

# THERMOANALYTICAL STUDIES ON COMPLEXES OF FUROSEMIDE WITH $\beta$ -CYCLODEXTRIN DERIVATIVES

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## Abstract

Solid formulas obtained between furosemide and two  $\beta$ -cyclodextrin derivatives (HP- $\beta$ -CD and RAMEB) were prepared by different methods and in various ratios (1:1 and 1:2). The inclusion complex formation between the drug and the  $\beta$ -CDs of 1:1 ratio was evaluated by mean of thermal analysis (DSC, TG and EGD). Supplementary techniques, such as X-ray diffraction, were also applied to interpret the results of the thermal study of physically mixed and kneaded products. Both studies demonstrated the formation of inclusion complexes in all samples except the physical mix samples; formation of true inclusion complexes was then possible only when the components were in melted form. The complexation increased the solubility and the rate of dissolution of the drug. RAMEB was found to be a better complexing agent than HP- $\beta$ -CD; in both ratios it can be selected as a vehicle in furosemide tablet preparations.

**Keywords:** furosemide, HP- $\beta$ -CD, RAMEB, thermal analysis

## Introduction

The thermal analysis of cyclodextrins (CDs) and their derivatives, and also of their inclusion complexes, has been used first to differentiate inclusion complexes from adsorbates, and to characterize the special thermal effects due to molecular entrapment during a well-defined, standard heating process. Only complexes in which the guest substance has a melting point below the thermal degradation range of the CD or which are volatile in the temperature range of 60–250°C can be studied by these methods. Thermoanalytical methods can also be used to determine the host-guest ratio, or the water or volatile component(s) content (in w/w%) in the investigated product, and in the identification of products with a spherical appearance [1–3].

In previous publications, we reported on the solubility of furosemide [5-(aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)amino] benzoic acid] (F) with  $\beta$ -CD and its derivatives ( $\beta$ -CDs). It was found that the solubility of F increased 29-fold with HP- $\beta$ -CD, 75-fold with RAMEB and 137-fold with DIMEB [4, 5]. The rate of dissolution of tablets prepared with granules of a kneaded product containing 11.3% F with  $\beta$ -CD increased 21-fold [6]. Complex formation involving different preparative methods was proved by XRD, IR and NMR spectroscopic techniques, and thermal analysis (DSC) was applied to precipitated products of F with  $\beta$ -CD. It was found, for example, that the precipitate which formed from 75 to 2°C was not homogeneous; it contained at least three components; free F, free  $\beta$ -CD and the inclusion complex F+ $\beta$ -CD. The results of DSC analysis indicated that the compositions of the individual fractions of the precipitates depend on the temperature prevailing during the process of precipitation, the solubilities of F,  $\beta$ -CD and the inclusion complex F+ $\beta$ -CD in the given range, the original ratio of F and  $\beta$ -CD in the solution, and the degree of complex formation [7-10].

The main purpose of our experiments was to improve the solubility characteristics of F which is practically insoluble in water [11]. The previous literature on F complexes with  $\beta$ -CDs does not deal with the thermal analysis of F. The present paper, which involves the thermal analysis of products of F with two different  $\beta$ -CDs as disintegrant agents, reveals the advantageous influence of the guest, reflected in different tablet technology parameters.

## Materials and methods

### Materials

F was obtained from Chinoin-Sanofi Chemical and Pharmaceutical Works Ltd. (Hungary); hydroxypropyl- $\beta$ -CD (HP- $\beta$ -CD; with a degree of substitution DS=2.8), and randomly methylated  $\beta$ -CD (RAMEB; DS=1.8) were supplied by Cyclolab R & D Ltd. (Hungary).

### Methods

Different methods were applied for the preparation of the F solid formula: simple powder mixing using a mortar and pestle, kneading with 50% aqueous alcohol, freeze-drying with a Leybold GT 2 lyophilizer (Germany), and spray-drying with a Niro Minor Atomizer apparatus (Denmark) with an inlet air temperature of  $105 \pm 5^\circ\text{C}$ , in F: $\beta$ -CDs molar ratios of 1:1 and 1:2. The Erweka rotating basket apparatus (Germany) was applied in the determination of dissolution rates [12]. The XRD spectra were measured on a DRON UM-1 instrument (Russia).

