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Interaction between Sulfaproxyline and β-Cyclodextrin in the Solution and Solid States

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Abstract. The 1 : 1 inclusion complex between sulfaproxyline (SP) and β-cyclodextrin (β-CD) was prepared by the freeze-drying and the kneading method. Complex formation was confirmed in the solid state by X-ray diffractometry and by infrared spectroscopy. The interaction between sulfaproxyline and β-cyclodextrin in solution was studied by the solubility method and ^{13}C-NMR spectroscopy. Phase solubility studies in water revealed a A_N type diagram and a stability constant of 930 ± 120 M^{-1} for a 1 : 1 inclusion complex was derived. Complexation was found to improve the dissolution rate of sulfaproxyline.

Key words: β-cyclodextrin, sulfaproxyline, phase-solubility analysis, X-ray powder diffractometry, IR and ^{13}C-NMR spectroscopy.

1. Introduction

The interaction of guest molecules with cyclodextrins may induce useful modifications of the chemical and physical properties of the guest molecule which may lead to improved stability, solubility in aqueous media and bioavailability [1–6]. The complexes can be obtained in different ways in liquid or in solid media and characterised using different methods, e.g., NMR, IR, X-ray and thermal analysis [7–9]. However, elucidation of the solid state structure of the inclusion compounds can be difficult as the method requires a single crystal.

Sulfaproxyline is a bacteriostatic drug of the sulfonamide group. It is used in the treatments of bronchitis, bile ducts and meningitis. The drug has only slight solubility in water, however, which limits its use as a therapeutic agent. Increasing the solubility of sulfaproxyline in aqueous media by complexing with β-cyclodextrin would improve its bioavailability. In our previous study we found that sulfaproxyline-like compounds could be included into the cavity of β-cyclodextrin (β-CD) by freeze-drying and kneading processes, resulting in an inclusion complex [10].

This work reports the preparation of a sulfaproxyline-β-cyclodextrin complex (SP-β-CD), using different methods.

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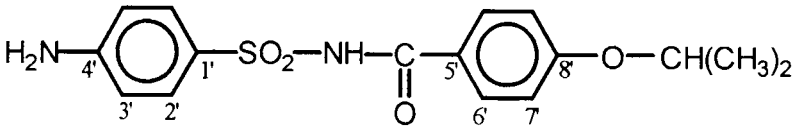

Sulfaproxyline (SP)

Selective physicochemical determinations based on IR spectroscopy, X-ray diffraction and ^{13}C-NMR spectroscopy were used to analyse this complex. The aim of this study was also to gain an insight into the stereochemical aspects of the complexation process and the interpretation of the ^{13}C-NMR spectra of the complexes in DMSO-d_6 solution.

2. Experimental

2.1. MATERIALS

β-Cyclodextrin (β-CD), FW (formula weight) 1134.98, (Chinoin, Budapest, Hungary) and sulfaproxyline (SP), FW 334.39 (Pharmaceutical Company 'Polfa', Poznań, Poland) were used as received.

2.2. PREPARATION OF THE INCLUSION COMPLEX

The inclusion complex was prepared using kneading and freeze-drying methods as described previously [11].

2.3. PHYSICAL MEASUREMENTS

^{13}C-NMR spectra were recorded on a Varian Gemini 300VT Fourier Transform spectrometer. The chemical shifts ($\pm$0.05 ppm) were measured at 75.46 MHz. Typical conditions for the carbon spectra were pulse width 60°, FT size 64 K and digital resolution 0.6 Hz per point. Chemical shifts were measured relative to the internal solvent DMSO-d_6 at 39.5 ppm, relative to TMS. The samples were prepared by dissolving the solid complex, substance alone or their physical mixture in DMSO-d_6. The concentration of the sample was 0.3 M.

FT IR spectra of samples were recorded as KBr tablets in the 4000–400 cm^{-1} region on a Bruker IFS 113v spectrophotometer.

X-ray powder patterns were obtained with a TUR M62 (Germany) diffractometer with a Ni monochromator utilising CuK_α (1.5418 Å) radiation with 30 kV and 25 mA at a scan rate of 1°/min.

