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Studies on Inclusion Complexes of Felodipine with β-Cyclodextrin

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Abstract. The inclusion behaviour of β-cyclodextrin (β-CD) with felodipine (FL) as a guest molecule was studied. Inclusion complexes were obtained by the kneading method in a binary or ternary system with an addition of polyethylene glycol 6000. Formation of inclusion complexes was studied by IR spectroscopy, differential scanning calorimetry (DSC), and ^{13}C-NMR. It has been shown that an aromatic phenyl ring was involved in the process of complexation, and that in the solid clathrates the solubility of FL increased two fold when compared to the physical mixture, while it increased 10 fold in liquid three-component complexes. Moreover, the photochemical stability of felodipine was studied in its crystalline form and in the inclusion complexes with β-CD. Quantitative assessment of the felodipine photochemical decomposition was made on the basis of the rate constants of decomposition (k) in the first order kinetic reaction, half life time ($t_{0.5}$) and the time of decomposition of 10% of the compound ($t_{0.1}$). It was shown that complexation of FL with β-CD causes a two fold increase of the rate of the photodegradation process.

Key words: Felodipine, inclusion complexes, β-cyclodextrin, photodegradation of felodipine

1. Introduction

Felodipine, a second-generation calcium antagonist of the 1,4-dihydropyridine (DHP) type, lowers blood pressure by selective dilation of arterial smooth muscles in peripheral resistance vessels. Clinical studies have demonstrated that felodipine, which is approved for marketing in several countries, is an effective, well tolerated antihypertensive drug [1–4]. Felodipine is a selective vasodilator in cardiovascular disorders, primarily arterial hypertension and has no negative inotropic effects at clinically administered doses [5–8].

Like other DHP derivatives, felodipine shows certain undesired physical and chemical properties such as low solubility in water and fast photochemical decomposition. The exposure of FL to light leads to its photodecomposition. This drug undergoes important chemical changes, accompanied by alterations in its activities or potencies and the loss of therapeutic activity [9–11].

One of the methods of improving the physico-chemical properties of DHP derivatives is complexation of the drug [12]. Recently, β-cyclodextrin and its alkyl derivatives have been widely applied in this process [13–18]. Inclusion of

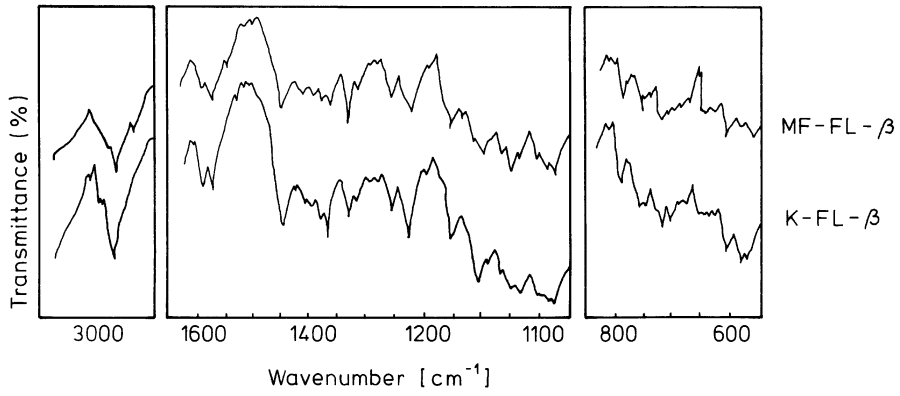


Figure 1. IR spectra of the physical mixture of felodipine with β-cyclodextrin (MF-FL-βCD) and the corresponding inclusion complex obtained by kneading (K-FL-βCD).

these drugs in CDs results in many changes in their properties, e.g. solubility, photochemical sensitivity etc. [19–22].

The present paper describes formation of the solid complexes between FL and β-CD and their properties. In addition, the photostability of the inclusion complexes was investigated.

2. Experimental

2.1. Materials and methods

2.1.1. *Materials*

β-cyclodextrin (β-CD), Merck, m. w. 1134, 98 g/mol; felodipine (FL), Cipla Ltd. Bombay, m. w. 384,08 g/mol; polyethylene glycol 6000, Serva Feinbiochemica, Heidelberg – Germany.