The thermoanalytical measurements were performed with a DuPont 910 DSC and a Derivatograph-C TG/DTG system (Hungary). A DuPont 916 (Carle 3000) Thermal Evolution Analyser (Evolved Gas Detection, EGD) was used to detect the gas-phase decomposition products liberated upon heating. 0.1–0.8 mg of pure guest and 4–5 mg of each product were introduced into a heated quartz tube, in an open aluminium sample holder. A heating rate of  $8^{\circ}\text{C min}^{-1}$  and a nitrogen purge gas atmosphere with a flow rate of  $1.8 \text{ l h}^{-1}$  were applied.

## Results and discussion

### *F+HP- $\beta$ -CD*

In the TG curves of *F*, a 0.14% mass loss was observed in the temperature range  $30\text{--}203^{\circ}\text{C}$  and a further 0.5% change between  $220$  and  $330^{\circ}\text{C}$ , which are due to the evaporation of organic decomposition products. The TG curve of HP- $\beta$ -CD shows a 6% mass loss between  $30$  and  $98^{\circ}\text{C}$ , due to the evaporation of adsorbed water. The material started to decompose at around  $311^{\circ}\text{C}$ . The curves of the solid formulas indicated complex formation between host and guest, the complex starting to decompose at around  $250^{\circ}\text{C}$  (Table 1).

The DSC curve of *F* alone exhibits a strong exothermic effect at about  $220^{\circ}\text{C}$ . For HP- $\beta$ -CD, a double endothermic peak was observed between room temperature and  $100^{\circ}\text{C}$ . The DSC curves of the solid products illustrate complex forma-

Table 1 Numerical evaluation of the TG curves

Systems of <i>F</i> + $\beta$ -CDs, in 1:1 ratio	1st-step	2nd-step	Final-step
	$T_{\text{interval}}/^{\circ}\text{C}$		
mass loss/%			
<i>F</i>	30–95	30–203	30–330
	0.0	0.14	0.5
RAMEB	30–100	30–217	30–330
	6.0	5.0	6.0
<i>F</i> +RAMEB	30–101	30–311	30–330
	4.0	18.0	30.0
HP- $\beta$ -CD	30–98	30–250	30–330
	6.0	23.0	31.0
<i>F</i> +HP- $\beta$ -CD	30–100	30–250	30–330
	7.0	23.0	31.0

