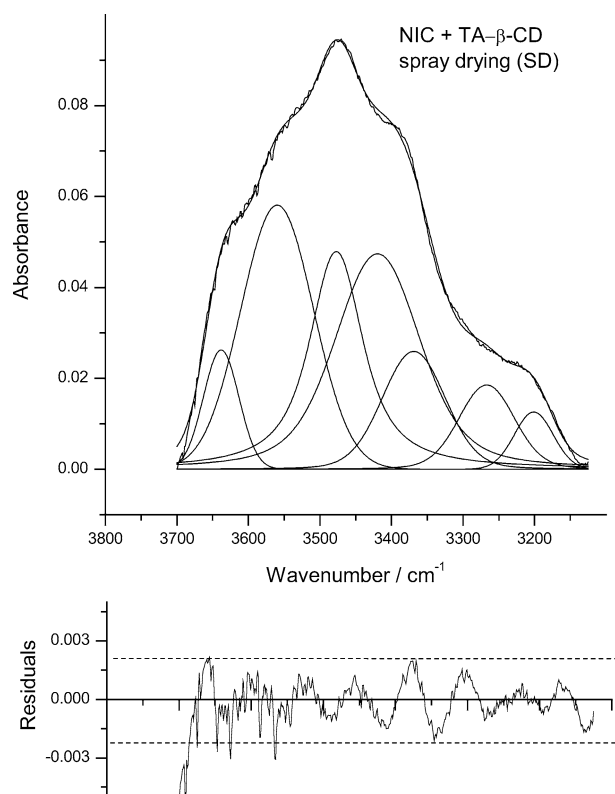
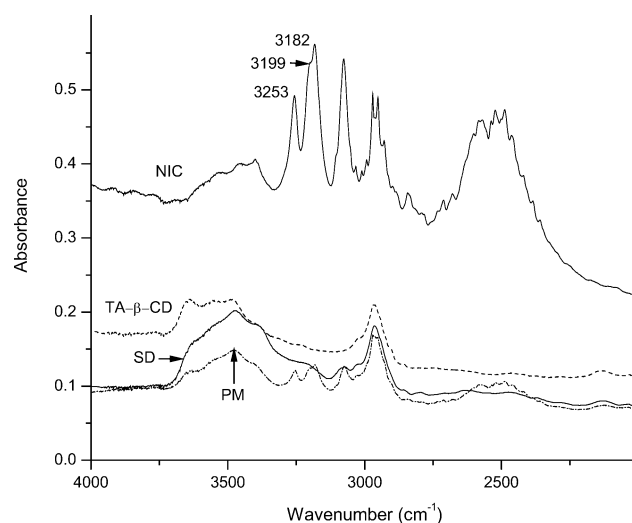Fig. 5. O–H stretching region for the spray drying product.

Fig. 6. FT IR spectra (4000–2000 cm^{-1}) of NIC, TA-β-CD, PM and SD.
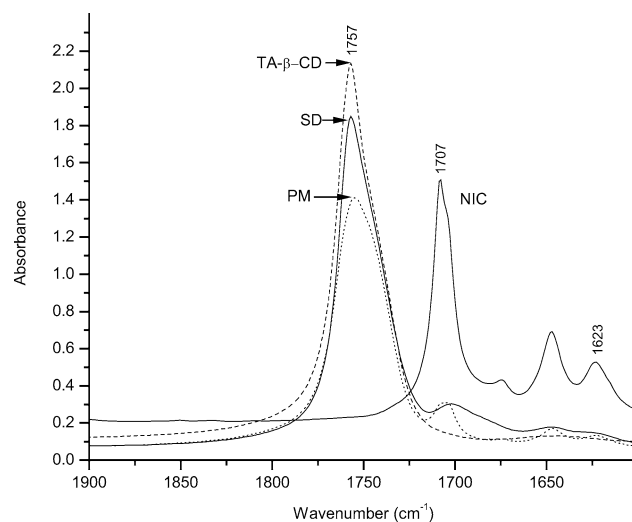

Fig. 7. FT IR spectra (2000–1600 cm^{-1}) of NIC, TA-β-CD, PM and SD.

The band at 789 cm^{-1}, see Fig. 9, in the spectrum of NIC and assigned to vibrations of the –CH$_2$– group is shifted to lower frequencies (782 cm^{-1}) and broadens in SD spectrum. The band at 745 cm^{-1} is unchanged in position upon complexation but broadens.

Finally, the doublet band at 711 and 700 cm^{-1} in NIC and PM spectra, become a broad band centred at 704 cm^{-1} in SD spectrum.

From this spectral analysis it can be concluded that the most sensitive functional groups, involved in the complexation process, are the carbonyl and the nitro groups. The NH group is also affected by possible host/guest hydrogen bond formation. The formation of the CD inclusion complexes is usually accompanied [19] with the lost of intracavity water molecules. The release of water molecules from the CD cavity into the gas phase is considered a thermodynamic step in CD complexation [20].
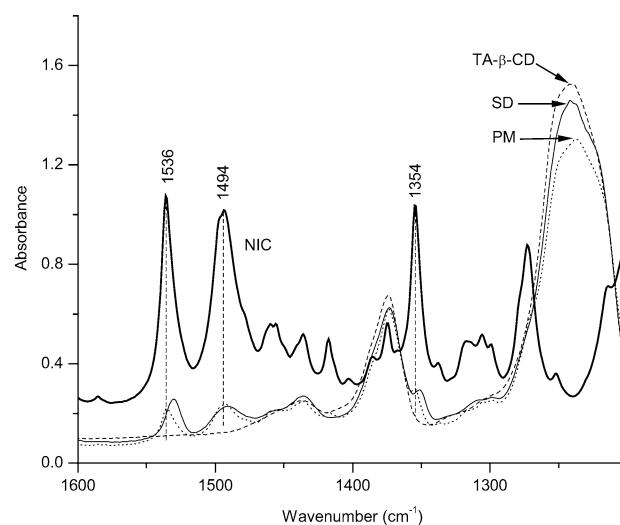
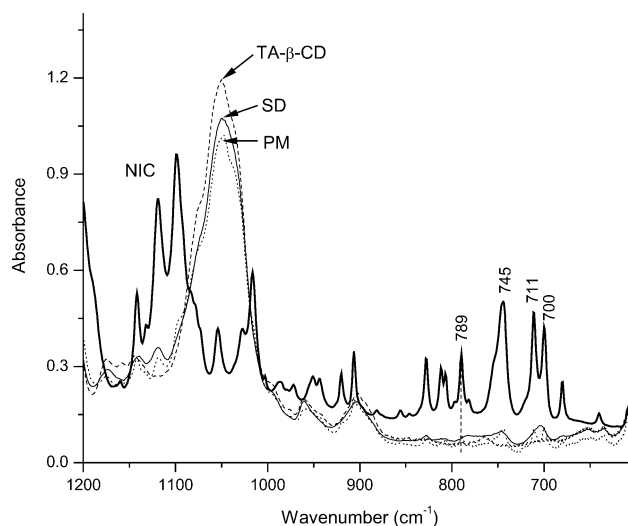Fig. 8. FT IR spectra (1600–1200 cm^{-1}) of NIC, TA-β-CD, PM and SD.

Fig. 9. FT IR spectra (1600–600 cm^{-1}) of NIC, TA-β-CD, PM and SD.

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