Journal of Inclusion Phenomena and Molecular Recognition in Chemistry **31:** 189–196, 1998.

The Influence of β-Cyclodextrins on the Solubility of Furosemide

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(Received: 31 January 1997; in final form: 10 June 1997)

Abstract. Furosemide (F) is practically insoluble in water (10.26 mg/100 mL). Different β-cyclodextrins (β-CD derivatives) were applied as host to improve the solubility of furosemide as guest molecule via inclusion complex formation. Various molar ratios of F : β-CD derivatives (1 : 1/2, 1 : 1 and 1 : 2) and different preparative methods (physical mixing, kneading, precipitation, spray-drying and freeze-drying) were used. The increase in the dissolution characteristics and the solubility of furosemide depends on the type of β-CD derivative, on the furosemide concentration in the product and on the method of preparation. The inclusion complexes formed between the hosts and the guest were investigated by XRD, IR, and ^{1}H-NMR spectral methods.

Key words: cyclodextrins, furosemide, inclusion complexes, solubility.

1. Introduction

Physicochemical methods can be used to investigate the complex formation of β-CD derivatives in solution. Crystal structure analyses afford a description of the geometry of the host–guest interaction and show the β-CD derivative molecules packed in cage or channel modes in the crystal lattice, depending on the type and size of the guest molecule. The CD derivatives provide a unique opportunity to study intermolecular complex formation through non-covalent forces and the complex formation is based on their cyclic shape [1–3]

Furosemide (F), a frequently used diuretic and antihypertensive pharmacon [4], has the structural formula shown in Figure 1. Its Hungarian registered tablets and injections contain 40 mg and 20 mg of furosemide in 2 mL, respectively [5–8]. On complexation with β-CD derivatives, furosemide is molecularly dispersed in a hydrophilic matrix and becomes soluble. This improved solubility results in faster dissolution, which can potentially lead to a better bioavailability [9].

In earlier publications, we dealt with the influence of the β-CD derivatives on the solubility and tablet preparation and the kinetic changes in the composition of precipitates formed during cooling from 70 to 2 °C [6–8, 10].

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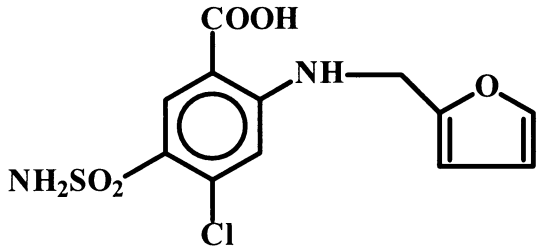

Figure 1. Chemical structure of furosemide.

Table I. Percentage composition of the products investigated.

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

Products containing various ratios of F : β-CD derivatives, prepared by different methods, have now been investigated by various techniques, such as XRD, IR and ^{1}H-NMR.

2. Materials and Methods

Furosemide was obtained from Chinoin-Sanofi Chemical and Pharmaceutical Works Ltd. (Budapest, Hungary). β-CD, hydroxypropyl-β-CD (HP-β-CD with degree of substitution DS = 2.8), dimethyl-β-CD (DIMEB; DS = 14.0) and random-methylated β-CD (RAMEB; DS = 1.8) were obtained from Cyclolab R & D Ltd. (Budapest, Hungary). All materials were used as received.

Different methods were applied in the preparation of the inclusion complexes: simple powder mixing, kneading with 50% aqueous alcohol, precipitation, spray-drying with a Niro Atomizer apparatus with an inlet air temperature of 105 °C, and freeze-drying with a Leybold GT 2 apparatus, using F : β-CD derivative molar ratios of 1 : 1/2, 1 : 1 and 1 : 2, calculated on the basis of their molecular weights (Table I).

Spectrometric investigations of the products were made on a Specord UV VIS (C. Zeiss, Jena, Germany) to determine the furosemide peak in the concentration range 2–15 μg/g in distilled water (λ = 282 nm), and a Spektromom 195 (MOM, Budapest, Hungary) was used to determine the concentration of furosemide in the complexes at 20–25 °C (room temperature) at the same wavelength. The presence of the different β-CD derivatives in the usual concentration did not influence the absorbance of the solution.

