EXAMPLES OF THE APPLICATION OF CYCLODEXTRIN IN FORMULATION OF ORAL DRUG PREPARATIONS

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ABSTRACT. Fendiline hydrochloride [N-/1-phenylethyl/-3,3-diphenylpropylamine.HCl] is a sparingly soluble and hardly absorbable coronary vasodilator. The fendiline base forms complex with β-cyclodextrin in a molar ratio of 1:2. The enhanced solubility and dissolution rate of the complex resulted in a better bioavailability of the drug, which is represented by the elevated blood levels in rats. The β-cyclodextrin complex of PGI_2Me /3 % active ingredient content/ was prepared. The freeze-dried powder can be stored at 0 °C for 1.5 years, while the pure substance only for 4 months. The biological effectiveness of the complex agrees well with that of the active ingredient. After oral administration the cytoprotective effect of the free and complexed drug on indomethacin induced ulcers in rats was similar in their order of magnitude, however the prolonged effect of the complex was detected in this case too.

INTRODUCTION.

The application of β-cyclodextrin in pharmaceutical technology of oral preparations is illustrated by the complexation of fendiline and prostacyclin-methylester.

Fendiline-hydrochloride [trade name: Sensit, chemical name: N-/1-phenylethyl/-3,3-diphenylpropylamine.HCl] is a coronary vasodilator, a sparingly soluble drug /1/. Its absorption is rather limited; the plasma level of fendiline in human is only 5-25 ng/ml after oral treatment with a daily dose of 3x50 mg.

In recent years publications of increasing numbers have been devoted to the enhancement of the solubility and bioavailability of hardly soluble drugs by cyclodextrin complexation /2-5/. Fendiline seemed to be an appropriate guest molecule for β-cyclodextrin. By the complexation of the drug a better solubility and enhanced bioavailability was expected.

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The spreading applications of prostanoids-especially that of the prostacyclin, the effective antiplatelet and cytoprotective agent - is limited by their instability. To overcome this problem either new, more stable analogues are synthetized, or the endogeneous substance is stabilized by cyclodextrin complexation /7/. The rates of hydrolysis of prostacyclin /PGI_2/ and its methyl-ester /PGI_2Me/ in aqueous solution are significantly retarded by α-, β- and γ-cyclodextrin /8/. The highest stability constant could be rendered to PGI_2Me-β-CD complex.

This complex was prepared by freeze-drying, and its prolonged stability makes possible the pharmaceutical formulation of the drug for oral formulations.

The physico-chemical properties of PGI_2Me- β-cyclodextrin complex in solid-state have been discussed in this paper.

The more detailed investigations concerning the fendiline-β-cyclodextrin complex will be published elsewhere /9/.

MATERIALS AND METHODS

β-cyclodextrin and fendiline-hydrochloride are marketed products while prostacyclin-methylester is a pilot product of Chinoin Pharmaceutical and Chemical Works, Budapest.

Preparation of the PGI_2Me-β-cyclodextrin complex

11,6 g /$8,8.10^{-3}$M/ β-cyclodextrin /moisture content: 14 %/ was dissolved in 300 ml of 30 % v/v ethanolic aqueous solution containing $1,3.10^{-3}$M tris-/hydroxymethyl/--aminomethan /TRIS/ at 50 °C. 0,32 g /$8,0.10^{-3}$M/ PGI_2Me dissolved in 10 ml ethylalcohol was added dropwise to the vigorously stirred cyclodextrin solution. The temperature of the homogeneous solution was kept at 50 °C for ten minutes. Then the ethylalcohol was evaporated by vacuum distillation and the aqueous solution was freeze-dried. The PGI_2Me content of the product was 3,0 %.

Determination of PGI_2Me in the complex

The active ingredient content of the complex was determined by HPLC method. A Perkin-Elmer Series 3 liquid chromatograph equipped with an UV-detector /LC55/ set to 200 nm and a Perkin-Elmer Sigma 10 Data System were applied. The packing material of the column /250 mm x 4,6 mm/ was Chromosil C_{18} /Labor MIM, Hungary/. The chromatographic solvent /flow rate: 1 ml/min/ was a mixture of acetonitrile and sodium borate buffer /pH= 9,2/ in a ratio 7:3 v/v. Since no internal standard was used, a calibration curve was taken from PGI_2Me dissolved in acetonitrile. The complex /33,3 mg/ was dissolved in 1 ml of 30 % /v/v/ etha-

nolic sodium borate buffer solution and 10 µl was injected to the column.

