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Fendiline-β-Cyclodextrin Inclusion Complex

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Abstract. Fendiline (*N*-[1-phenylethyl]-3,3-diphenylpropylamine hydrochloride, trade name: Sensit) is a β-receptor blocker and a Ca antagonist. It is a viscous oil and even its crystalline hydrochloride is a very hydrophobic and sparingly soluble compound in water. β-Cyclodextrin complexes fendiline base in a molar ratio of 2 : 1. In aqueous β-cyclodextrin solution, the significantly increased solubility and the intensive induced circular dichroism prove the formation of true inclusion complexes with both the base and the hydrochloride. In artificial gastric juice, the solubility of the complexed forms of the fendiline base and its hydrochloride is 40 and 22 times higher, respectively, than that of free drugs. The complexation with βCD resulted in a two-threefold increase in the rate constants of diffusion and absorption determined in a Sartorius apparatus.

Key words: β-cyclodextrin, fendiline, Sensit, solubility enhancement, induced optical activity, inclusion complex.

1. Introduction

Fendiline-hydrochloride [trade name: Sensit, chemical name: *N*-(1-phenylethyl)-3,3-diphenylpropylamine · HCl] is a coronary vasodilator applied orally for the prevention and after-treatment of cardiac infarction [1].

The fendiline base is a viscous oil of very low solubility in water. Even the crystalline hydrochloride salt is very hydrophobic; it is sparingly soluble and its absorption is rather limited. The weak absorption is a general characteristic of the aryl-alkyl-amines. The plasma level of fendiline in human is only 5–25 ng/ml after treatment with a daily dose of 3 × 50 mg.

In recent years a series of methods have been published for the enhancement of the solubility and bioavailability of sparingly soluble drugs with cyclodextrins [2–7]. The problem of solubilizing fendiline offered a challenge to cyclodextrin complex chemistry. Complexing the fendiline base with cyclodextrin was expected to yield a product of higher solubility and better bioavailability. According to previous experience with molecules of similar structures, two β-cyclodextrin molecules were expected to encapsulate one molecule of fendiline base. However, one molecule of the hydrochloride salt – because the ionized groups are weak complex-forming partners – was assumed to be capable of reacting with only one molecule of β-cyclodextrin. Therefore, two different fendiline-β-cyclodextrin complexes could be prepared, having different amounts of active ingredient and different physico-chemical properties.

The aim of the present work was to reveal the advantages of cyclodextrin complexation of fendiline; moreover it had to be decided, which one – the base or the hydrochloride salt – would be suitable for developing as a new pharmaceutical product.

2. Preparation of the Complexes and their Characterization in the Solid State

2.1. β-CYCLODEXTRIN COMPLEX OF FENDILINE BASE

Fendiline base readily forms a complex with β-cyclodextrin. The complex can be prepared from a homogeneous solution by mixing an aqueous solution of β-cyclodextrin and an alcoholic solution of fendiline at elevated temperature. After cooling, the crystalline product can be separated. Alternatively, by adding an alcoholic solution of fendiline base to an aqueous suspension of β-cyclodextrin and mixing vigorously, it is converted to the complex.

The X-ray powder diagram of the product proves its complex nature. Characteristic reflections of the complex and those of β-cyclodextrin are compiled as $2\theta°$ values in Table I. Since the complexed compound is a liquid, the significantly-different reflections are diagnostic for complex formation.

The thermoanalytical studies also prove that the substance is an inclusion complex. Evaporation and decomposition of fendiline starts at 130°C and up to 250°C a 98% loss of mass is observed. The decomposition is initially endothermic, but it becomes exothermic above 220°C (Figure 1). The thermoanalytical behaviour of a fendiline-β-cyclodextrin complex is similar to that of β-cyclodextrin except for an endothermic peak (at 63°) on the DSC curve of β-cyclodextrin which is attributed to the alteration of its crystal structure. This unambiguously shows that no decomposition of the guest molecule can be detected before the decomposition of the molecule as a whole, indicating that the fendiline base forms a complex with β-cyclodextrin.

Table I. Characteristic reflections in the X-ray powder diagrams of β-cyclodextrin and of fendiline-β-cyclodextrin complex. (The most intense peaks are underlined; the fendiline base is a liquid and has no reflection.)