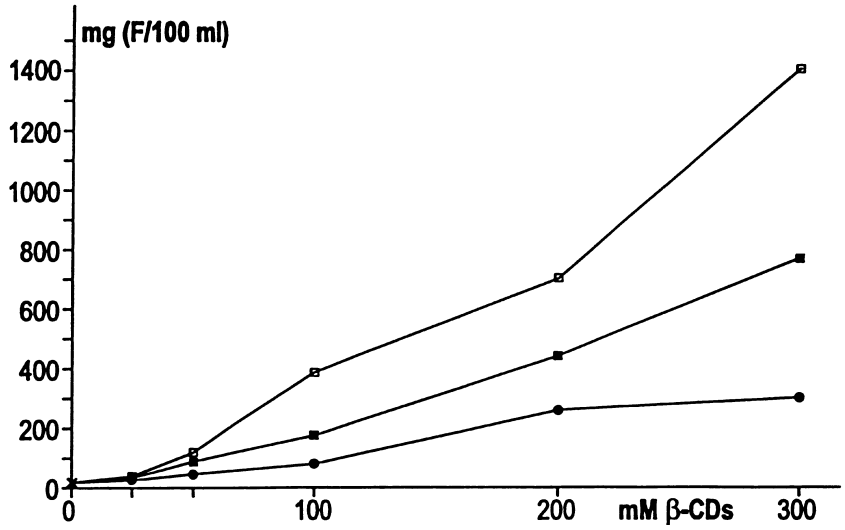

Figure 2. Influence of β-CDs on the solubility of furosemide. Ordinate: solubility in mg/100 mL; abscissa: concentration of β-CDs in mM.

The dissolution rate was determined by the basket method according to USP XXIII at 37 °C and 100 rpm in 900 mL distilled water of the nominal capacity under sink conditions [11, 12]. An appropriate amount of the inclusion products containing 100 mg of the drug was used. A 5 mL sample of this solution was diluted to different extents (depending on the β-CD derivative), the absorbance was measured with a Spectromom 195 and the concentration of furosemide was calculated in mg per 900 mL.

XRD diffraction spectra were recorded with a DRON UM-1 instrument, and IR spectra in KBr on a Perkin-Elmer Paragon FT-IR instrument. The ^{1}H-NMR spectra were recorded with a Bruker Avance DRX-400 instrument: the samples were dissolved in D_2O at room temperature and the deuterium signal of the solvent was used to lock the magnetic field. The chemical shifts are given in ppm relative to the methyl signal of the standard, sodium 2,2-dimethyl-2-silapentane-5-sulfonate

3. Results and Discussion

The ability of the β-CD derivatives to form water-soluble inclusion complexes is based on the general physicochemical properties of the guest substance [13]. It is interesting that the particle size distribution depends on the crystalline properties of the β-CD derivatives and on the complex preparation method [9], and these can influence the rate of dissolution and the solubility of the guest.

