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Increasing the Solubility Characteristics of Iomeglamic Acid with β-Cyclodextrin

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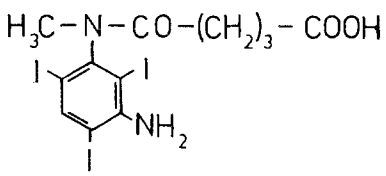
Abstract. Iomeglamic acid has been successfully applied for radioscopy of the gall-bladder since 1972. This pharmacon has the disadvantageous property that it is practically insoluble in water. Preparations containing the drug in different concentrations were made with β-cyclodextrin by different methods, and their dissolution characteristics were determined. In the best situation the solubility increased ten-fold. The tablets were made from the most suitable complex, with β-cyclodextrin. The conditions of tableting, the parameters and the dissolution of the tablets were tested.

Key words. cyclodextrin complexation, β-cyclodextrin, iomeglamic acid, increase of solubility characteristics, tableting, tests on tablets.

1. Introduction

Iomeglamic acid (**1**) was synthesized as an iodinated aryl dicarboxylic acid monoamide by Cassebaum in 1972, and it has been applied for radioscopy of the gall-bladder and bile-ducts [1, 2].



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Its pharmacological characteristics were determined by Bekker [3], *in vitro* resorption examinations were made by Fahr [4], and its analyses were developed [5] and its human biotransformation studied by Pfeifer *et al.* [6–9].

An advantageous feature of the drug is that, as a consequence of its high iodine content (62.2%), as early as the fourth hour after application it is present in sufficient quantity in the bile and its concentration remains over the MEC (minimum effective concentration) value for at least five hours [3]. It is eliminated quickly and fully from the intestines and kidneys. Falignost® tablets contain 375 mg of iomeglamic acid (Intermed, Berlin, GDR) [10, 11].

It is barely soluble in water (<1 mg/100 g), and is thus one of the "problem pharmaca" [12]. For this reason, attempts have been made to increase the solubility characteristics of iomeglamic acid by using different auxiliary materials and different preparative methods.

The solubility was practically unchanged in a solid dispersion with sorbic acid. The solubility was increased 2-fold from the melt, 3-fold with mannite, 4-fold from methylcellulose + macrogol 6000 spray-embeddings, about 6-fold with PVP 25 and spray-drying, and about 8-fold from solid dispersions with succinic acid [12–16].

It was found that the solubility and rate of dissolution of iomeglamic acid from the products were generally higher than those of pure iomeglamic acid. The increase depends on the auxiliary material or materials, on their ratio, on the ratio of pharmacon and auxiliary material and on the methods of preparation of the products, which were examined by DTA, X-Ray and REM (raster electron-microscopy) [14, 15, 17–20].

Further experiments appeared to be justified. For this purpose, cyclodextrins (CDs) were applied as the auxiliary material, the importance of which has been discussed in books, international symposia and papers published in *Pharm. Industrie* [21–29].

2. Experimental

2.1. MATERIALS AND INSTRUMENTS

Iomeglamic acid and Falignost® tablets, Intermed (Berlin, GDR), α, β, γ and dimethyl-β-CD, Chinoin Chemical and Pharmaceutical Works Ltd. (Budapest, Hungary).

Sorboxethene laurate (Polysorbatum 20, Tween 20, Pharm. Hung. VII), Atlas Chemical Industries Ltd. (UK).

Avicel PH 101®, FMC Export Corp. (Philadelphia, USA). Polyplasdone XL®, GAF GmbH (Austria).

Aerosil 200®, Degussa (Frankfurt, FRG).

Magnesium stearate, E. Merck (Darmstadt, FRG).

The other materials used (acetone, ethanol, dimethylformide, etc.) met the requirements of USP XXI [30] and Pharmacopoeia Hungarica VII [31].