2.2. Preparation of the inclusion complex

The inclusion complex was obtained by the method of "kneading" (K-FL-β). A mixture of FL with β-CD at a 1 : 1 molar ratio was wetted with ethanol and kneaded thoroughly for 60 min. During this process an appropriate quantity of the solvent was added (approx. 1.2 g) [23].

2.3. Physical and chemical properties of the inclusion complex

2.3.1. *IR spectra*

The IR spectra recorded on a Carl Zeiss, Jena, M-80 Spectrophotometer (Figure 1) were taken in potassium bromide disks.

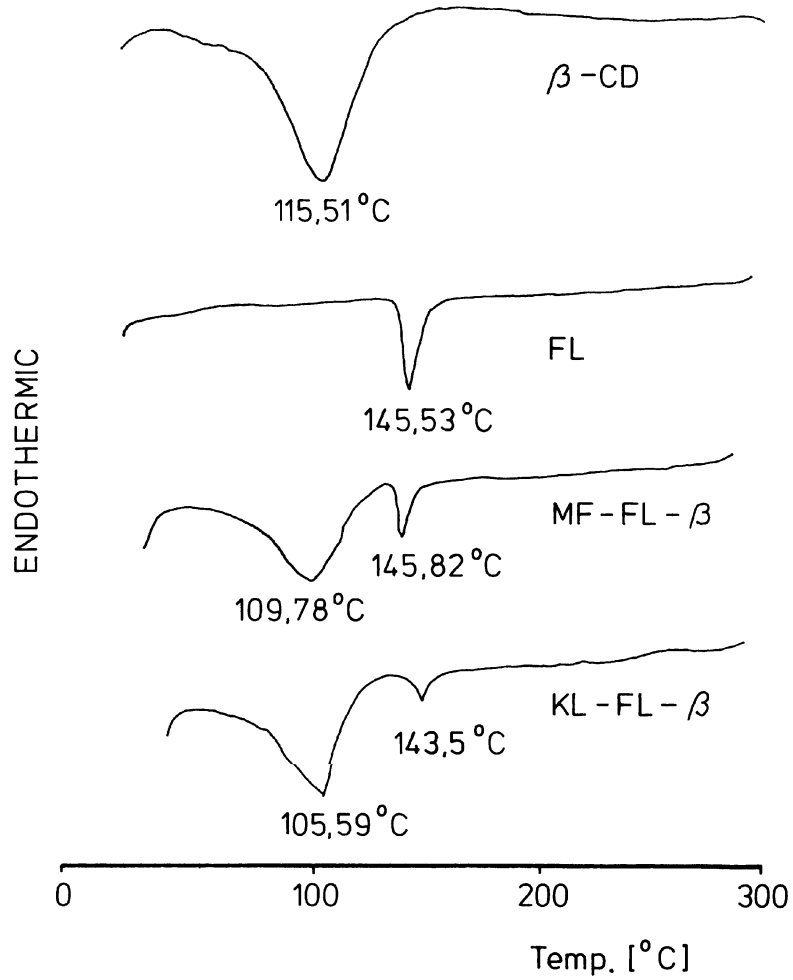


Figure 2. DSC curves of felodipine (FL), β-cyclodextrin (β-CD), their physical mixture (MF-FL-βCD) and the inclusion complex (K-FL-βCD).

2.3.2. *Differential Scanning Calorimetry (DSC)*

DSC scans were recorded on a Shimadzu DSC-50 system equipped with TA-50 WSI. Samples of FL (3 mg) and its inclusion complex (5 mg) were placed in closed aluminium pans. The DSC determinations were performed in a nitrogen atmosphere, at a heating rate of 20 °C/min. in the temperature range of 30 to 480 °C.

DSC curves of the pure components and of their 1 : 1 mol/mol physical mixture and inclusion complex are shown in Figure 2.