β-cyclodextrin ($2\theta°$)	Fendiline-β-cyclodextrin 1 : 2 complex ($2\theta°$)
4.5	
6.2	5.9
	6.6
	7.0
8.8	
9.7	
10.6	11.0
12.3	11.7
14.6	
15.3	
16.1	
17.1	16.9
17.7	17.4
18.0	18.1
18.9	18.5
19.5	19.2
20.8	20.1
21.4	21.0
	21.9

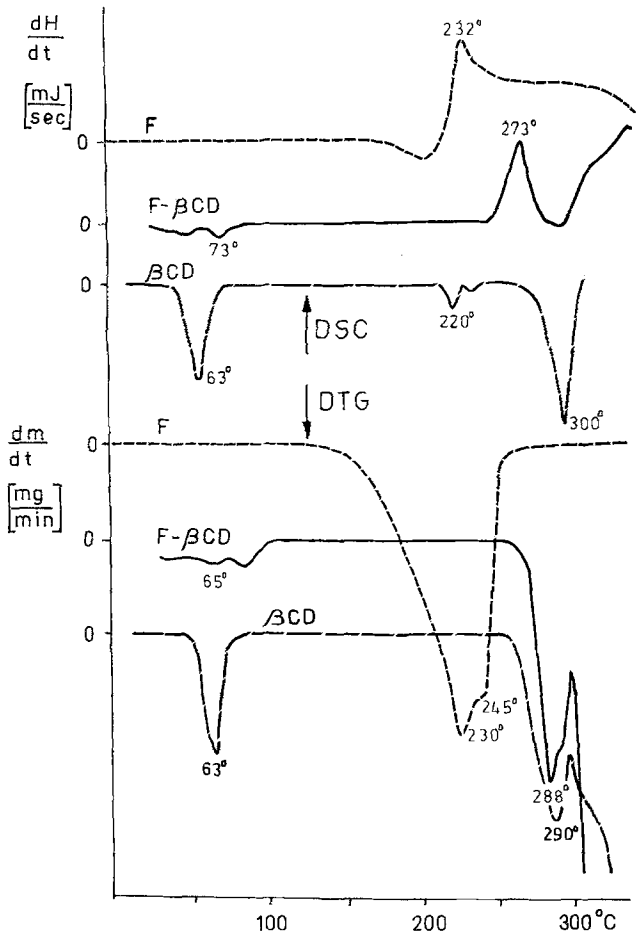

Fig. 1. DSC and DTG curves: fendiline base (F), β-cyclodextrin (βCD), and fendiline-base-β-cyclodextrin complex (F-βCD).

By EGA measurements, even the quantitative composition of the complex can be estimated (Figure 2). If the complex crystals contain free (adsorbed) base on their surfaces, mass changes (DTG curves) and evolution of volatile organic material (EGA curves) can be observed in the temperature range of 150–250°C.

The molar ratio of β-cyclodextrin and fendiline base in the complex is 2 : 1. In this case, no mass change (Figure 1) and evolution of organic gases (Figure 2) were observed in the temperature range of 150–250°C. Complexed fendiline escapes from the sample only above 270°C, simultaneously with the decomposition of cyclodextrin itself.

2.2. β-CYCLODEXTRIN COMPLEX OF FENDILINE HYDROCHLORIDE

The preparation of the fendiline · HCl-β-cyclodextrin (F · HCl-βCD) complex could only be performed in suspension because of the low solubility of the guest molecule.

The guest molecule, F · HCl, also modifies the thermal behaviour of β-cyclodextrin in a physical mixture. The β-cyclodextrin does not decompose below 300°C, while the decompo-

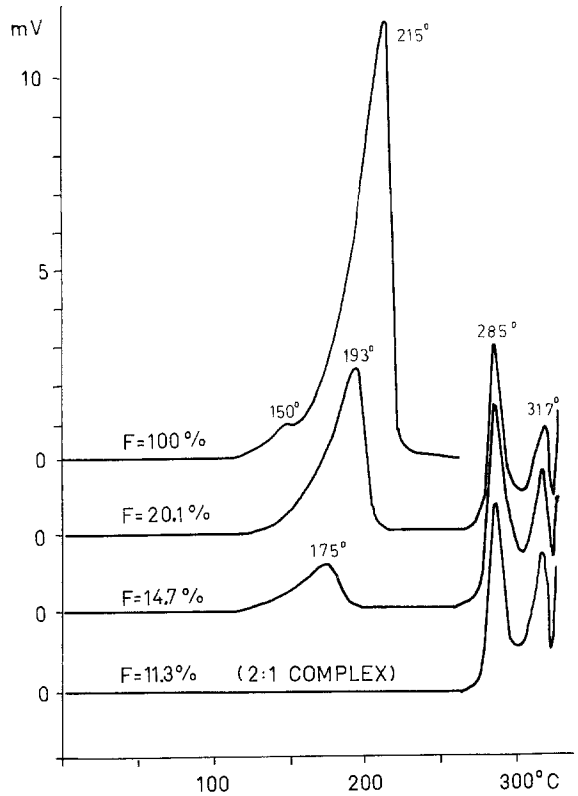

Fig. 2. EGA curves: fendiline base (F = 100%); fendiline-base-β-cyclodextrin complex (F = 11.3%); F : βCD = 1 : 2, water content: 7%; free fendiline adsorbed by the complex (F = 14.7 and F = 20.1%).

sition of its physical mixture with F · HCl starts earlier and a 55% loss of mass can be observed up to 300°C. This decomposition can be attributed to the effect of released HCl. Thus, the thermoanalysis does not give any information on the fendiline · HCl-βcyclodextrin system in the solid state.