Instruments: NIRO Minor Atomizer (Copenhagen, Denmark), USP rotating-basket dissolution apparatus, Type DT (ERWEKA Apparatebau GmbH.), Spektromom 195 (MOM, Budapest, Hungary) and Specord UV-VIS (C. Zeiss, Jena, GDR) spectrophotometers. KORSCH EKO tableting machine with regulated pressing power and flat punch 13 mm in diameter (Korsch Maschienenfabrik, Berlin, FRG), Roche friabilator (ERWEKA).

2.2. PRELIMINARY EXPERIMENTS

An examination was first made of the influence of the CD derivatives on the solubility of the drug. In these experiments the ratio of iomeglamic acid and CD molecules was 1 : 1.

We next investigated the influence of the concentration of the CDs, and of β-CD (found to have the greatest effect) in the presence of sorboxethene laurate.

The roles of some solvents, e.g. dimethylformamide, acetone and ethanol, were also studied.

Following this, we determined the rates of dissolution of the pure drug and of the drug from the products. We made 3–5 parallel determinations on the 7 products and on the pharmacon in all cases.

2.3. PREPARATION OF THE PRODUCTS

Physical mixtures: after grinding, the components were mixed in a mortar and then sieved through a DIN 0.315 mm sieve.

Kneaded products: the physical mixtures of the drug and β-CD were mixed in the same quantity of acetone + ethanol + water (1 + 1 + 2 parts) as solvent. They were kneaded until the bulk of the solvent mixture had evaporated. After this they were dried at room temperature, and then at 105°C, and were next pulverized and sieved (DIN 0.315 mm).

Spray-embeddings: 2.0 g of iomeglamic acid and the calculated quantities of β-CD were dissolved in 600 g warm acetone + ethanol + water (1 + 1 + 2 parts), and the warm solutions were spray-dried with a NIRO Minor apparatus. Spray-drying parameters:

- rate of rotation of atomizer disk: 25 000 rpm,
- temperature of inlet air: 105 ± 5°C,
- feeding rate: about 2400 g/h.

The product of iomeglamic acid and β-CD made by spray-drying is a very fine (average particle size 9 μm) and definitely adhesive powder which has disadvantageous powder flow characteristics and this causes some difficulties in the tablet production. The best composition for tableting was as follows:

Iomeglamic acid + β-CD complex (containing 74.11 mg of drug)	484.00 mg
Avicel PH 101	30.28 mg
Polyplasdone XL	27.50 mg
Aerosil 200	2.72 mg
Magnesium stearate	5.50 mg
	550.00 mg

The pressing power was 1.5 kN, and the rate of tableting was 30 tablets/min.

2.4. DETERMINATION OF DISSOLVED PHARMACON AND OF EQUILIBRIUM CONCENTRATION

In the USP rotating-basket dissolution apparatus, 100 mg of iomeglamic acid, or samples containing 100 mg of drug were examined in 900.0 g of distilled water at 37 ± 1°C. The basket was rotated at 100 rpm. Sampling was performed after 2, 5, 10, 15, 30 and 60 min. The volume of the samples was 5.0 ml. The iomeglamic acid contents of the samples after dilution were determined spectrophotometrically at 234 nm.

For determination of the equilibrium concentration, samples of all products containing 100 mg of drug were placed into 50.0 g of distilled water, left at 37°C for one week, and carefully shaken daily. After filtration and dilution, the drug content was measured spectrophotometrically.

2.5. DETERMINATION OF TABLET PARAMETERS

The average weight of the tablets was determined, the height was measured with a screw-micrometer, the friability with an ERWEKA-Roche friabilator, the strength with an ERWEKA TB apparatus and the disintegration in a flask test, while the tests on the dissolution of the drug from the tablets were performed with the rotation basket method. In all cases an ERWEKA apparatus (ERWEKA Apparatebau GmbH) was used. Iomeglamic acid contents were measured spectrophotometrically at 234 nm.

The tests on the tablets were performed both immediately after tablet preparation and after storage.

3. Results

In the pre-experiments it was found that the CDs increase the solubility of iomeglamic acid, the influence gradually increasing in the sequence α, γ, dimethyl-β and β-CD (Figure 1).