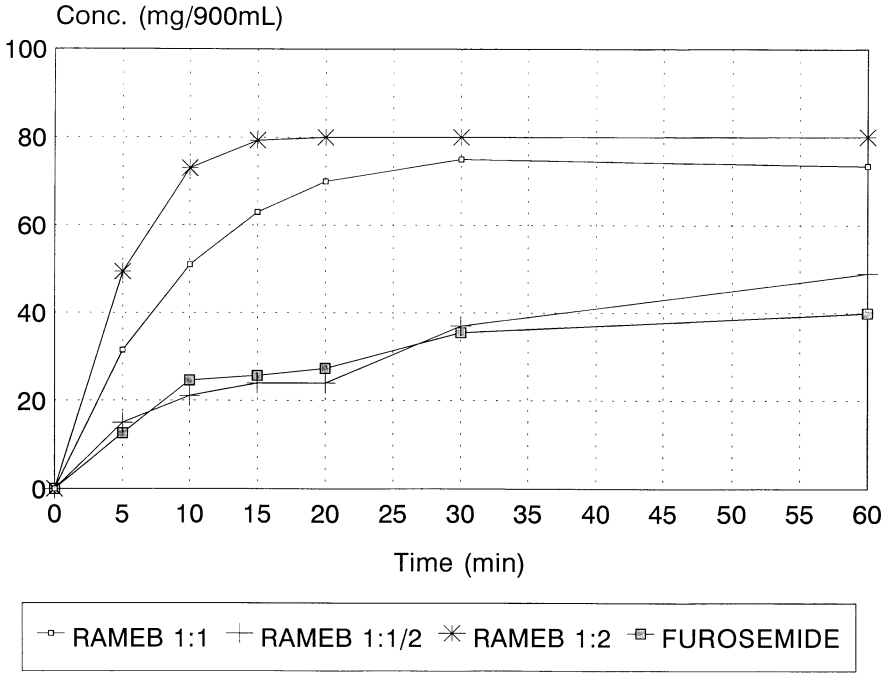

Figure 3. Influence of RAMEB and its ratio on the dissolution of furosemide from kneaded product. Ordinate: concentration of furosemide in mg/900 mL; abscissa: time of dissolution, min.

3.1. DISSOLUTION RATE AND SOLUBILITY

The β-CD derivatives strongly influenced the solubility of furosemide, the solubility increasing in the sequence β-CD < HP-β-CD < RAMEB < DIMEB. Type A_L phase-solubility diagrams were observed. These determinations were performed at room temperature during one week (Figure 2).

It was found that 300 mM DIMEB increases the solubility of furosemide 137-fold, RAMEB increases it 75-fold and β-CD increases it only 3-fold. DIMEB increases the solubility properties of furosemide for all methods of preparation of the inclusion complexes. The effects of the β-CD derivatives on the solubility of furosemide were influenced by their concentrations and the preparative method.

The extent of dissolution of pure furosemide during 60 min at 37 ± 1 °C is 39.96 mg per 900 mL distilled water (further furosemide would dissolve during a longer period). The dissolution properties of products containing RAMEB were better than those of the products of HP-β-CD and β-CD complexation (Figure 3), which may be influenced by the particle size.

As concerns the methods of preparation, HP-β-CD gave similar results for the kneading and spray-drying products. On the basis of the equilibrium concentration of the β-CD derivatives in the complex, the ratio 1 : 2 affords the best results on

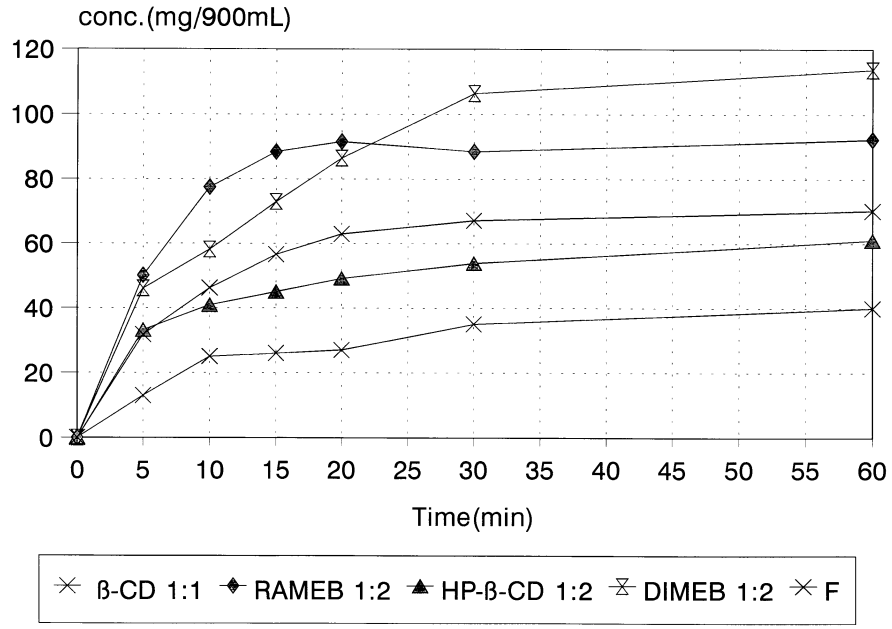

Figure 4. Influence of β-CDs on the dissolution of furosemide from spray-dried products. Ordinate and abscissa see Figure 3.

the rate of dissolution of furosemide, particularly for the spray-dried products of all β-CDs (Figure 4).