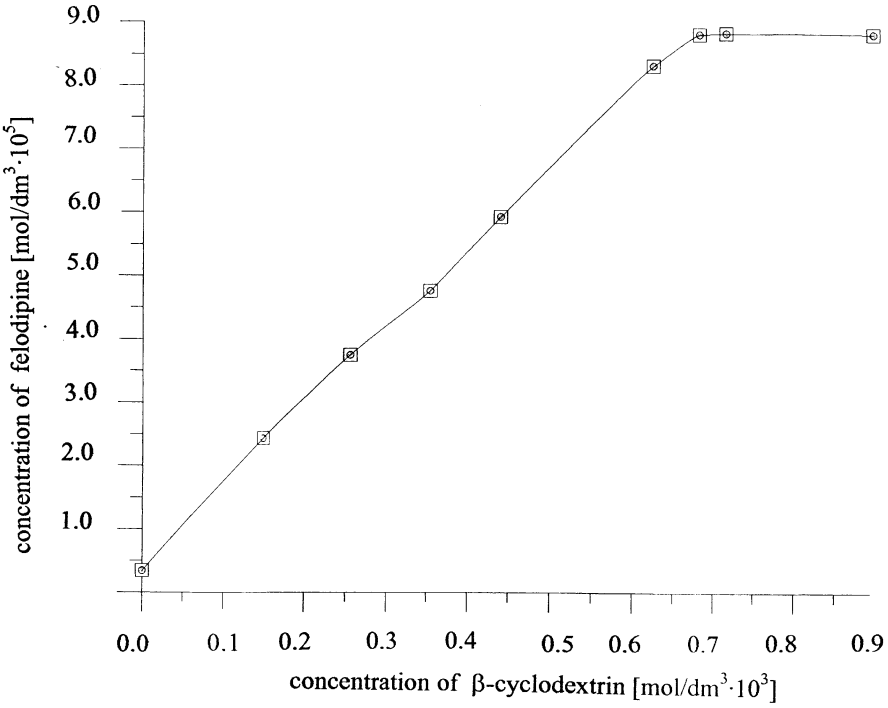


Figure 3. Phase solubility diagram of felodipine and β-cyclodextrin.

2.3.3. ^{13}*C-NMR*

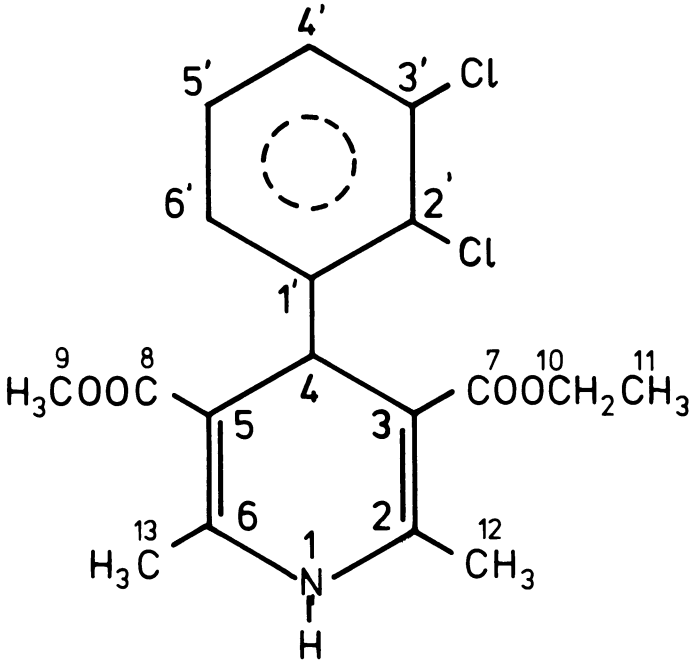
^{13}C-NMR spectra were obtained on a Varian Gemini 300 VT Fourier Transform Spectrometer Computer, using TMS as external reference. The samples were dissolved in dimethyl sulfoxide (DMSO-d_6) and the spectra were recorded in the range from 10 to 175 ppm. Chemical shifts ($\Delta\delta$) were measured relative to solvent DMSO at 39.5 ppm, relative to TMS (Table I).