X-ray powder diffraction

The powder diagrams were recorded on a Phillips powder diffractometer using Cu-K_α irradiation. The samples of free PGI_2Me and β-CD were treated similarly to the preparation of the complex.

Thermoanalytical investigations

The investigations were carried out on the DuPont 990 Thermal Analysis System 5 °C/min heating rate and air flow /10 l/h/ were applied in the 910 DSC cell and the 951 thermobalance. In the 916 TEA apparatus the samples were heated in a nitrogen stream /1,8 l/h/ with a rate of heating of 8 °C/min, and the evoluted organic gases, vapours were detected by means of a hydrogen flame ionization detector. Pure β-cyclodextrin, the guest molecule PGI_2Me, their mechanical mixture and the complex were investigated.

Anti-ulcerogenic test in rats

200-250 g female Wistar rats starved for 24 h with free water uptake were administered i.p. with 30 mg/kg indomethacin to provoke ulcers. Simultaneously with the ulcer provocation and 2 h later the animals were administered with PGI_2Me or PGI_2-Me-βCD complex by means of a stomach tube. After 4 h the rats were exterminated and their stomach was investigated for erosion, ulcer, bleeding and perforation. The extent of these noxious effects was expressed by the "ulcus index" /10/.

RESULTS

Dissolution rate and solubility of the fendiline-base- β-cyclodextrin /F- βCD/ complex at the pH of the gastric juice is much higher than those of the presently marketed fendiline hydrochloride /F.HCl/. The ^{14}C-labelled F.HCl and F- βCD were orally administered to rats in a dose 5 mg/kg and the activity of the blood, serum, urine and faeces was detected for 48 h.

The absorption of the drug from the complexed form was very rapid; the maximum serum level was achieved in 30 min, while from the free drug only in 4 h. The ratios of excreted fendiline from the complexed and from the non-complexed drug in urine was 1,51, while in faeces 0,39 after 48 h /Figure 1./.

It agrees well with the blood level results. So an enhanced bioavailability was attained by the complexation.

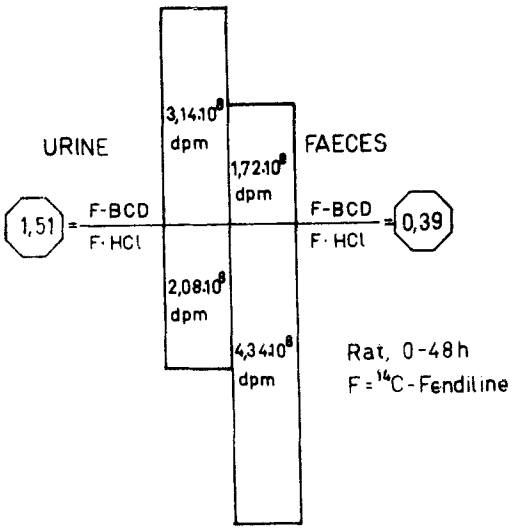

Fig.1. Ratios of excreted fendiline administered orally to rats from fendiline-base-β-cyclodextrin complex /F-βCD/ and from fendiline hydrochloride /F.HCl/.

Figure 2.a. shows the thermoanalytical curves of PGI_2-Me. The endothermic peak at 52 °C on the DSC curve belongs to the melting of PGI_2-Me. Its exothermic decomposition starts at 150 °C in air atmosphere.

In the case of the mechanical mixture of PGI_2-Me and βCD the sample looses its water content up to 80° C and the decomposition of the PGI_2-Me starts about 150 °C with a sharp exothermic peak at 198 °C on the DSC curve. The endothermic peak at 226 °C belongs to the crystal structure transformation of β-cyclodextrin. The separated peaks, attributed to the decomposition of the PGI_2-Me and the β-cyclodextrin are clearly seen on the TG and DTG curves. The exothermic decomposition of the complex begins above 200 °C and decomposes in one step.

The mechanical mixture and the complex show remarkable different behaviour on the TEA curves /Fig.3./.