Tween 20 did not alter the solubility-increasing effect of β-CD. However, a change of the drug: β-CD ratio from 1:1 to 1:2 increased the solubility.

Of the solvents, dimethylformamide caused strong 'subpeak formation' in the UV spectrum of the drug. Acetone and ethanol had no such effect. The absorption

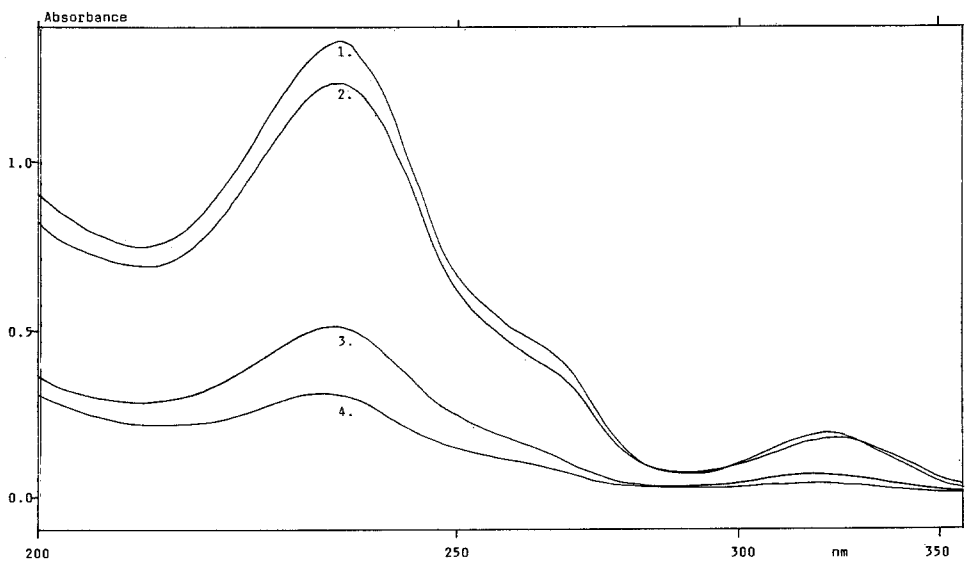

Fig. 1. Influence of CD derivatives on the UV spectrum of iomeglamic acid: (1) β-CD; (2) γ-CD; (3) α-CD; (4) iomeglamic acid, only.

maximum of the drug in ethanol solution is at 234 nm. The calibration plot revealed that the absorption obeys the Bouguer–Lambert–Beer law in the concentration interval 0–20 μg/g.

The preliminary experiments showed β-CD to be best. Kneaded products and spray-embeddings with drug:β-CD ratios of 1:1, 1:2 and 1:3 and a physical mixture with a ratio of 1:3 were made from iomeglamic acid and β-CD, i.e. the