2.4. SOLUBILITY AND DISSOLUTION STUDIES

The solubility studies were carried out according to the method of Higuchi and Connors [12]. An excess amount of SP was added to an aqueous β-CD solution and

shaken at 25 °C for 24 h until the system attained equilibrium. Then the solutions were filtered through a Whatman 0.65 μm filter and analysed spectrophotometrically for SP at λ_{max} 267 nm using a Carl Zeiss Jena M40 spectrophotometer. The presence of β-CD did not interfere with the spectrophotometrical assay. The complex formation constant was calculated from the phase diagram obtained according to the Higuchi and Connors method [12].

3. Results and Discussion

3.1. IR SPECTRA

IR techniques are not generally suitable for the detection of inclusion compounds because the resultant spectra have a superposition of host and guest bands [13, 14]. Fortunately, in this study, due to the fact that SP has some characteristic IR absorption bands in the region where β-CD does not absorb, this region could be used to detect a guest interaction.

The IR spectra of free SP and its physical mixture with β-CD show four well-resolved bands at 1575, 1596–1602, 1628, 1656 cm^{-1} due to the ring stretching and amide modes (Figure 1). In the complex obtained by kneading, the intensity of the band at 1604 cm^{-1} is increased compared with the resultant spectrum of the physical mixture (Figure 1d). In the complex obtained by freeze-drying the band at 1628 cm^{-1} is less resolved and a hipsochromic effect is observed from 1628 to 1633 cm^{-1}. The intensity of the band at 1598 cm^{-1} corresponding to the amide group is increased (Figure 1e).

These observations suggest that the guest molecule is included into the cavity of the host.

3.2. ^{13}C-NMR

The numbering of the carbon atoms of β-CD is according to the proposal of Alves and Fonseca [15]. In the case of SP, chemical shifts for the benzene residue were estimated from SCS (substituent chemical shifts in monosubstituted benzenes) data listed by Ewing [16]. The data for the physical mixture of β-CD with SP can be interpreted as an approximate superposition of the components. The chemical shifts for the complex is dependent on the method used to prepare it.

The largest variation of chemical shifts are observed for the carbon atoms of SP in the freeze-dried complex: atoms 1′ (+1.39 ppm), 5′ (+1.27 ppm) and carbonyl (+0.67 ppm) are deshielded while 4′ ($-$0.58 ppm), 6′ ($-$0.36 ppm) and 8′ ($-$0.40 ppm) are shielded (Table I). The chemical shifts for the carbon atoms of β-CD are shielded from $-$0.11 ppm to $-$0.17 ppm. The chemical shifts for the kneaded product are not as large as for the freeze-dried complex. The largest variation of the chemical shifts in this case are observed only for the carbon atoms of SP: 1′ (+0.15 ppm), 5′ (+0.17 ppm) and carbonyl (+0.15 ppm) are deshielded. This suggests, that the amount of the inclusion complex is relatively low.