X-ray diffractometry does not provide information on the complexation of fendiline · HCl in the solid state, either. Almost each intensive peak of β-cyclodextrin and those of the F · HCl are coincident, and there are no significant differences between the diffraction pattern of β-cyclodextrin and that of the complex.

3. Properties of the Complexes in Solution

3.1. SOLUBILITY ISOTHERM OF FENDILINE HYDROCHLORIDE

The solubility of F · HCl in water increases linearly with an increasing β-cyclodextrin concentration up to about fourfold. As is seen in Figure 3, the slope of the isotherm is 0.5.

3.2. CIRCULAR DICHROISM

Circular dichroism, induced in the electronic transitions of achiral guest molecules by the perturbing effect of a chiral cyclodextrin cavity, constitutes one of the most convincing proofs

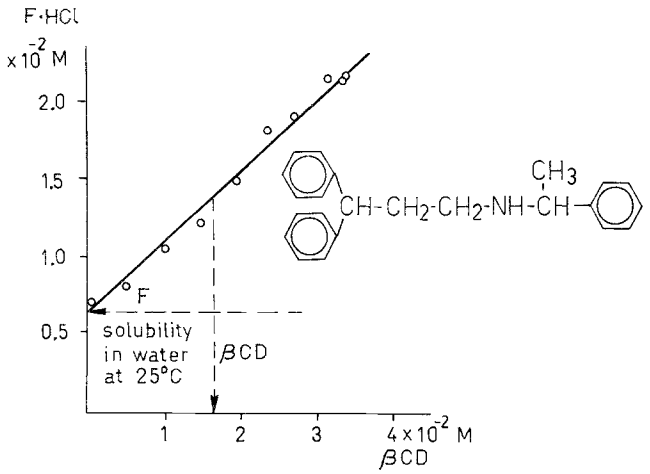

Fig. 3. Mutual solubility enhancement of fendiline · HCl and β-cyclodextrin.

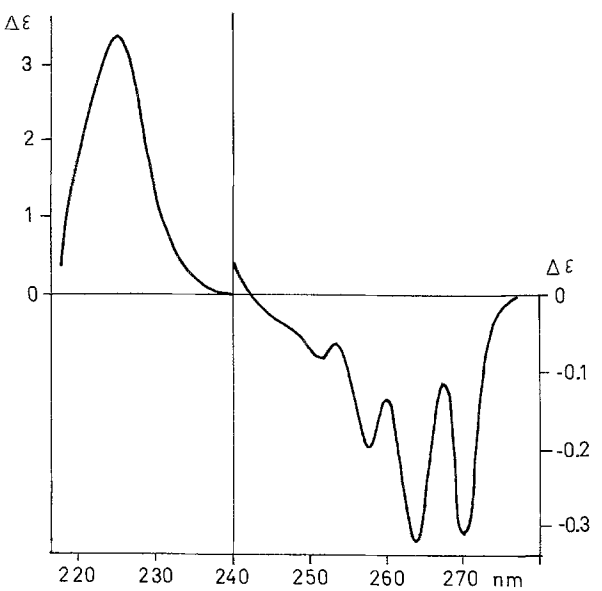

Fig. 4. Circular dichroism spectrum of racemic fendiline · HCl in aqueous β-cyclodextrin solution. (Data refers to 100% complexation.)

for the formation of inclusion complexes. With the aim of demonstrating such an effect, we also investigated the chiroptical properties of fendiline complexes. Figure 4 shows the circular dichroism (c.d.) spectrum of racemic F · HCl in the presence of a tenfold molar excess of β-cyclodextrin in water. The signs of the, surprisingly intensive, induced c.d. bands (negative for the vibronic components of the ^1L_b band and positive for the ^1L_a band of the phenyl chromophore) correspond to the rules based on the study of cyclodextrin complexes of simple aromatic guests [10]. This c.d. spectrum is, therefore, an unambiguous indication of the presence of a real inclusion complex of F · HCl and β-cyclodextrin in solution. The aqueous

Table II. UV and c.d. data of racemic fendiline hydrochloride in aqueous β-cyclodextrin solution. (The data were extrapolated to 100% complex formation.)