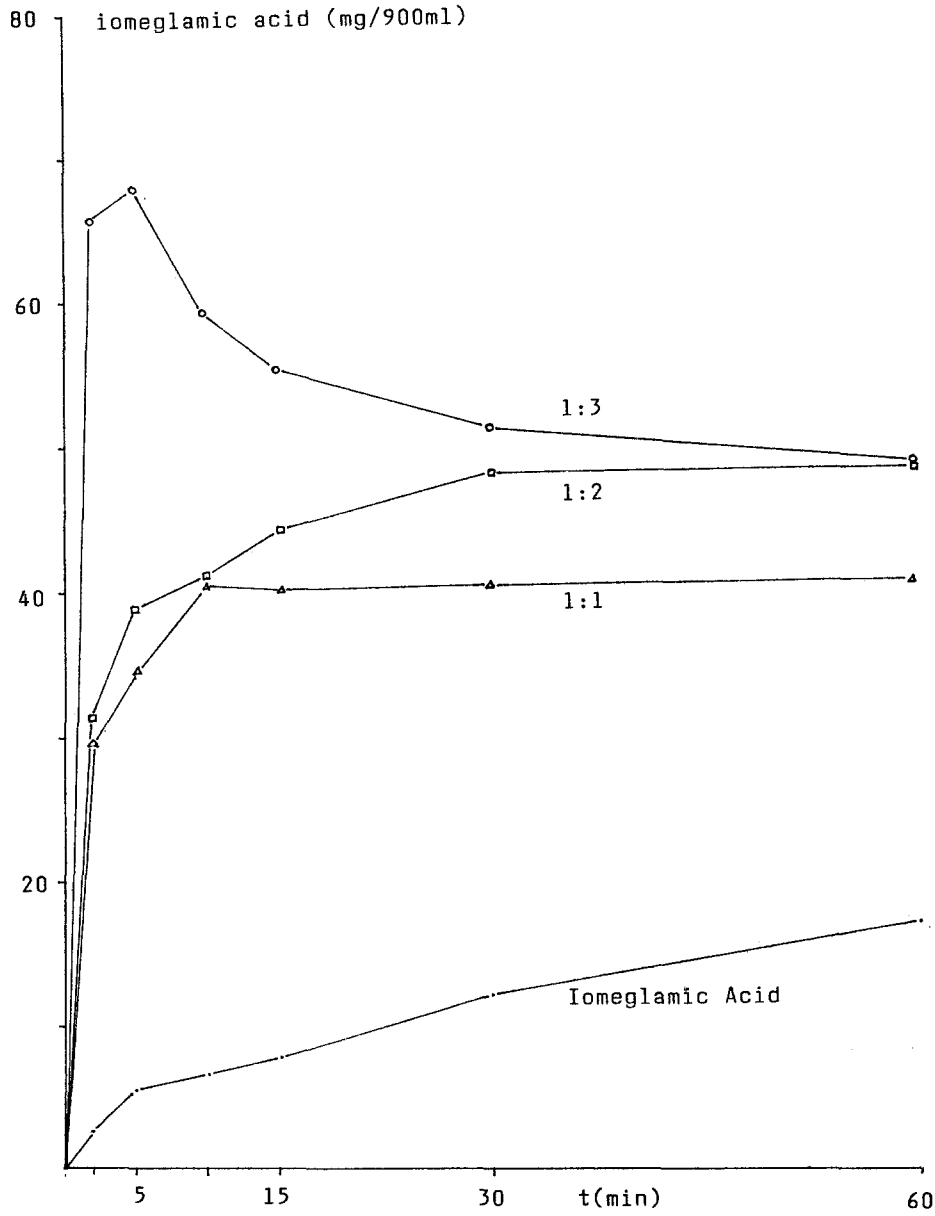

Fig. 2. Influence of the drug: β-CD ratio on the rate of dissolution of kneaded products (at 37°C, from 100 mg pure drug).

