# INCREASING THE SOLUBILITY OF FUROSEMIDE WITH CYCLODEXTRINS

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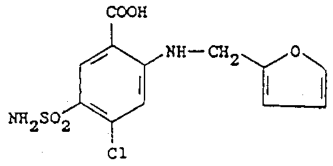
## ABSTRACT

In the past 20 years, cyclodextrin (CD) research has achieved considerable results, as indicated by the seven earlier symposia on CDs, and the new dosage forms prepared with them. Furosemide (F) is slightly soluble in water (10.26 mg/100 g) [1-3]. Different CDs increase the solubility of F to various degrees, depending on their ratios and the methods of preparation. The parameters of the solutions are changed and the inclusion complex formation was analysed.

## 1. INTRODUCTION

F, a frequently used diuretic and antihypertensive pharmacon, was discovered by Sturn et al. in 1962 (Hoechst). It is slightly soluble in water, although its sodium salt is very soluble. Its registered tablets contain 40 mg and its injections 20 mg of F in 2 ml. Its structural formula is as follows:




The aims of the experiments were to improve the bioavailability of F by increasing its solubility and dissolution properties by complexation with CDs in various ratios, using different methods of preparation, and to investigate the products by various techniques [4-6] such as X-ray analysis, etc.



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TABLE 2. Extent of dissolution of products, in mg/900 mL during 60 min

| Methods | Ratios | β-CD | HP-β-CD | RAMEB |
|---|---|---|---|---|
| Mixing | 1:2 | 28.13 | 61.21 | 62.01 |
| | 1:1 | 37.88 | 62.50 | 56.57 |
| | 1:1/2 | 20.30 | 54.34 | 60.58 |
| Kneading | 1:2 | 66.65 | 63.77 | 78.31 |
| | 1:1 | 64.34 | 63.13 | 73.52 |
| | 1:1/2 | 57.06 | 55.78 | 49.23 |
| Spray-drying | 1:2 | 62.82 | 33.33 | 92.27 |
| | 1:1 | 70.17 | 51.62 | 79.12 |
| | 1:1/2 | 69.85 | 61.00 | 42.52 |

The dissolution properties of products containing **RAMEB** and **HP-β-CD** exhibit good results, while the products containing **β-CD** are the poorest. For **HP-β-CD**, there is practically no difference in the extent of dissolution at the different ratios.

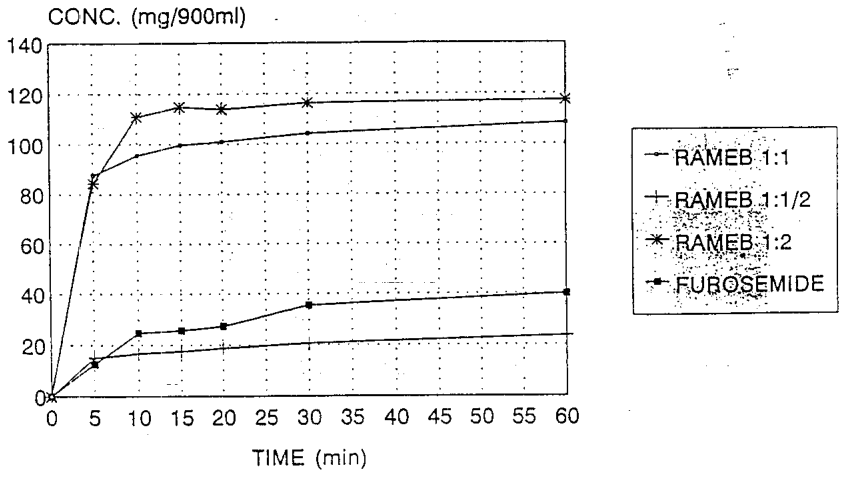


Fig. 1. Influence of RAMEB and its ratio on the dissolution of **F** from freeze-dried products

As concerns the methods of preparation, the **RAMEB** and **HP-β-CD** kneaded products are the best, while **β-CD** gives similar results for the spray-dried and kneaded products. Inclusion complex formation was investigated by X-ray and IR techniques. It was established that **F** and **β-CD** have crystalline structures, whereas **HP-β-CD**, **DIMEB** and **RAMEB** have amorphous structures. Consequently, all physical mixes contain characteristic peaks of **F** and, of course, powder mixtures and precipitated products of **F** and **β-CD** also give characteristic peaks of both components.
All kneaded products exhibit such peaks, their intensities being in direct proportion to their **F** content. Finally, all freeze-dried and spray-dried products were completely amorphous.
$\Delta H_{sol}$ of **F** is 16.37 kJ/mol at 20-40 °C and 33.98 kJ/mol at 40-60 °C.
The IR spectra confirm the earlier findings.

## 4. CONCLUSIONS

The different **CDs** increase the solubility of **F** to various degrees, depending on their ratios and the methods of preparation. **DIMEB** increases the solubility properties of **F** to the largest extent (at 300 mM, the increase is 137-fold). An **F:CD** ratio of 1:2 was generally the best, and the dissolution of spray-dried and kneaded products was the highest. In parallel with this, the parameters of the solutions also changed. The findings of these investigations are confirmed by the X-ray and IR spectral results on **F**, **CDs** and their products.

## ACKNOWLEDGEMENT

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## 2. MATERIALS AND METHODS

### 2.1. Materials

F and F-Na (Chinoin, Budapest); α-CD, β-CD, γ-CD, hydroxypropyl-β-CD, dimethyl-β-CD and random-methylated β-CD (= **HP-β-CD**, **DIMEB** and **RAMEB**; Cyclolab Ltd., Budapest).

### 2.2. Methods of preparation

Powder mixing, kneading, precipitation, spray-drying and freeze-drying in 1:1/2, 1:1 and 1:2 molar ratios (**F:CD**).

TABLE 1. Composition of investigated products in %

| Ratios | β-CD | HP-β-CD | RAMEB | DIMEB |
|---|---|---|---|---|
| 1:2 | 12.72 | 12.17 | 11.15 | 12.45 |
| 1:1 | 22.60 | 21.71 | 20.06 | 22.14 |
| 1:1/2 | 33.39 | 35.67 | 33.41 | 36.26 |

### 2.3. Analysis

The products were investigated by spectrophotometry at 282 nm in the concentration range 2-15 μg/g (Spektromom 195, MOM, Budapest), where the presence of the different CDs in the usual concentrations does not influence the absorbance of the solutions. The dissolution rate was determined at 100 rpm according to USP XXIII [1, 3]. The X-ray spectra were recorded with a DRON UM-1 instrument and the IR spectra with Perkin-Elmer Paragon FT-IR apparatus.

## 3. RESULTS AND DISCUSSION

Determination of solubility. In a pre-experiment, the CDs increased the solubility of **F** in the sequence **F** < γ-**CD** < α-**CD** < β-**CD** < **RAMEB** < **HP-β-CD** < **DIMEB** (under the usual conditions, i.e. at room temperature, during 1 week). In pre-formulation experiments, it was found that 300 mM **DIMEB** increases the solubility 137-fold, **RAMEB** increases it 75-fold.

The extent of dissolution of pure **F** during 60 min is 39.96 mg/900 mL distilled water. The effects of CDs on the extent of dissolution: **DIMEB** increases the solubility properties of **F** to the largest extent: the quantity of **F** dissolved was in all cases more than that for pure **F**.