3.2. XRD, IR AND ^{1}H-NMR SPECTRA

Inclusion complex formation was investigated by means of the X-ray spectra. It was established that the original furosemide and β-CD have crystalline structures which yield peaks, whereas the original HP-β-CD, DIMEB, and RAMEB have amorphous structures; all physical mixtures gave the characteristic peaks of furosemide, while the precipitated products of furosemide with β-CD displayed their characteristic peaks. All kneaded products exhibited such peaks, their intensities being in direct proportion to the furosemide concentration, while all spray-dried and freeze-dried products had typical amorphous structures, as shown in Figure 5.

IR investigation of furosemide and its products revealed that the skeletal vibrations of the —SO_2NH_2 group belong to the amide bonding. For furosemide alone, two bands exist at 1593 and 1565 cm^{-1}, while RAMEB does not give these lines, but its spectrum totally conceals the intense vibrations of the furosemide CH groups at 3400–3200 cm^{-1}, while the ring vibrations at 1000–1200 cm^{-1} obscure the aromatic vibrations of furosemide (Figure 6).

The IR spectra of the powder mixture and the kneaded, spray-dried and freeze-dried products of furosemide and RAMEB at a ratio of 1 : 1 were analysed. Figure 6

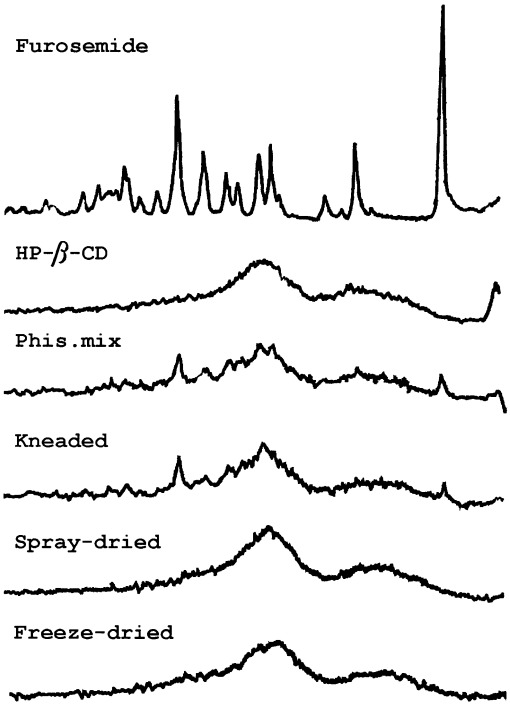

Figure 5. X-ray spectra of furosemide, HP-β-CD and their products.

shows that for the powder mixture the lines of furosemide are not shifted to higher wavenumbers as compared with furosemide alone. As concerns the other products, the shifts are to 1596 and 1567 cm^{-1} for the kneaded product, and to 1597 and 1571 cm^{-1} for the freeze-dried and spray-dried products, indicating an interaction between the NH_2 group of furosemide and the RAMEB molecule. Although the differences are small (3–4 cm^{-1}), they are significant.

This interaction is weaker in the case of β-CD: the shifts are to 1592 and 1562 cm^{-1} only. The aromatic skeleton vibration is in nearly the same position.

The ^{1}H-NMR spectrum of furosemide (Figure 7) does not change as regards the chemical shifts of the corresponding protons in the spectra of the complexes. The slight difference in linewidth of the NH protons at 8.62 ppm shows that the complexation does not occur close to the aromatic group.