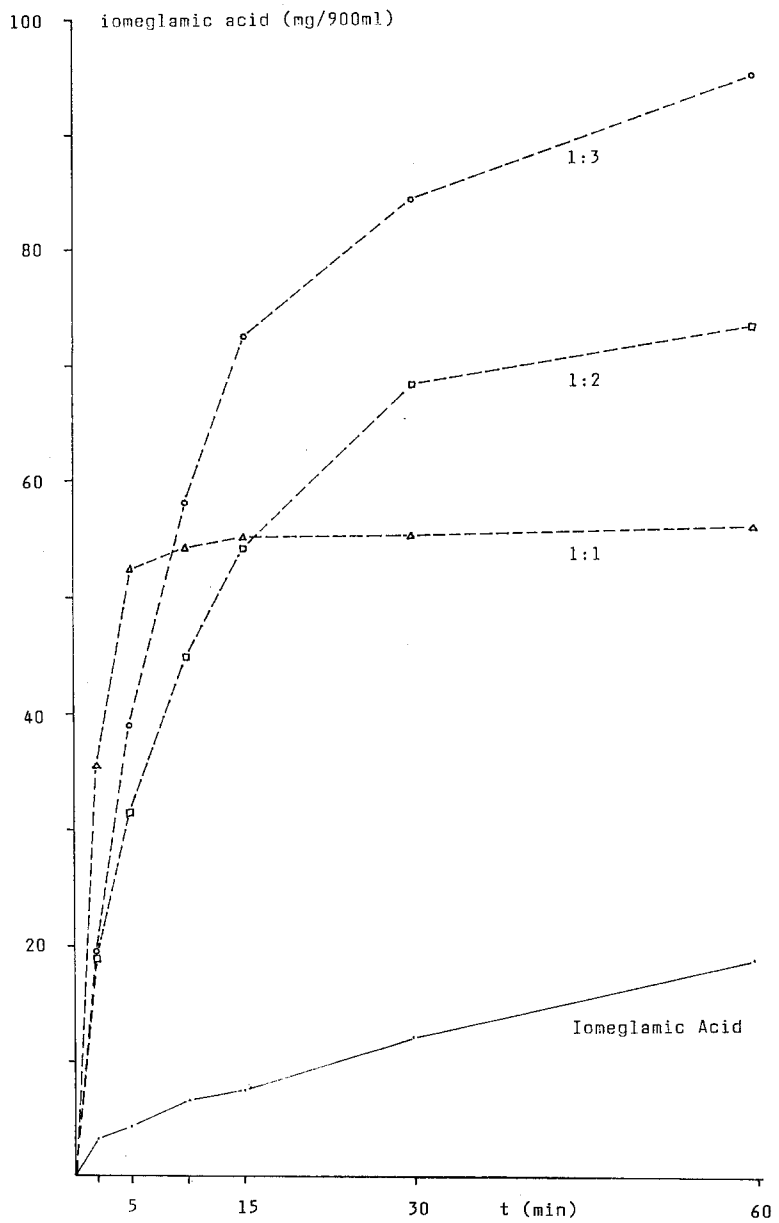

Fig. 3. Influence of the drug: β-CD ratio on the rate of dissolution of spray-embeddings (at 37°C, from 100 mg pure drug).

iomeglamic acid contents of these products were 35.11%, 21.29% and 15.28%, respectively.

The investigations revealed that the dissolution for both the kneaded products and the spray-embeddings increased in the sequence 1:1, 1:2 and 1:3 (Figures 2 and 3).