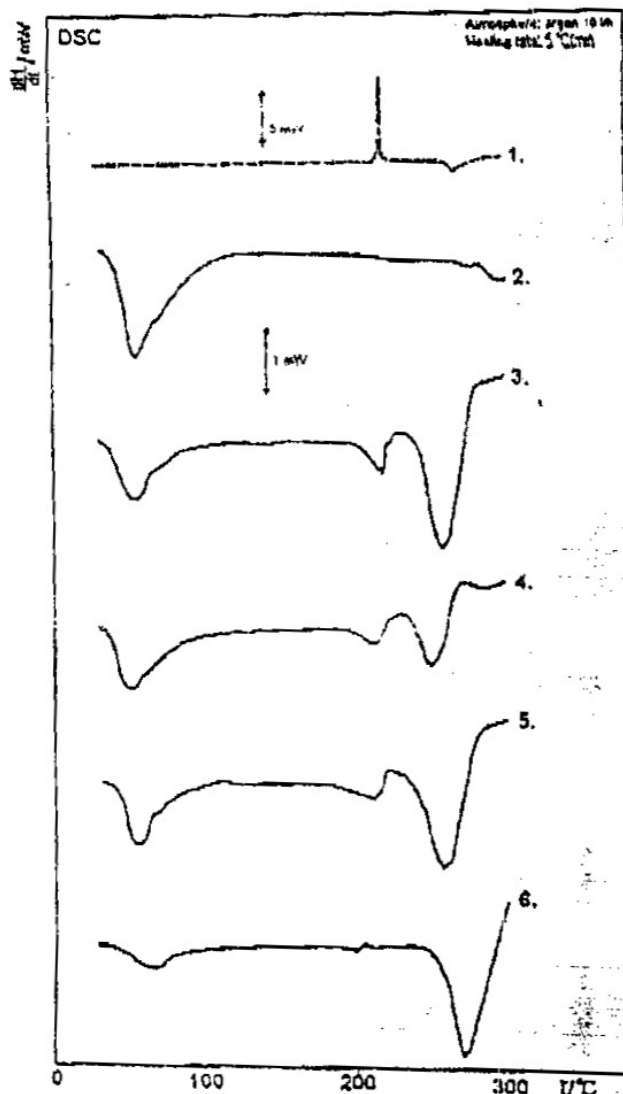


Fig. 1 DSC curves of furosemide, HP- $\beta$ -CD and their products; 1 - furosemide; 2 - HP- $\beta$ -CD; 3 - phys. mix; 4 - kneaded; 5 - freeze-dried; 6 - spray-dried

tion, detected in the form of less endothermic peaks at 220°C, followed by broader ones at around 260°C as the products reach their decomposition temperatures (Fig. 1).

The EGD curve of pure F contains two peaks, a sharp one at 200–220°C and a broad one between 230 and 370°C. The former may be attributed to the evaporation of small amounts of organic compounds when F melts, and the second peak represents the thermal degradation of F (Fig. 2/1). In the EGD curve of HP- $\beta$ -CD, a broad peak may be observed above 270°C, which can be attributed to the thermal decomposition of the substance (Fig. 2/2).

The EGD curve of the mechanical mixture of F and HP- $\beta$ -CD cannot be regarded as a simple superposition of the curves of the pure components (Fig. 2/3). The sharp EGD peak at about 210°C (which represents the presence of pure F) is decreased and somewhat broadened, while the broad peak between 280 and

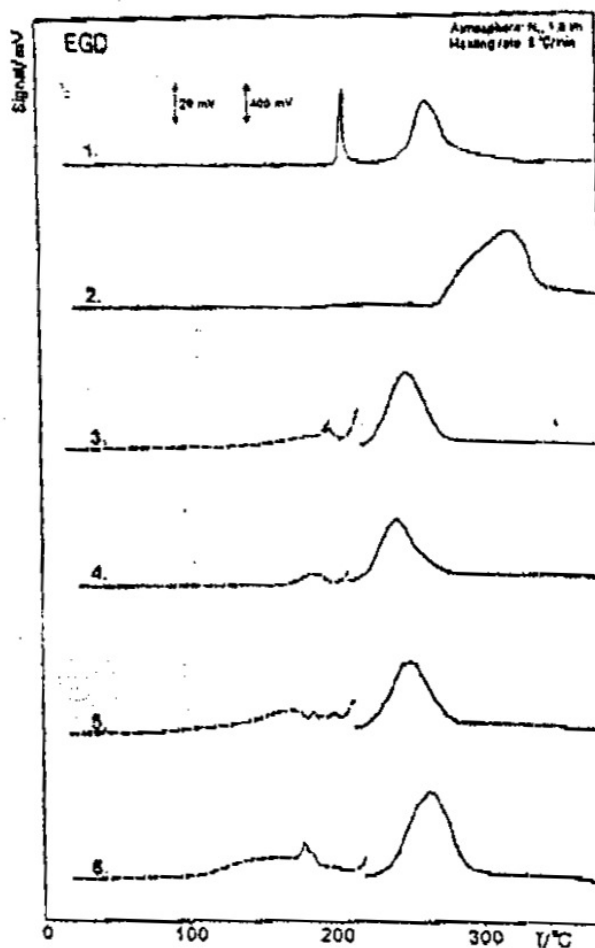


Fig. 2 EGD curves of furosemide, HP- $\beta$ -CD and their products; 1 - furosemide; 2 - HP- $\beta$ -CD; 3 - phys. mix; 4 - kneaded; 5 - freeze-dried; 6 - spray-dried

380°C, which is due to the decomposition of HP- $\beta$ -CD is markedly decreased. This phenomenon may be explained in that solid-solid phase interaction (chemical reaction or inclusion complex formation) occurred between the components during the heating of the sample.

The EGD profiles of the solid formulas prepared by other techniques (Figs 2/4-6) are more or less similar to the curve of the physical mixture. The small peak at about 190-210°C is probably related to uncomplexed F, indicating incomplete inclusion complex formation between the host and guest. The broad peak between 230 and 300°C is related to the decomposition of F, the complex formed or both.