UV		c.d.		$g = \varepsilon/\Delta\varepsilon \times 10^4$
λ (nm)	ε	λ (nm)	$\Delta\varepsilon$	
269	390	270.5	−0.31	−7.9
262	620	263.5	−0.32	−5.2
256.5	600	257	−0.20	−3.3
250	460	251	−0.08	−1.7
221	8800	225	+3.37	+3.8

solution of the crystalline F-base · β-CD complex exhibits a similar but more intensive c.d. spectrum. Numerical data of the UV and c.d. spectra of the β-cyclodextrin complex of F · HCl are compiled in Table II. (The true $\Delta\varepsilon$ values corresponding to 100% complexation could be calculated on the basis of the previously determined stability constants.)

The intensity of the induced optical activity of the complexes of *racemic* fendiline is almost one order of magnitude higher than that observed with simple aromatic hydrocarbons [10]. This is especially striking when the anisotropy factors ($g = \Delta\varepsilon/\varepsilon$) of the individual bands are considered. The magnitude of the g value for the cyclodextrin complexes of simple aromatic molecules is generally lower than 10^{-4} [10], while for the fendiline complexes it reaches a value almost as high as 10^{-3} (cf. Table II).

The observation of this unusually strong induced optical activity with the β-cyclodextrin complexes of *racemic* fendiline also prompted us to investigate the chiroptical properties of the optically active enantiomers of this chiral compound. The c.d. spectrum of (−)-F · HCl recorded in aqueous ethanol displays a rather curious feature (Figure 5). The successive

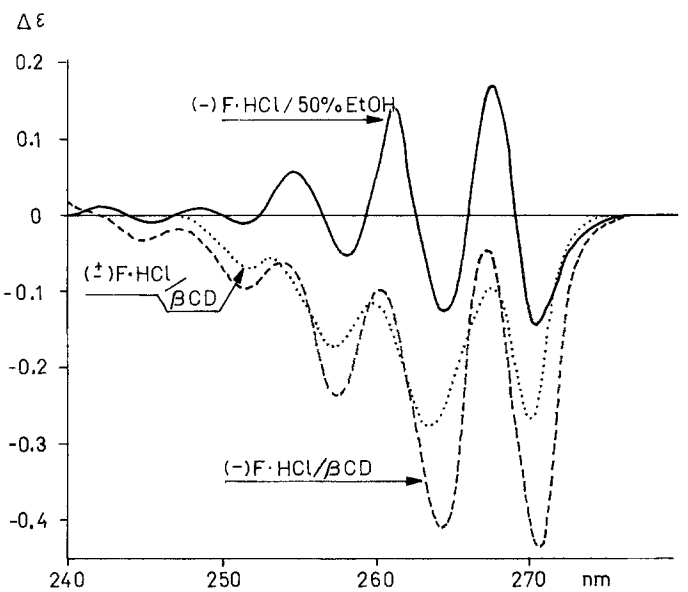

Fig. 5. Circular dichroism spectra of (−)-fendiline hydrochloride in 50% aqueous ethanol and in 10^{-2} M aqueous β-cyclodextrin solution, and the c.d. spectrum of racemic fendiline-hydrochloride in 10^{-2} M β-cyclodextrin solution (only the L_b-bands are shown, the values of $\Delta\varepsilon$ are calculated from the initial concentrations of the base).

vibronic components of the ^1L_b band are of opposite signs, so that the integrated intensity of the whole band is almost equal to zero. The (+)-enantiomer exhibits, of course, the exact mirror image of this curious c.d. spectrum.

In the presence of β-cyclodextrin, the c.d. spectra of the F · HCl enantiomers also change characteristically. The difference between the c.d. spectra of the β-cyclodextrin complex and of the respective free enantiomer of F · HCl is, within the limits of experimental error, identical to the spectrum of the complex of *racemic* F · HCl (Figure 5). These results clearly show that (a) the optical activity induced by the cyclodextrin molecule is additively superimposed on the intrinsic optical activity of the chiral guest molecule, and (b) no observable enantioselectivity operates in the complexation of β-cyclodextrin with (+)- or (−)-fendiline.