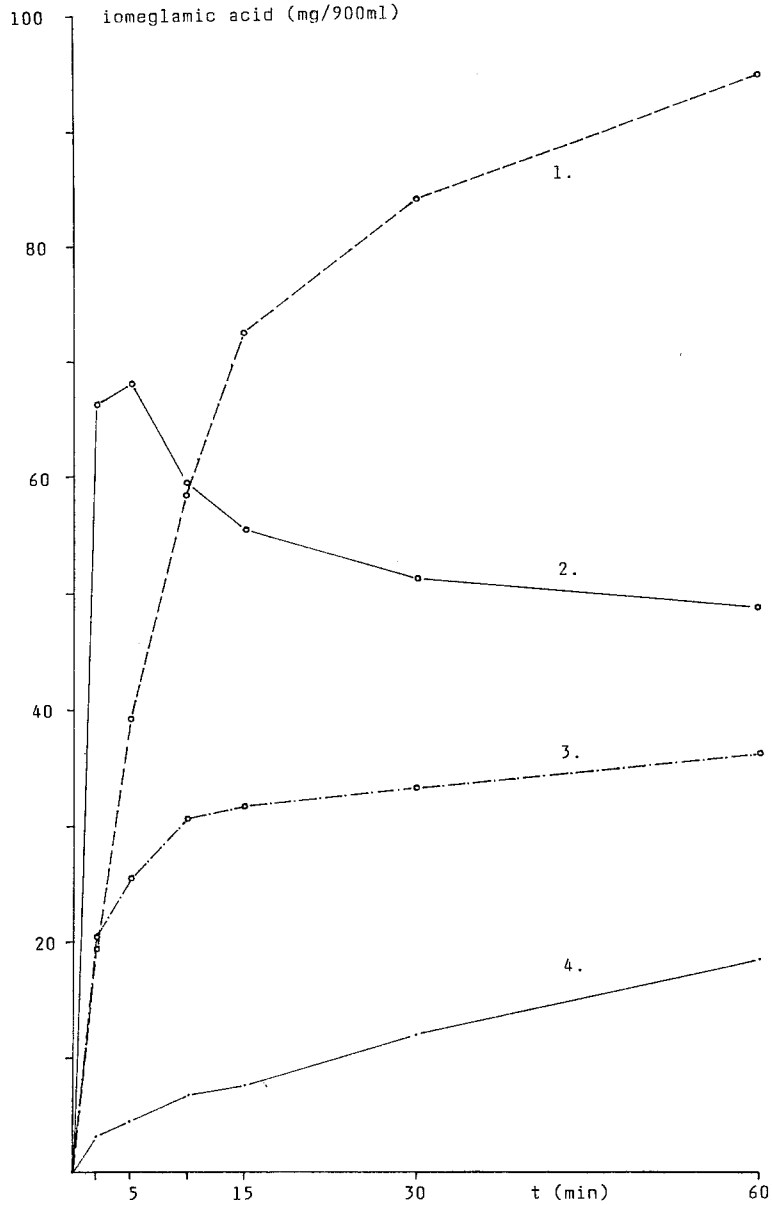

Fig. 4. Comparison of the rates of dissolution of 1:3 products made by different methods (at 37°C, from 100 mg pure drug); (1) spray-embedding; (2) kneaded product; (3) physical mixture; (4) iomeglamic acid/reference.

For the 3 kneaded products the measured dissolution data after 60 min were 41.14%, 48.87% and 49.12%, whilst for iomeglamic acid it was only 18.91%.

Accordingly, the dissolution depends on the ratio of iomeglamic acid and β-CD. The figures show that the dissolutions are different for the kneaded products and the spray-embeddings when the compositions of the products are equivalent. For

Table I. Results on tested tablets containing drug + β-CD complex

Tests	(a) immediately after preparation		(b) after storage for 3 months	
average weight, g	3.46		4.63	
height of tablets, mm	5.09	$S = \pm 0.04$	5.126	$S = \pm 0.03$
friability test, %	1.02	$S = \pm 0.17$	0.46	$S = \pm 0.16$
strength of tablets, N	103.6	$S = \pm 16.16$	87.3	$S = \pm 13.12$
disintegration time, s	98	$S = \pm 13.04$	82	$S = \pm 15.17$

Table II. Dissolution of drug from tablets containing β-CD

Time of sampling, min		2	5	10	15	30	60
(a) Dissolved drug	mg/900 ml	14.92	29.35	44.22	51.82	55.56	58.33
	$S^{\pm}$	3.16	3.81	4.46	3.05	2.30	1.27
(b) Dissolved drug	mg/900 ml	11.92	30.14	42.45	48.49	57.15	58.52
	$S^{\pm}$	1.13	7.81	1.77	3.67	4.31	2.58

the 1 : 3 kneaded product the increase in solubility is about 2.6-fold with respect to the drug, while that for the spray-embedding is about 5-fold.

In order to study the influence of the preparative methods a 1 : 3 physical mixture was also made. Figure 4 shows that the preparative method has a strong influence on the dissolution of iomeglamic acid. Spray-embedding was the best of the methods investigated, and physical mixing was the least effective.

The tablets containing drug + β-CD complex were examined according to USP XXI [30]; the results are given in Table I. During storage these data underwent practically no change and all the parameters met the requirements of USP XXI.

Data on the dissolution tests are given in Table II. These did not change either during the storage period.