2.4. SOLUBILITY STUDIES

2.4.1. *Phase Solubility Diagram*

The solubility measurements were carried out according to the method of Higuchi and Connors [24]. An excess amount of FL was added to Britton-Robinson buffer solutions (pH = 5.68) containing 1.0 g of polyethylene glycol. Then β-CD was added in different concentrations (from $1.76 \cdot 10^{-3}$ to $8.80 \cdot 10^{-3}$ mol/dm^3), the mixture was supplemented with the buffer to a volume of 25 mL and shaken for 24 h at 37 °C. After reaching equilibrium (4 days), the samples were filtered through a 0.45 μm Whatman filter and analyzed spectrophotometrically at λ = 362 nm (Figure 3).

Table I. Chemical shift values of felodipine (FL), β-cyclodextrin (β-CD) and the inclusion complex (K-FL-βCD)



FL [ppm]	β-CD [ppm]	Chemical shifts Kneading complex K-FL-β [Δ ppm]
C_2 131.19		
C_3 101.63		
C_4 37.91		
C_5 101.25		
C_6 129.43		<0.100
$C_{2'}$ 148.90		
$C_{3'}$ 145.61		
$C_{4'}$ 127.87		0.253
$C_{5'}$ 127.95		0.147
$C_{6'}$ 129.25		0.193
C_7 166.92		
C_8 166.39		
C_9 50.48		
C_{10} 58.94		<0.100
C_{11} 14.16		
C_{12} 18.19		
C_{13} 18.24		
	$C_{3\beta}$ 73.14	0.155
	$C_{6\beta}$ 60.03	0.157

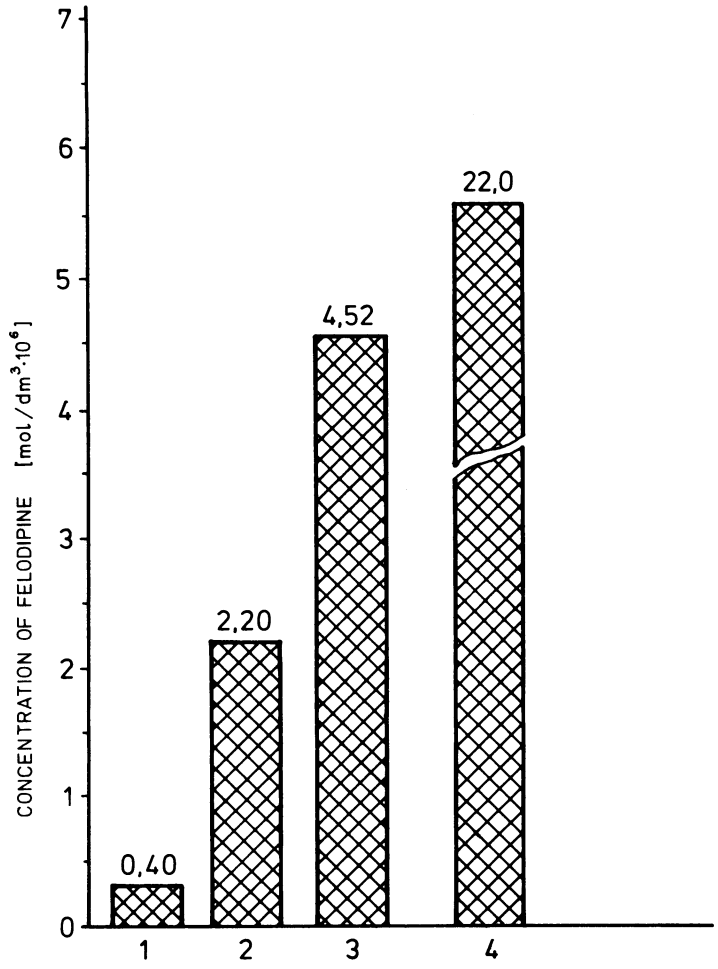


Figure 4. Total solubility of 1. felodipine (FL); 2. physical mixture of FL with β-cyclodextrin (β-CD); 3. inclusion complex of FL with β-CD; 4. inclusion complex of FL with β-CD and polyethylene glycol.

2.4.2. *Total Solubility*

For the purpose of FL total solubility determination, about 0.2 g of the appropriate physical mixture or inclusion complex were introduced into 100 mL of water and stirred for 3 h at 37 °C. Then the mixture was filtered and further treated as described in 2.4.1. Results of the total solubility measurements for all samples analysed are given in Figure 4.