The chiroptical behaviour of the fendiline complexes is worth attention for various reasons. First, the optical activity induced in a chromophore *intermolecularly* by the chiral cavity of a cyclodextrin molecule is normally about one order of magnitude weaker than that induced *intramolecularly* by the chiral surrounding represented by the other moieties of the *same* molecule. Therefore, the relative change in the c.d. spectrum of a *chiral* guest, caused by complexation with cyclodextrin, is normally so small that it can hardly be detected and, thus, cannot be used as an indication of complex formation. However, in the case of fendiline, the intensity of the c.d. induced by complexation is even higher than that of the intrinsic optical activity of the substance. Second, despite the strong, oriented host-guest interaction, which is a prerequisite for the appearance of intensive induced optical activity, the cyclodextrin molecules do not seem to differentiate between the two enantiomers of fendiline. To solve the problem arising from these seemingly contradictory facts, the structure of the complexes would have to be known. To this end, the cyclodextrin complexes of both primary amine components of fendiline, *viz.* 1-phenylethylamine (PEA) and 3,3-diphenylpropylamine (DPPA) were studied separately. 1-Phenylethylamine gives a c.d. spectrum characteristic of chiral monosubstituted benzene derivatives (Table III). This spectrum is, however, different from that of fendiline, though the latter molecule contains the same chiral centre. Upon adding β-cyclodextrin to the aqueous solution of PEA, little change in the c.d. spectrum can be observed. In an experiment with *racemic* PEA in β-cyclodextrin solution, no induced optical activity was detected. From these observations it can be concluded that either PEA does not form a complex with β-cyclodextrin or that the induced optical activity of the complex is so weak that it cannot be observed apart from the intrinsic activity of the chiral guest molecule.

In contrast to PEA, the *achiral* DPPA displays, in the presence of β-cyclodextrin, an induced c.d. spectrum which, in the spectral positions as well as intensities of the individual band components, is almost completely identical to that of the complex of *racemic* F · HCl

Table III. C.d. data of the ^1L_b band of (+)-1-phenyl-ethylamine in water and in diluted hydrochloric acid.

Free base		Hydrochloride	
λ (nm)	Δε	λ (nm)	Δε
267	+0.097	266.5	+0.083
261	+0.109	260	+0.088
253	+0.077	254.5	+0.055
249	+0.043	249	+0.028
243	+0.019	242	+0.012

Table IV. C.d. data of 3,3-diphenyl-propylamine (DPPA) and racemic fendiline hydrochloride in β-cyclodextrin solution.

DPPA		rac.-F · HCl	
λ (nm)^{water}	$\Delta\varepsilon$	λ (nm)	$\Delta\varepsilon$
270	−0.25	270	−0.27
263	−0.27	263	−0.28
257	−0.17	257	−0.17
251	−0.07	251	−0.07
245	−0.01		
242	0	242	0
225	+2.69	225	+2.90

The values of $\Delta\varepsilon$ are calculated from the actual concentrations of the guest molecules; [guest] = 10^{-3} M, [[βCD] = 10^{-2} M.

(Table IV). These rather surprising results indicate that the diphenylmethane end of the fendiline molecule interacts with β-cyclodextrin in dilute aqueous solution. Since this molecular moiety, being rather far removed from the chiral centre, may be considered achiral, it is understandable that the CD molecule does not differentiate between (+)- and (−)-fendiline, which are enantiomeric at the other end of the molecule. It cannot be known with certainty whether only one or both of the phenyl groups are included by CD molecules. However, for steric reasons, it seems rather improbable that both phenyl groups bound to the same carbon atom could be accommodated in two different cyclodextrin molecules.

Calculations of the equilibrium constants, based on the supposition of a 1 : 1 complex formation, gave sufficiently good straight lines when using Benesi–Hildebrand plots [11]. This supports the idea, at least in dilute solutions, that only one of the phenyl groups will be included by a β-cyclodextrin molecule. Since the two phenyl groups of DPPA are in an enantiotopic relationship, a chiral molecule, such as β-cyclodextrin, theoretically must be able to differentiate between them. It is, therefore, not impossible that the β-cyclodextrin molecule includes one (e.g., that with pro-*R* configuration) of the two enantiotopic phenyl groups to a significantly higher extent that the other. This might be an explanation for the unusually strong induced optical activity of the complexes of DPPA or fendiline.

On the basis of the results of our chiroptical studies, it can be concluded that fendiline, as both the free base and as the protonated species, forms an inclusion complex having a definite structure with β-cyclodextrin, even in dilute aqueous solution.

As far as the structures of the complexes in the solid state are concerned, it is interesting to note that the β-cyclodextrin complexes of both primary amine components of fendiline were isolated as crystalline substances. The products could be characterized by thermoanalysis, since the decomposition of the guest molecules occurs at relatively low temperatures. According to EGA curves, the crystalline complex of DPPA contains two β-cyclodextrin molecules for every one of the base. Also PEA proved to be a good complex-forming partner, giving a 1 : 1 complex with β-cyclodextrin in the solid state. Based on these results and also taking steric relations into account, it is assumed that in the crystalline complex of fendiline base, the two β-cyclodextrin molecules are located at opposite ends of the guest.