The free PGI_2-Me and its mechanical mixture with βCD decompose with sharp peaks at 250 °C and 240 °C, respectively; these peaks are attributed to decomposition of the free PGI_2-methylester. The β-cyclodextrin decomposes above 300 °C with a maximum at about 324 °C. Decomposition of the complex beginning near 50 °C is attributed to TRIS present in the system, which was necessary to prevent the decomposition of PGI_2-Me during the prepa-

ration of the complex. No peak appears around 240 °C, which is characteristic for the thermal decomposition of the PGI_2-Me.

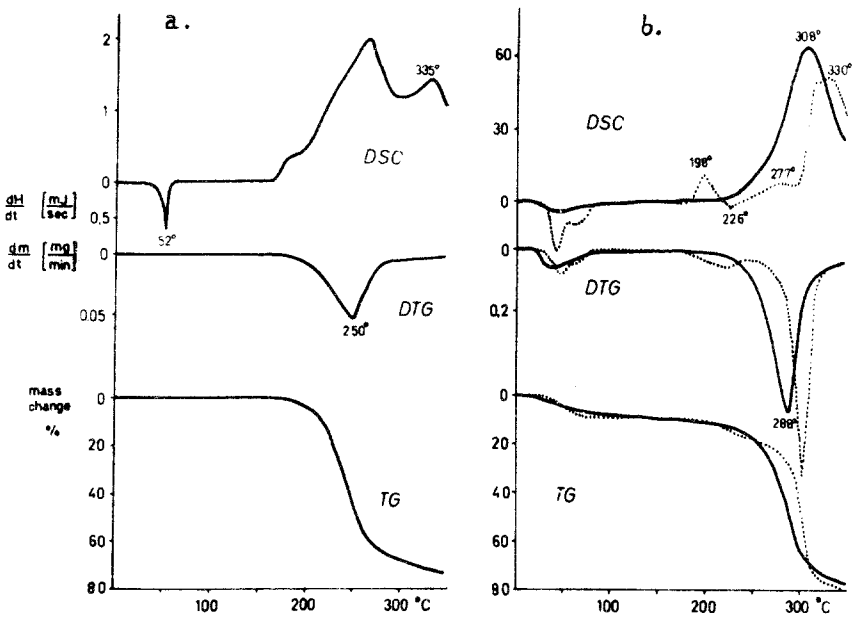

Fig.2. a DSC, DTG and TG curves of PGI_2-Me
b DSC, DTG and TG curves of the mechanical mixture of PGI_2-Me and βCD /----/ and those of their complex /——/.

The complex nature of the solid product was further proven by powder X-ray diffraction patterns. The characteristic reflections of the complex and of both components alone were observed at distinct values.

The decomposition of the free and complexed PGI_2-Me in solid state was followed during isotherm storage at 30, 35 and 40 °C. /Figure 4./.

The free PGI_2-Me sample contained only 48,8 % residual PGI_2-Me after 4 days, while in complexed form 62,5% of its PGI_2-Me content could be measured after 31 days at 40 °C. From these measurements can be calculated an expire date of 4 months for the free PGI_2-Me and 1,5 years for the complex at 0 °C /allowing 5 % loss of the active ingredient/.

The cytoprotective effect of the orally administered free or complexed PGI_2-Me on indomethacin induced ulcers in rats was similar as illustrated by the dose-response correlation /Table I./.