4. Conclusion

The β-CD derivatives are capable of forming inclusion complexes with compounds having a size compatible with the dimensions of their cavity. In this way, the β-CD derivatives can increase the solubility of furosemide to various degrees, depending on the ratio and the method of preparation. DIMEB increases the solubility of furosemide to the largest extent (the increase is 137-fold at 300 mM), proving to

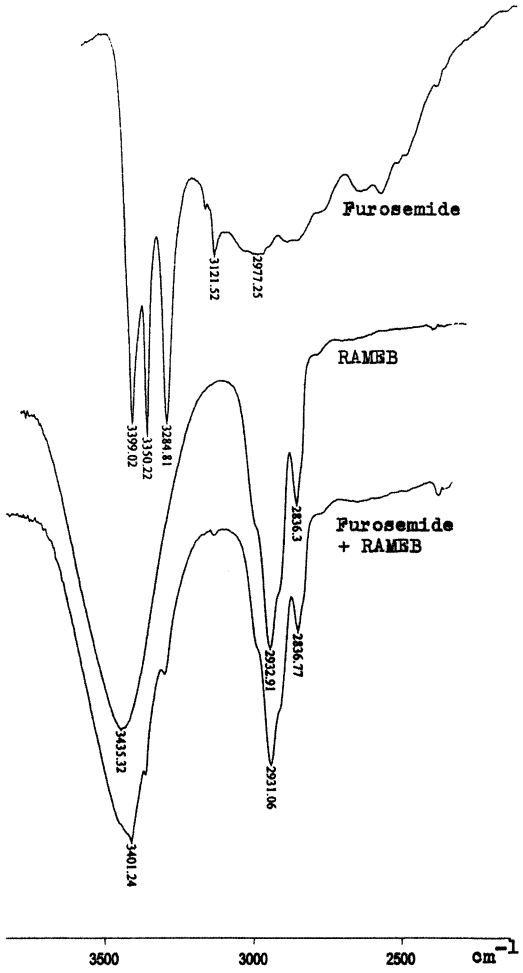

Figure 6. Graphical comparison of the IR-spectra of pure furosemide, pure RAMEB and furosemide + RAMEB powder mixture of ratio 1 : 1.

be the best β-CD derivative. An F : β-CD derivative ratio of 1 : 2 was generally the best, and the rate of dissolution of furosemide was the highest from spray-dried and kneaded products.

The solubility findings are in accord with the results of other research methods, i.e. X-ray analysis, IR spectroscopy and ^{1}H-NMR spectroscopy of furosemide, the β-CD derivatives and their products. It is interesting that complexation with the spray-drying method led to a particle size with a large surface area that appeared to favour dissolution of the complexes, and this method may be appropriate for tabletting.

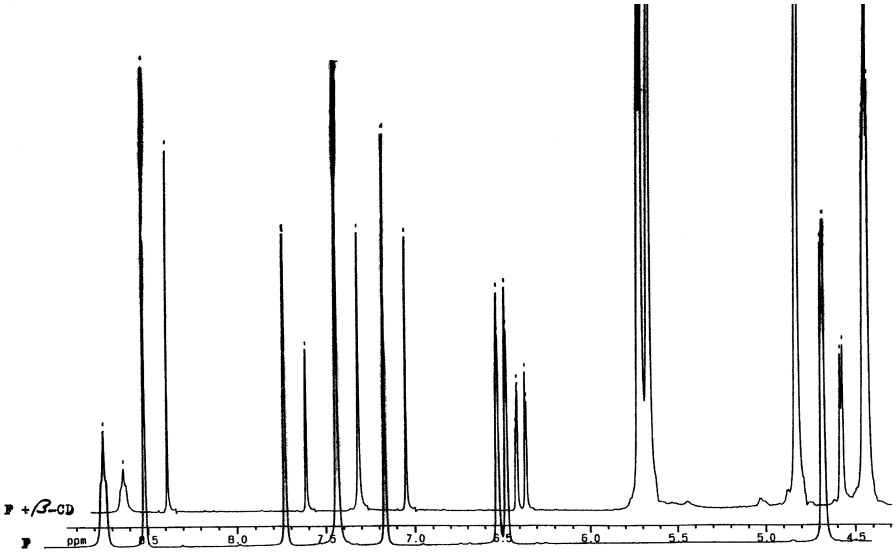

Figure 7. NMR spectra of pure furosemide and furosemide + β-CD inclusion complex of precipitation method (shifted 1° to the left for better comparison).

Acknowledgement

The authors are grateful to Professor J. Szejtli for providing the CD products and for valuable advice.

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