4. Biopharmaceutical Studies on the Complexes

4.1. DISSOLUTION BEHAVIOUR OF THE COMPLEXES

Dissolution curves of β-cyclodextrin complexes of fendiline base and fendiline hydrochloride are illustrated in Figures 6 and 7. The tests were run with equivalent input concentrations of fendiline base (20 mg/ml). As is seen in Figure 6, the solubility of F · HCl after 1 h reaches only a very low value at 37 °C at gastric juice pH. The complexation of fendiline base does not result in enhanced solubility in a neutral aqueous solution; however, at the pH of gastric juice, the solubility of the complex is 40 times higher than that of the hydrochloride. The solubility of the F · HCl was significantly enhanced by complexing with β-cyclodextrin both in a neutral aqueous solution (about sixfold) and at the pH of the gastric juice (about 22 fold).

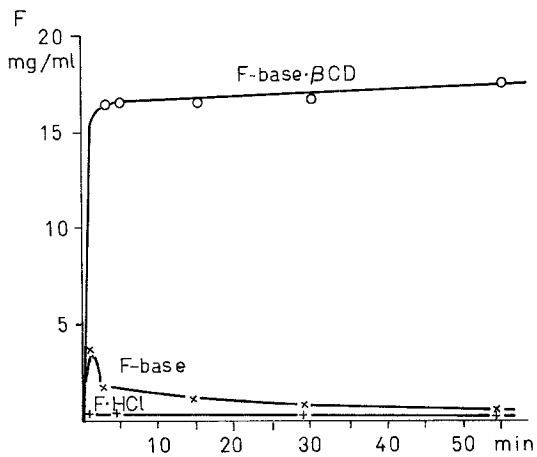

Fig. 6. Dissolution of fendiline-base, fendiline · HCl and fendiline-base-β-cyclodextrin complex. (Input for fendiline: 20 mg/ml, pH = 1.3, at 37 °C.)

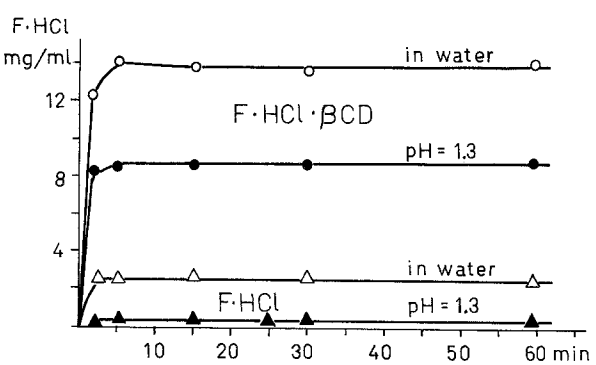

Fig. 7. Dissolution of fendiline hydrochloride (F · HCl) and its complex (F · HCl-βCD) in water and in aqueous hydrochloric acid (pH = 1.3). Input for fendiline: 20 mg/ml, at 37 °C.

4.2. DIFFUSION TESTS

The molecular mass of the cyclodextrin complex – especially when the high degree of hydration is also considered – is considerably higher than that of the relatively small included guest molecule. Therefore, its diffusion constant is significantly lower. Simultaneously, however, the complexation results in an enhanced solubility, in consequence of which a higher concentration of dissolved guest molecules can be achieved, which – in spite of the decreased diffusion constant – increases the rate of diffusion [9].

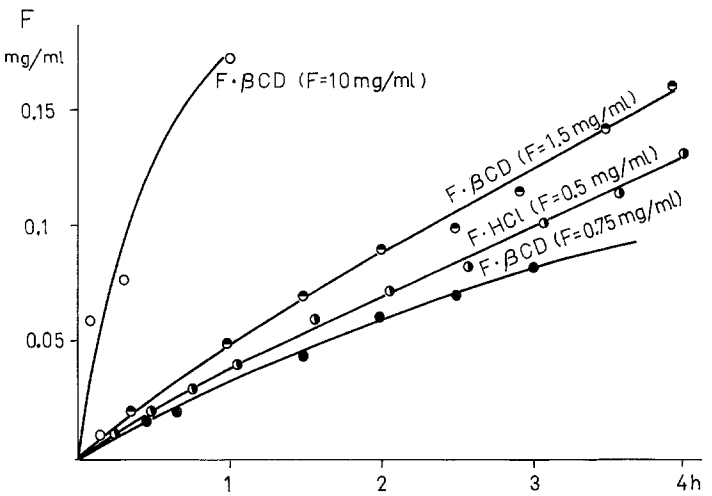

Fig. 8. Diffusion of fendiline through a cellophane-membrane from a saturated fendiline-hydrochloride solution (F · HCl; F = 0.5 mg/ml) and from solutions containing fendiline-base β-cyclodextrin complex of different concentrations.