### F+RAMEB

In the range 30-100°C, the TG curve of RAMEB revealed a 6% mass loss, which was due to the evaporation of water. In the TG curves of the complexes in the temperature range 80-100°C, approximately 7% loss of water was observed. All four products started to decompose at 250°C, at a temperature about 20-30°C lower than pure RAMEB (Table 1).

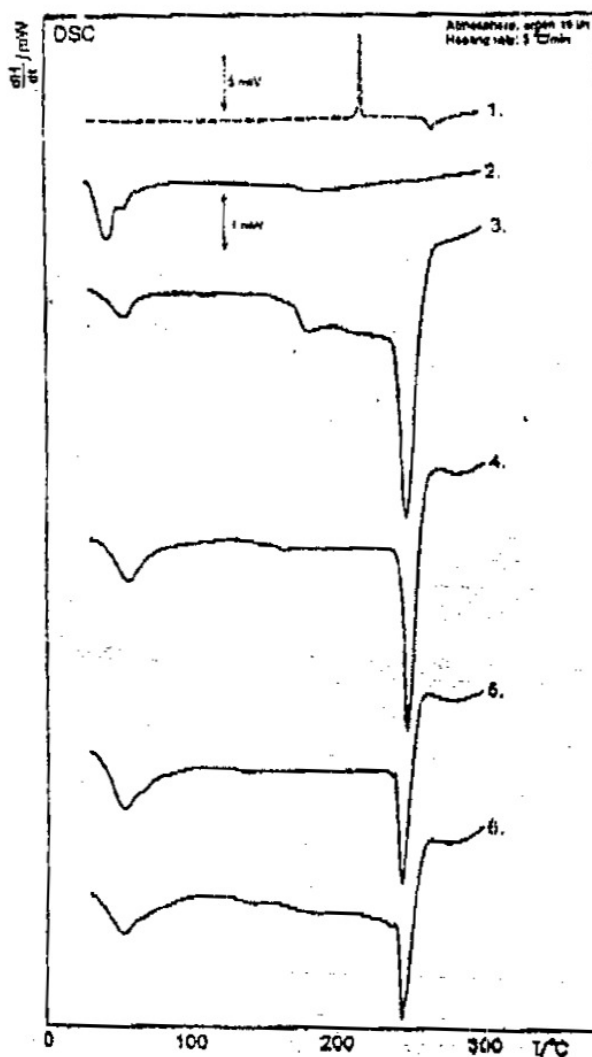


Fig. 3 DSC curves of furosemide, RAMEB and their products; 1 - furosemide; 2 - RAMEB; 3 - phys. mix; 4 - spray-dried; 5 - freeze-dried; 6 - kneaded

The loss of water can be followed in the DSC curves too, as represented by the broad endothermic peaks between room temperature and 100°C. The physically mixed product showed a small endothermic transition between 160 and 220°C, followed by a higher endothermic peak at around 250°C. Moreover, all DSC curves display an endothermic peak relating to the melting of the samples at the same temperature. Besides the phase transition, the occurrence of a chemical reaction between the host and the uncomplexed guest cannot be excluded (Fig. 3).

In the EGD profile of RAMEB, a wide and small peak appears between 80 and 180°C, and a second one begins at 280°C. The former is due to the evaporation of a small quantity of organic contamination, while the other represents the thermal degradation of RAMEB (Fig. 4/1). Furthermore, in the EGD curves of all products, the evaporation of the contamination products and the peak of F are shifted to the lower temperature region (Figs 4/2-6). Accordingly, we can conclude that thermoanalytical methods are useful to differentiate the solid products and to prove the presence of inclusion complexes.