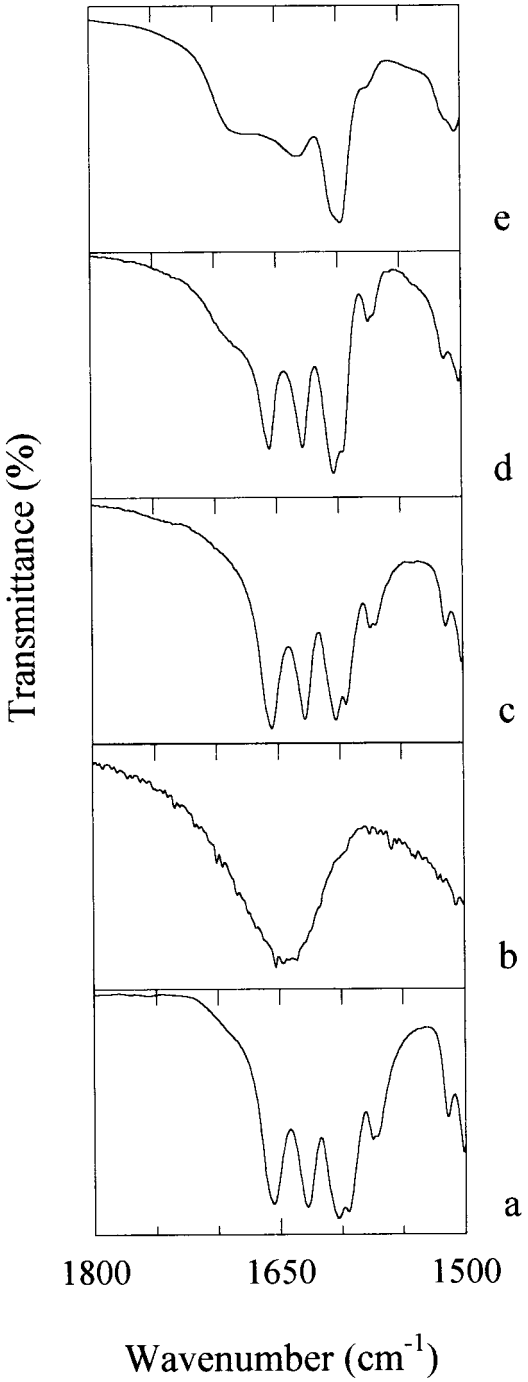

Figure 1. IR spectra (1800–1500 cm^{-1}) in KBr of: (a) SP; (b) β-CD; (c) physical mixture β-CD + SP; (d) kneaded product SP-β-CD; (e) freeze-dried complex SP-β-CD.

Table I. Carbon-13 chemical shifts (ppm) of β-cyclodextrin (β-CD), sulfaproxyline (SP) and the SP-β-CD complex in DMSO-d_6

Carbon[13]	β-CD/SP (δ)	SP-β-CD[a] ($\Delta\delta$)[c]	SP-β-CD[b] ($\Delta\delta$)[c]
β-CD	β-CD[d]		
1	101.96	−0.04	−0.14
2	72.46	−0.03	−0.11
3	73.14	−0.07	−0.17
4	81.59	−0.05	−0.12
5	72.12	−0.06	−0.15
6	60.03	−0.06	−0.15
SP	SP[e]		
1′	123.96	+0.15	+1.39
2′	130.33	+0.06	−0.13
3′	112.11	+0.07	−0.11
4′	153.39	+0.03	−0.58
5′	123.38	+0.17	+1.27
6′	129.88	+0.03	−0.36
7′	114.84	+0.09	−0.17
8′	161.05	+0.08	−0.40
CH_3	21.67	+0.07	+0.03
OCH	69.58	+0.09	−0.10
C=O	164.10	+0.15	+0.67

[a] Kneaded product.
[b] Freeze-dried complex.
[c] $\Delta\delta = \delta_{\text{complex}} - \delta_{\beta-\text{CD/SP}}$; + and − indicate deshielding or shielding, respectively.
[d] Chemical shifts of β-cyclodextrin.
[e] Chemical shifts of sulfaproxyline.

The data from ^{13}C-NMR analysis suggest that the molecule of SP is included into the host cavity. The SP molecule penetrates through the benzenesulfonamide ring into the β-CD cavity, therefore values of the chemical shifts of guest atoms C-1′ and C-4′ are larger than the chemical shifts of atoms C-5′ and C-8′, respectively.

3.3. X-RAY POWDER DIFFRACTION

The X-ray powder patterns for the individual components, the physical mixture and the complex are reported in Figure 2. A comparison of the SP-β-CD diffraction patterns with that of the physical mixture reveals marked differences. Furthermore, the data for the physical mixture can be interpreted as an approximate superposition

of the components. The SP-β-CD kneaded product exhibited lower crystallinity than the corresponding physical mixture, however characteristic SP peaks in the θ range from 4° to 13° were still observed.

3.4. SOLUBILITY AND DISSOLUTION STUDIES

Figure 3 shows an A_N type phase diagram for the effects of increasing concentrations of β-CD on the apparent solubility of SP. According to Higuchi and Connors, an A_N type curve is observed in the case of solute/solvent or solute/solute interaction [12]. The curve which was obtained indicates the formation of a soluble complex between the substrate (SP) and host (β-CD).

The stoichiometry of complexation was determined from the initial linear portions of the phase solubility diagram. Assuming the formation of a 1 : 1 complex in solution, the apparent stability constant (K_s) was calculated according to Equation (1) where S_0 is the drug solubility.

$$K_s = \frac{\text{slope}}{S_0(1 - \text{slope})} \tag{1}$$

The stability constant was found to be 930 M^{-1} (SD = 120, n = 4).