The degree of solubility enhancement necessary to compensate the decrease of the diffusion constant was determined experimentally. Figure 8 shows the diffusion of F · HCl from its saturated aqueous solution, [F] = 0.5 mg/ml at gastric juice pH, and that from solutions containing F-base · βCD in different concentration ([F] = 0.75; 1.5 and 10 mg/ml, respectively). According to these results, a three-fold solubility enhancement has already compensated the decrease of the diffusion constant with the applied membrane. A 20-fold solubility enhancement already results in a significant increase of the diffusion rate. Considering that

Table V. The rate constants of diffusion (K_d) and that of absorption (K_i) determined in a Sartorius apparatus (K_d = cm^2 min^{-1}; K_i = min^{-1}).

	(1) F-base	(2) F-base-βCD	$\left(\frac{2}{1}\right)$	(3) F · HCl	(4) F · HCl-βCD	$\left(\frac{4}{3}\right)$
K_d						
stomach (pH = 1.2)	–	–	–	–	4.63×10^{-4}	–
intestine (pH = 6.2)	6.9×10^{-4}	14.2×10^{-4}	2.05	6.7×10^{-4}	17.1×10^{-4}	2.55
K_i						
stomach (pH = 1.2)	–	–	–	–	16.8×10^{-4}	–
intestine (pH = 6.2)	51×10^{-4}	124×10^{-4}	2.43	49×10^{-4}	152×10^{-4}	3.10

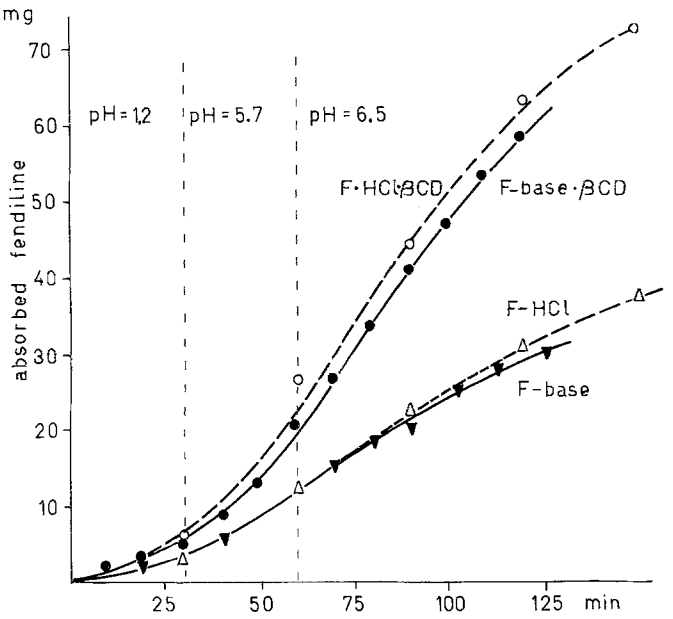

Fig. 9. Modelling of gastrointestinal absorption of fendiline-base (F-base), fendiline-hydrochloride (F · HCl) and fendiline-base β-cyclodextrin complex (F-base-βCD) in a Sartorius apparatus.

even higher solubility enhancements can be achieved by cyclodextrin complexation, the effect of the decreased diffusion constant can be substantially overcome by the solubility enhancement.

4.3. MODELLING OF THE ABSORPTION

The solubility enhancement and the dissolution rate of sparingly soluble drugs by cyclodextrins results in an increased absorption through which the bioavailability of the drug will be improved. The absorption of free and complexed fendiline was simulated in a Sartorius apparatus. The rate constants of diffusion (K_d) and of absorption (K_i), calculated according to Stricker [12, 13], are presented in Table V. The values of the constants are 2 to 3 times higher than those of the free drugs. Only the F · HCl-βCD complex showed a detectable absorption at the pH of gastric juice. The results of *in vitro* absorption tests (Figure 9) were also substantiated by *in vivo* experiments. The rate of absorption and the blood level of the drug were significantly enhanced, as will be presented in a subsequent paper [15].

5. Conclusions

The F-βCD complex can be isolated as a solid crystalline substance while the solid product isolated from F · HCl and β-cyclodextrin cannot be considered as a well defined inclusion complex, although the formation of the latter in solution could be unambiguously proved by c.d. spectroscopy. The pharmaceutical utility of the complexes is determined by their dissolution and absorption properties. The dissolution rate and solubility of the fendiline base complex at the pH of gastric juice is much higher than that of the currently marketed F · HCl (Sensit).