The dissolution of an official tablet containing 375 mg of iomeglamic acid, was compared with the tablet containing only 74.11 mg of drug and β-CD. This comparison showed that about 2 times more pharmacon was dissolved from the β-CD containing tablet than from the official tablet (Figure 5).

4. Discussion and Conclusions

The preparative method has an interesting influence on the rate of dissolution. During the first 10–15 min, the quantity of drug dissolved from the kneaded products is more than from the spray-embeddings.

Compared with the quantity dissolved from pure iomeglamic acid, 3.6 times more pharmacon was dissolved from the physical mixture, 7.1 times more from the spray-embedding and 7.5 times more from the kneaded product. It is a particular advantage that kneading is a simple method and is a preparatory operation in tablet production.

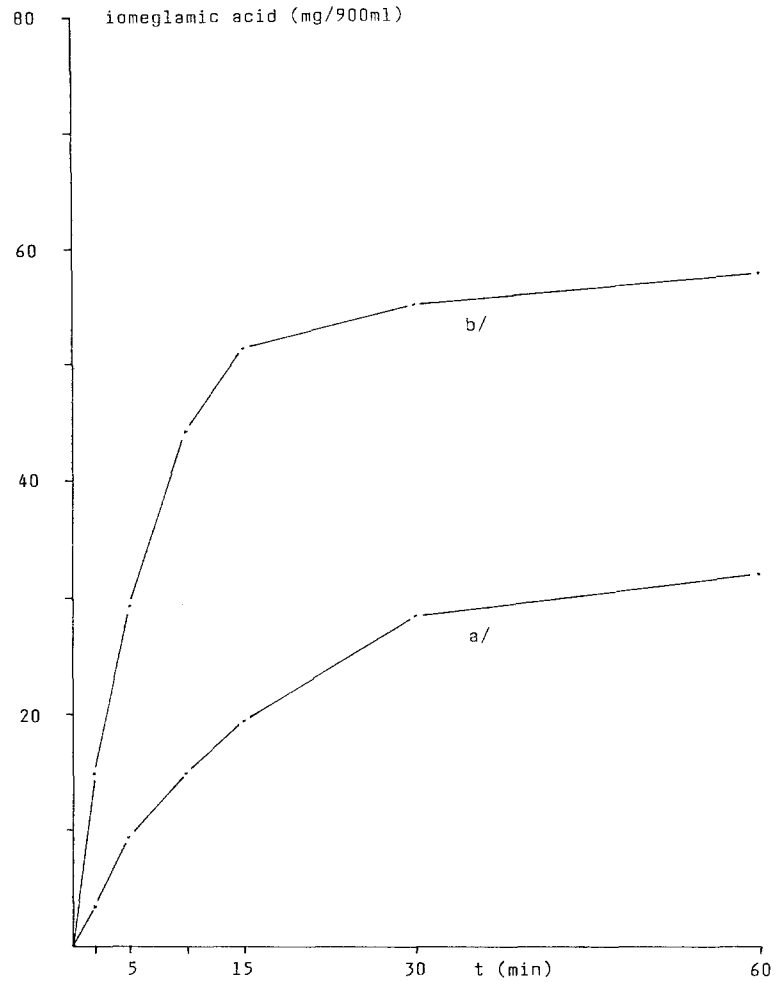

Fig. 5. Comparison of the rates of dissolution: (a) an official tablet; and (b) a tablet containing β-CD.

Determination of the equilibrium concentrations confirmed the sequence found in the dissolution tests (Table III).

3–4 times more iomeglamic acid dissolved from the 1 : 1 product than from the pure drug, 5–6 times more from the 1 : 2 product, and 10.7 times more from the 1 : 3 spray-embedding (than from iomeglamic acid).

To summarize, the cyclodextrin derivatives, and primarily β-CD, increase the solubility and rate of dissolution of iomeglamic acid. The ratio of the guest : host molecules and the methods by which the product is made also strongly influence the solubility characteristics.