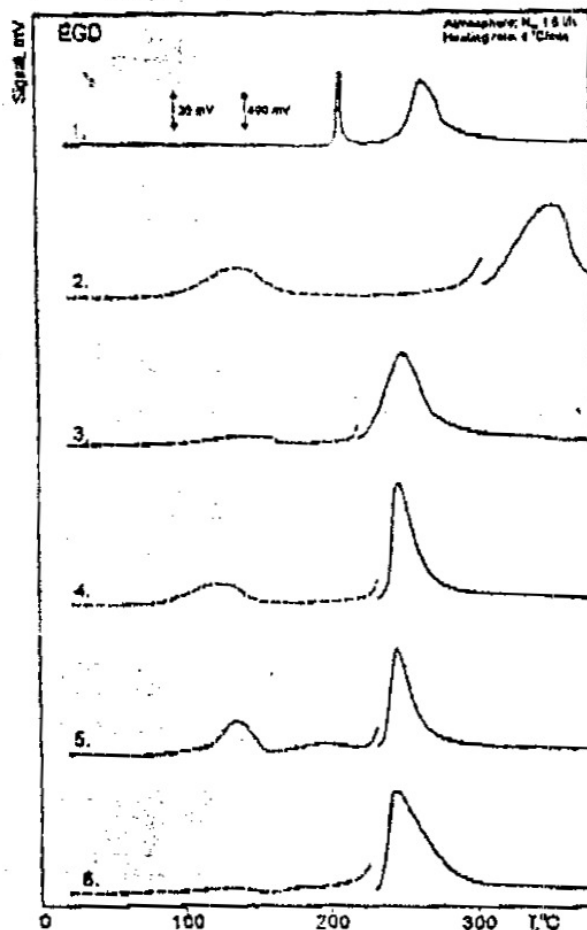


Fig. 4 EGD curves of furosemide, RAMEB and their products; 1 - furosemide; 2 - RAMEB; 3 - phys. mix; 4 - spray-dried; 5 - freeze-dried; 6 - kneaded

These results were confirmed by X-ray powder diffraction investigations. It was found that pure F has characteristic peaks and a crystalline structure, whereas pure HP- $\beta$ -CD and RAMEB have amorphous structures. The physical powder mixtures and kneaded products gave the characteristic peaks of F, but slight amorphization took place in the case of the kneaded RAMEB product. The peak intensities of the latter product depend on the amount of F in the inclusion complex (Fig. 5). All spray-dried products exhibited typical X-ray amorphous character, so these curves are not presented here.

## Conclusions

Products containing different amounts of F and  $\beta$ -CD derivatives were prepared by using different preparative methods. The amount of F was 21.7% (w/w) with HP- $\beta$ -CD, and 20.1% (w/w) with RAMEB. The pure components, their physical mixes and all products were investigated by thermoanalytical methods. To prove inclusion complex formation by these methods alone was rather difficult, so other instrumental analytical techniques, such as X-ray powder diffrac-

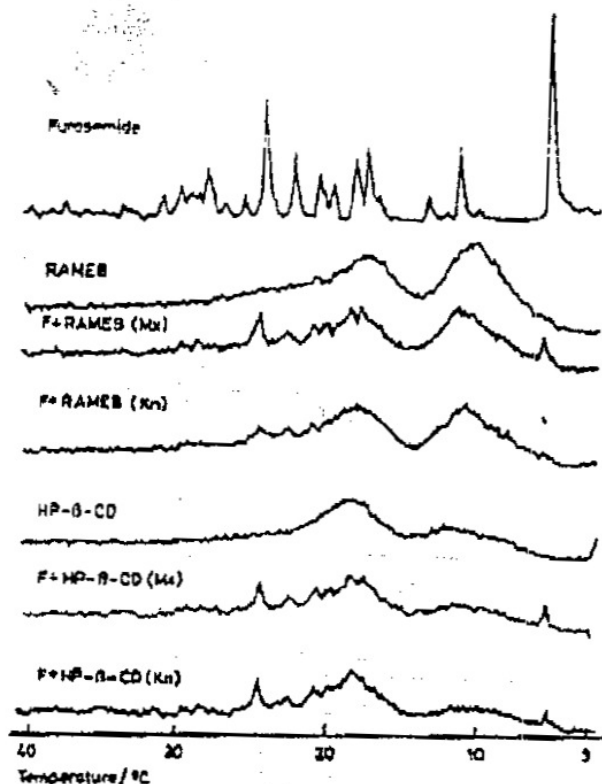


Fig. 5 X-ray powder diffraction patterns of the pure components, their physical mix and the kneaded products

tion, were used to supplement the thermoanalytical results. When RAMEB was used as host molecule, the interaction between the parent CD and F was more pronounced. The EGD method indicated that the representative peak of F is shifted towards the lower temperature range and seems smaller, while for the simple physical mix, any interaction may only occur during heating and after melting of the components. These results support our earlier data concerning the increased solubility and dissolution rate of F.

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