The F · βCD complex administered orally to rats resulted in such a rapid increase in blood level, that it resembled an intravenous administration [14].

The dose of the free or complexed drug is a question of cardinal importance. The F · βCD complex contains 10% (theoretically 11.3%) fendiline, while isolated F · HCl-βCD contains nearly twice as much. The fendiline content of the F · HCl (Sensit) tablets as currently available are 50 or 100 mg. According to the *in vitro* and *in vivo* experiments, the absorption of fendiline can be almost double by complexing the fendiline base with β-cyclodextrin.

Human pharmacokinetic studies are needed to ascertain whether the enhanced bioavailability observed with rats can also be reproduced in humans. If so, the actual 50 and 100 mg/tablet doses can be reduced to 25 and 50 mg/tablet, respectively, i.e., a dispensing unit should contain 250 or 500 mg F · βCD complex only.

6. Appendix: Experimental

6.1. SOLUBILITY ISOTHERMS

The fendiline · HCl in excess was equilibrated in aqueous βCD solutions of increasing concentration at 25 °C for three days. The maximal input concentration of βCD was 80 mg/ml. The dissolved concentration of βCD was determined by measuring the optical rotation ($[\alpha]_{546}^{25} = +191.0$ ($c = 1$, water)).

The amount of F · HCl dissolved was determined by UV spectrophotometry

$$\left(E_{258,\ 1\text{ cm}}^{1\%\ \text{fendiline}} = 20.5\ ; \qquad E_{258,\ 1\text{ cm}}^{1\%\ \text{F}\cdot\text{HCl}} = 18.2 \text{ in } 50\% \text{ aqueous ethanol} \right).$$

6.2. PREPARATION OF FENDILINE BASE β-CYCLODEXTRIN COMPLEX [8]

Thirty grammes of fendiline base dissolved in 100 ml 96% aqueous ethanol was added, dropwise, to a suspension of 300 g βCD in 1000 ml water and vigorously stirred for 1 h. The suspension was stirred a further 12 h, then filtered and dried at 40 °C. The weight of the product was 296 g, its fendiline base content was 9.5%. Both fendiline and CD are products of Chinoin.

Preparation of fendiline HCl-βCD. 70 g fendiline · HCl and 267 g βCD (water content 14%) were stirred in 1000 ml of 20% aqueous ethanol at 40 °C for 4 h and left at room temperature overnight. The product was filtered off and dried at 40 °C. Its weight was 280 g, and F · HCl content, 20%.

6.3. X-RAY POWDER DIFFRACTION

The powder diagrams were recorded on a Philips powder diffractometer using CuKα radiation.

6.4. THERMOANALYTICAL INVESTIGATIONS

The investigations were carried out on the DuPont 990 Thermal Analysis System. A heating rate of 5 °C/min and an air flow of 10 l/h were applied in a 910 DSC cell and 951 thermo-

balance. In the 916 TEA apparatus, the samples were heated in a nitrogen stream (1.8 l/h) at a heating rate of 8 °C/min, and the evolved organic gases and vapours were detected by means of a hydrogen flame ionization detector.

Pure β-cyclodextrin, the guest substance fendiline and fendiline · HCl and their mechanical mixtures with βCD, as well as the complexes were measured.

6.5. CHIROPTICAL MEASUREMENTS

The c.d. spectra were recorded on a Roussel–Jouan Dichrograph No. III (Jobin–Yvon) instrument at an ambient temperature in quartz cells of 0.1–2 cm.

6.6. DIFFUSION TESTS

A cellophane membrane (Visking 32/32, average pore diameter 24 Å) was applied with a surface of 8.5 cm^2 and diffusion cell compartment volumes were 20 and 50 ml. Both compartments contained aqueous hydrochloric acid (pH = 1.3, 37 °C) and were agitated with magnetic stirrers. The samples were then put into a 50 ml volume compartment, and the diffused fendiline concentration was determined periodically in a smaller compartment by UV spectrophotometry.

6.7. BIOPHARMACEUTICAL INVESTIGATIONS WITH SARTORIUS APPARATUS

One cell of the Sartorius SM 16750 Resorption Model Apparatus contained 100 ml artificial gastric or intestinal juice, the other, 100 ml of plasma liquid; both were maintained at 39 ± 1 °C. The two aqueous phases were separated by a Sartorius membrane. The input dose was 100 mg. The initial concentrations were determined and samples were taken 30–120 min after modelling the absorption from the stomach, and 30–360 min after modelling the absorption from the intestine. The rate constants of diffusion and absorption were calculated according to Stricker [12, 13] and the drug concentration was determined by UV spectrophotometry.

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