The results of the solubility study carried out in water (Figure 4), show that the presence of cyclodextrins leads to an improvement in the solubility of SP (solubility after 90 minutes: SP 15.30 μg/mL, physical mixture β-CD + SP 23.54 μg/mL, kneaded product SP-β-CD 28.13 μg/mL). This is probably caused by formation of the 1 : 1 inclusion complex. The observed decreasing solubility of SP with time suggests that in aqueous solution the 1 : 1 inclusion complex is in an equilibrium with β-cyclodextrin and SP. The solubility of the physical mixture and a kneaded product were similar after 180 minutes.

4. Conclusions

The freeze-drying method leads to the formation of a stable 1 : 1 inclusion complex of sulfaproxyline with β-cyclodextrin. Incorporation of sulfaproxyline into β-cyclodextrin caused a variation of some carbon-13 chemical shifts and absorption bands in the IR spectrum of the guest molecule. Formation of the inclusion complex of SP-β-CD increased the aqueous solubility of the pure drug by about 84%. The stability constant is 930 ± 120 M^{-1}. The kneading method gave a mixture of the complex and a physical mixture.

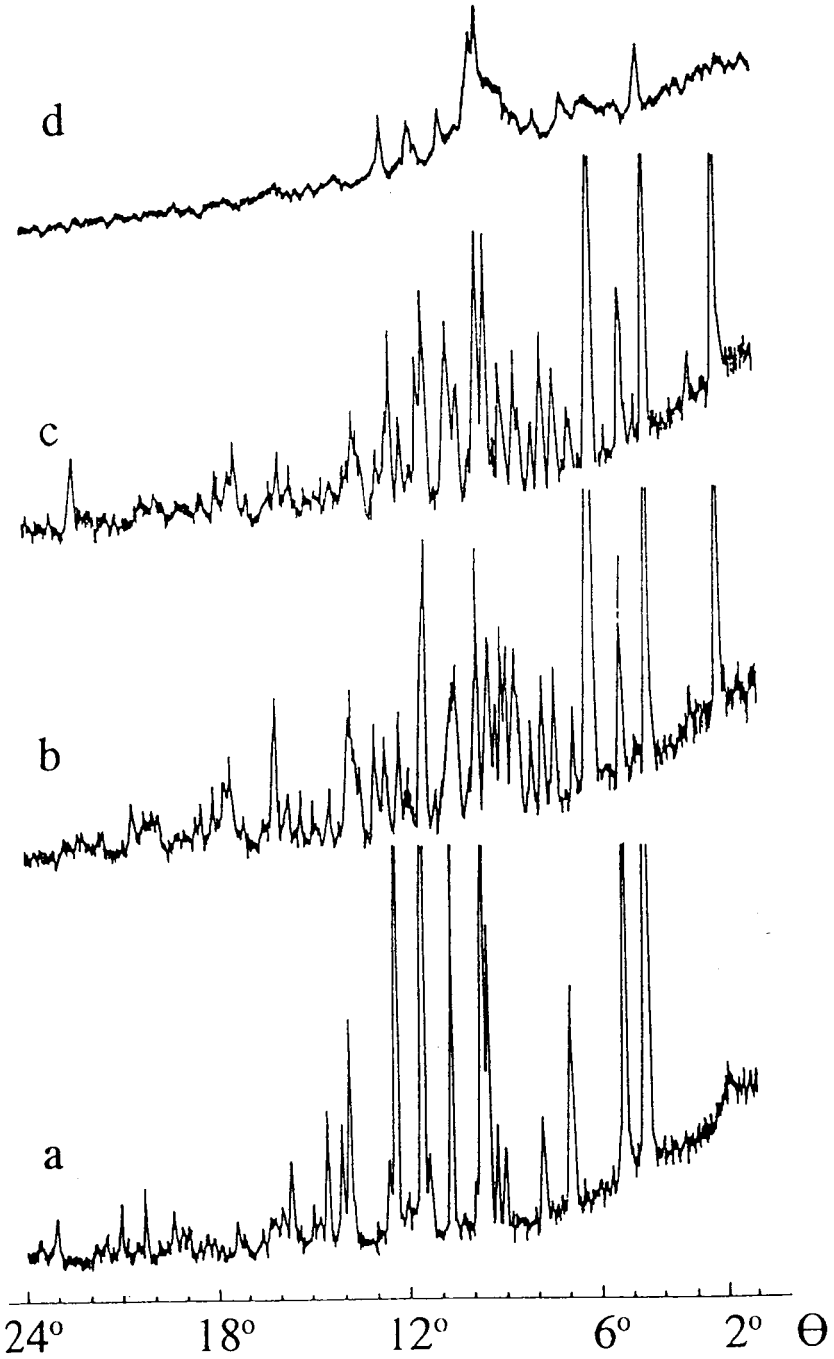

Figure 2. X-ray diffraction patterns of: (a) SP; (b) β-CD; (c) physical mixture β-CD + SP; (d) kneaded product SP-β-CD.

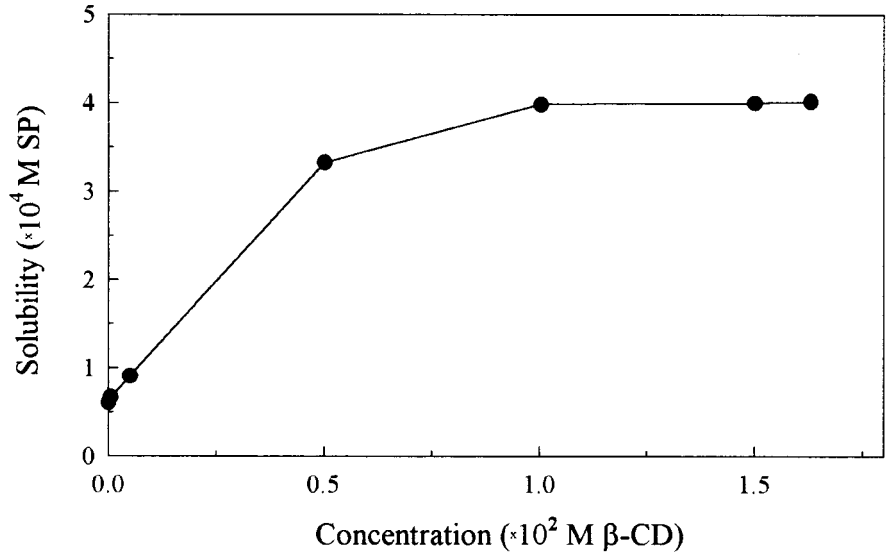

Figure 3. Phase solubility diagram for SP with β-CD at 25 °C.

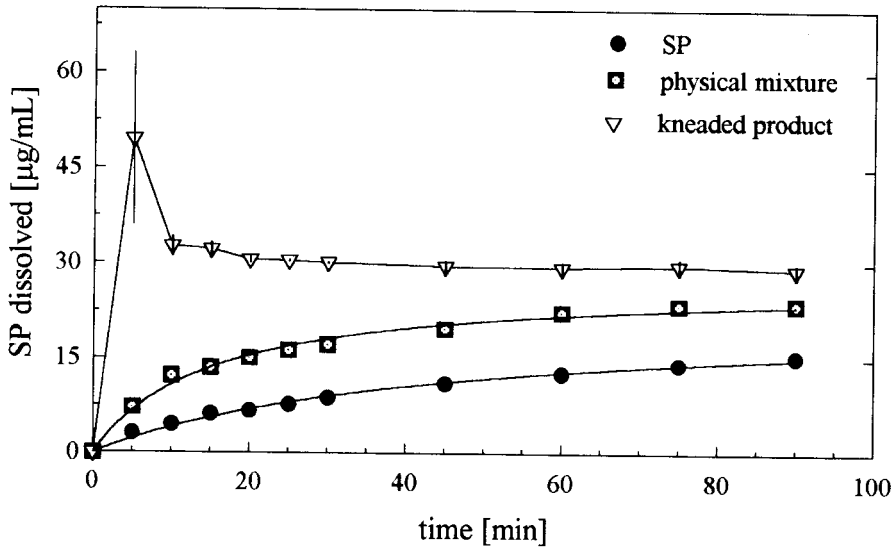

Figure 4. Dissolution profiles of SP, physical mixture and its kneaded product in distilled water at 50 rpm and 37 °C. Each data point of the dissolution profile of the kneaded product is the mean of three measurements.

Acknowledgements

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