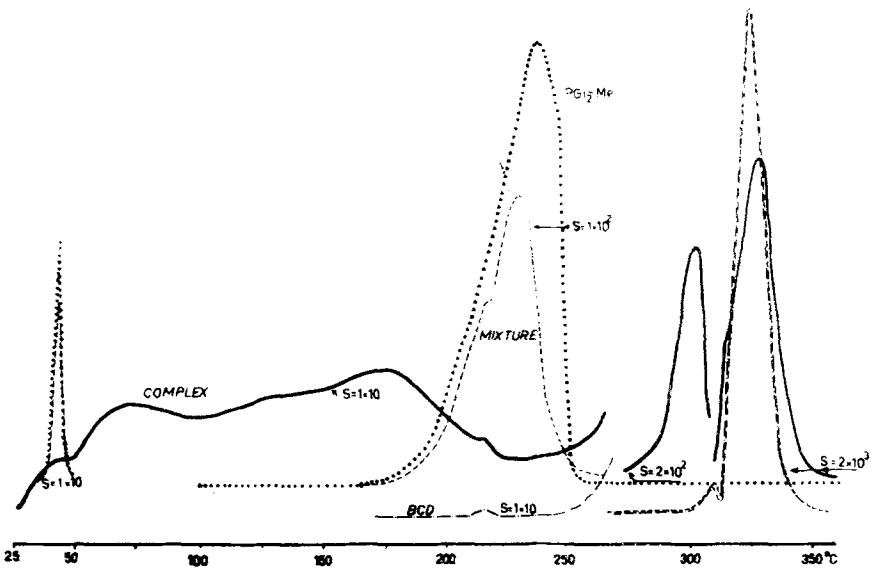

Fig.3. Thermal Evolution Analysis /TEA/ of PGI_2-Me /.../, βCD /-.-./, their mechanical mixture /---/ and the complex /——/.

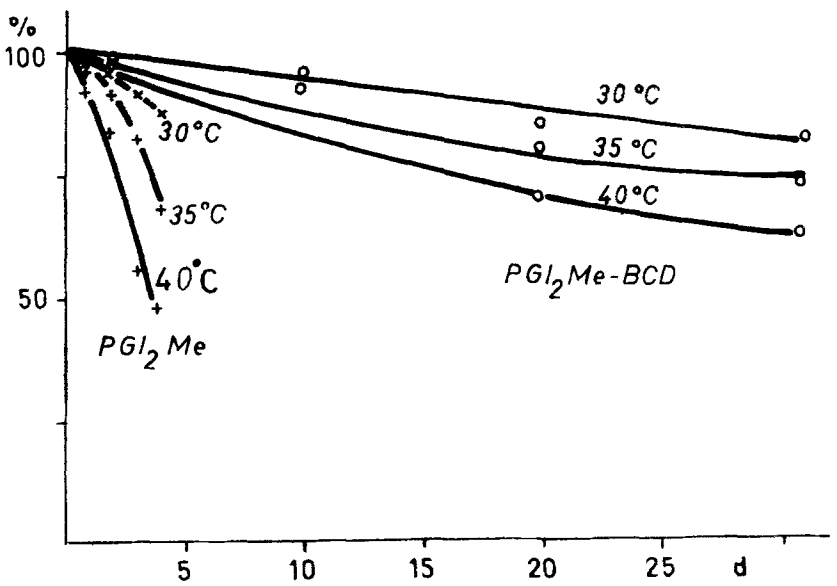

Fig.4. The decomposition of PGI_2-Me and PGI_2-Me- βCD complex at 30, 35 and 40 °C.

Table I. Dose-response correlation of PGI_2-Me and its β-cyclodextrin complex on indomethacin induced ulcers in rats.

Dose PGI_2-Me [µg/kg] p.o.	ulcer index Δ%	
	PGI_2-Me	PGI_2-Me- βCD complex
control	100	100
1	66,9	82,3
5	54,7	57,8
10	31,1	54,2
50	28,4	32,8
100	25,7	26,6

Nevertheless when the administration was carried out pior to ulcer provocation, the PGI_2-Me in complexed form had a greater anti-ulcerogenic effect /Figure 5/

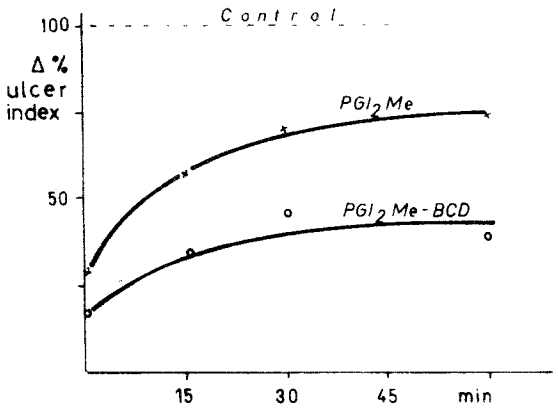

Fig.5. Anti-ulcerogenic effect of PGI_2-Me and its β-cyclodextrin complex in rats /100 µg/kg was administered 60, 30, 15, 0 min prior to ulcer provocation.

The enhanced effectivity probably should be attributed to improved stability of PGI_2-Me in complexed form under in vivo experimental conditions.

The fendiline and the prostacyclin-I_2-methylester can be considered as two typical examples for the application of cyclodextrin in oral preparations; the bioavailability enhancement of a poorly soluble drug and improvement of the stability of a very labile substance.

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