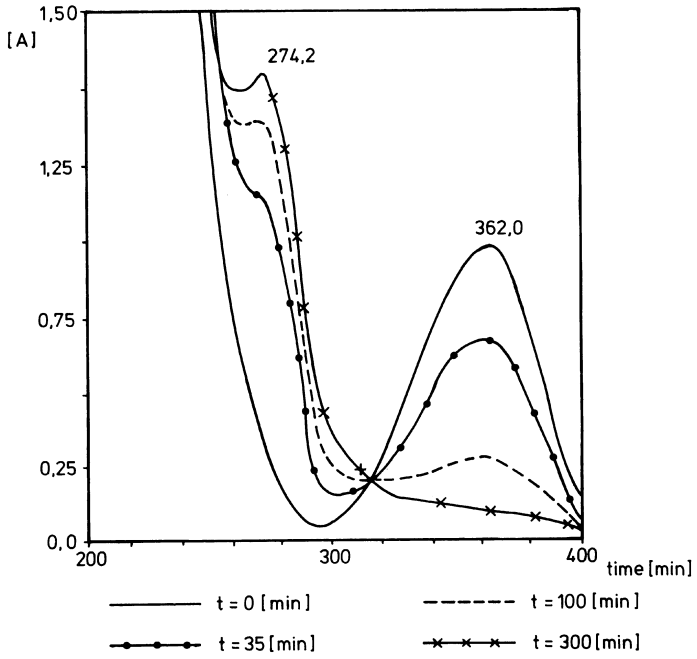


Figure 5. Spectral changes of the inclusion complex of felodipine with β-cyclodextrin appearing on irradiation with UV light.

2.5. PHOTOCHEMICAL STABILITY OF FELODIPINE

2.5.1. *Qualitative Studies*

Solutions of FL and its ternary inclusion complexes with β-CD at concentration $9.0 \cdot 10^{-5}$ mol/dm^3 were placed in quartz cells. The samples were exposed to UV radiation ("Fluotest" lamp, model NN 15/30; λ = 300–400 nm) from a 50 cm distance. To check the irradiation effect, UV spectra of the samples were recorded in the range from 200 to 400 nm. Changes in the spectra after different irradiation times are illustrated in Figure 5.

2.5.2. *The Kinetic Parameters*

The concentration changes of FL during exposure to the radiation source are described by the equation:

$$\ln c = \ln c_0 - k \cdot t,$$

where: c is the concentration of the FL; k is the photodegradation rate constant, t is the time of the photodegradation. The results obtained are presented as the dependences $\ln c = f(t)$.

Table II. Kinetic parameters of the photochemical decomposition of felodipine (FL) and the inclusion complex of FL with β-cyclodextrin (β-CD)

λ [nm]	Kinetic process stage	Rate constant k [$\text{min}^{-1} \times 10^{-3}$]	$t_{0.5}$ [h]	$t_{0.1}$ [h]
Felodipine				
362.0	I	4.00	2.88	0.43
	II	9.75	1.18	0.18
372.0	I	4.05	2.85	0.43
	II	9.31	1.24	0.18
363.0	I	4.05	2.85	0.43
	II	9.36	1.23	0.18
Inclusion complex of FL with β-CD				
362.0	I	1.68×10^{-2} [min^{-1}]	0.69	0.10

On the basis of the above equation the following kinetic parameters were estimated: the rate constants of the first order reaction (k), $t_{0,5}$ – the half life time, $t_{0,1}$ – the time of the decomposition of 10% of the compound.

The first-order rate constants were calculated from the slope of the linear plots of ln c versus time, where c is the concentration of the remaining intact FL. The kinetic parameters of the process of FL photodegradation are given in Table II.

3. Results and Discussion

Previous studies have indicated that inclusion complexes of drugs with CD are formed with no involvement of electronic interactions, but with the help of hydrophobic and van der Waals interactions. For this reason the identity of inclusion complexes was verified using a few analytical methods including IR and ^{13}C-NMR spectra and DSC.

Analysis of the IR spectra of the inclusion complexes and a physical mixture (MF-FL-β) of the components revealed the most frequent changes to be in the range 2950–3050 cm^{-1}, which were interpreted as the valence bands of the C–H in plane vibrations of the aromatic ring.

Differences were also found in the 1480 cm^{-1} region, attributed to the skeleton vibrations of the C=C bonds in the aromatic ring. Considerable differences were also noted in the low frequency range; in the IR spectra of the inclusion complexes strong absorption bands appeared and were interpreted as due to the out-of-plane deformational vibrations of the ring. Moreover, in the spectra of MF-FL-β and K-FL-β the differences were observed at 760 and 720 cm^{-1}, which were attributed to vibrations of the α-glucopyranose ring (Figure 1).

Another method used to identify the inclusion complexes of FL with CD was differential scanning calorimetry, DSC. As seen from Figure 2, presenting DSC

curves taken for physical mixtures and inclusion complexes, for the latter the characteristic endotherm ascribed to the melting point of the crystalline form of the drug (melting point 145.53 °C) is shifted towards lower (K-FL-β) or higher (MF-FL-β) temperatures. The characteristic broad peaks corresponding to the endothermal processes and found in the initial part of the curves, were interpreted as related to the release of water from the cavity in the CD cone taking place on heating. It should be emphasized that the endotherm of felodipine was never observed to disappear completely on the DSC curves, it only significantly diminished.

The identity of the inclusion complexes of FL with β-CD was also checked by ^{13}C-NMR spectroscopy. A felodipine molecule is built of 18 carbon atoms of different order; the attribution of individual absorption lines to particular atoms is shown in Table I. Analysis of the ^{13}C-NMR spectra of FL was performed on the basis of the calculated chemical shifts of individual carbon atoms with respect to FL and β-CD. In the spectra of the inclusion complex of FL with β-CD, only the shift of three carbon atoms were observed, i.e. the aromatic carbons in the phenyl ring ($C_{4'}$; $C_{5'}$ and $C_{6'}$). Moreover, shifts greater than 0.1 ppm were noted for only two carbon atoms of the α-glucopyranose molecule ($C_{3\beta}$ and $C_{6\beta}$).

The next stage of the studies involved an attempt at obtaining liquid inclusion complexes in the ternary system with addition of polyethylene glycol. The results proved that the use of such a high-molecular weight solubilizer considerably improved the solubility of FL. As follows from the data in Figure 4, the solubility of FL bound in ternary complexes with β-CD increased 10 times.

Finally the effect of complexation on the photochemical decomposition of FL was checked. During irradiation of FL, its UV spectra were taken and the observed changes i. e. disappearance of the absorption band with a maximum at λ = 362.0 nm and the simultaneous appearance of a new band at 274.2 nm were observed. Quantitative estimation of the process of photodegradation was a bit more difficult as the results indicated that the process can be both a zero or 1st order reaction. Therefore, to solve this question, the kinetic parameters of the photochemical decomposition of FL at wavelengths other than λ_{max} , i.e. 274.2; 372.0 and 382.0 nm, were determined. For each of these wavelengths the rate constants of decomposition, k, the half-life time $t_{0.5}$, and the time of decomposition of 10% of the compound, $t_{0.1}$ were calculated. The kinetics of FL photodegradation indicated that it is a two-stage process (I and II) with each of the processes occurring at a different rate. The first stage was slower and the photodegradation constants were k_1 = 4.00 and k_2 = 9.75 [$\text{min}^{-1} \cdot 10^{-3}$]. The influence of the presence of CD on the photodegradation of FL was studied in ternary complexes with addition of polyethylene glycol 6000. A comparison of the values of parameters given in Table II indicates that the photodegradation of FL in the ternary complexes with β-CD is twice as fast as for felodipine. This finding can be explained by the catalytic effect of CD on the process of decomposition.

4. Conclusions

It was established that the phenyl ring takes part in the process of complexation of FL with β-CD.

The best solubility of felodipine was obtained in liquid ternary inclusion complexes with addition of ethylene glycol 6000. It increased 10 fold when compared to that of crystalline FL.

The formation of inclusion complexes with β-CD did not increase the photochemical stability of felodipine; FL in the liquid inclusion complexes decomposed twice as fast as the drug in the crystalline form.

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