The quantity of the dissolved pharmacon increased 7.5-fold, and the equilibrium concentration 10.7-fold. This permits the hope that the iomeglamic acid content of Falignost® tablets could be decreased, while the availability remains unchanged or even improved.

Table III. Equilibrium concentrations

IA: β-CD	Kneaded product		Spray-dried product		Physical mixture	
	mg/100g	%	mg/100g	%	mg/100g	%
1:1	22.88	378	23.76	393	–	–
1:2	35.61	588	27.26	450	–	–
1:3	38.05	629	64.73	1070	31.13	514

Iomeglamic acid = 6.05 mg/100g (= 100%)

From the spray-dried product containing 15.28% iomeglamic acid, tablets can be made without wet granulation. These tablets have good tablet parameters which do not change during storage. The dissolution of the drug from tablets containing only 74.11 mg pharmacon and β-CD was about 2 times more than from the official tablets containing 375.0 mg of iomeglamic acid. Accordingly, β-CD increased the rate of dissolution from the tablets 10-fold.

The combinations of CDs together or with Tween 20 do not have a considerable influence on the solubility characteristics.

From a knowledge of the size and structure of the iomeglamic acid molecule when a true inclusion complex is formed, the molecular ratios 1:1 and 1:2 should be best. There appears to be a realistic possibility for the formation of outer sphere complexes in the case of iomeglamic acid.

References

1. H. Cassebaum, K. Dierbach, and H. Bekker: *Pharmazie* **27**, 391 (1972).
2. S. Pfeifer, J. Schäffner, and I. Bornschein: *Pharmazie* **27**, 617 (1972).
3. H. Bekker, H. Cassebaum, and W. Lietz: *Pharmazie* **27**, 411 (1972).
4. F. Fahr, R. Neubert, W. Fürst, H. Kala and F. Masthoff: *Pharmazie* **41**, 855 (1986).
5. S. Pfeifer, J. Schäffner, and I. Bornschein: *Pharmazie* **27**, 396 (1972).
6. S. Pfeifer, J. Schäffner, I. Bornschein, and R. Kraft: *Pharmazie* **27**, 403 (1972).
7. S. Pfeifer, J. Schäffner, and I. Bornschein: *Pharmazie* **27**, 616 (1972).
8. I. Bornschein, H. Borchert, and S. Pfeifer: *Pharmazie* **29**, 730 (1974).
9. I. Bornschein, J. Schäffner, and S. Pfeifer: *Pharmazie* **30**, 196 (1975).
10. *Index Nominum, 1980.* Laboratory of the Swiss Pharmaceutical Society, Zürich, Switzerland.
11. *Útmutató a gyógyszerkészitmények rendelésére*, Medicina, Budapest (1988).
12. F. Fahr, H. Kala, P. Pollandt, U. Wenzel and F. Masthoff: *Pharmazie* **40**, 408 (1985).
13. F. Fahr, H. Kala, and F. Scharrenweber: *Pharmazie* **40**, 60 (1985).
14. F. Fahr, H. Kala, P. Pollandt, and G. Zessin: *Pharmazie* **40**, 733 (1985).
15. F. Fahr, R. Mank, and Eva-Maria Meckel: *Pharmazie* **41**, 64 (1986).
16. F. Fahr, H. Kala, and Eva-Maria Meckel: *Pharmazie* **41**, 667 (1986).
17. F. Fahr, H. Kala, and P. Pollandt: *Pharmazie* **40**, 127 (1985).
18. F. Fahr, H. Kala, and F. Masthoff: *Pharmazie* **40**, 270 (1985).
19. F. Fahr, H. Kala, F. Masthoff, and G. Fries: *Pharmazie* **41**, 517 (1986).
20. F. Fahr, H. Kala, and P. Pollandt: *Pharmazie* **41**, 434 (1986).
21. M. L. Bender, and M. Komiyama: *Cyclodextrin Chemistry*, Springer-Verlag, Berlin, Heidelberg, New York (1978).
22. J. Szejtli: *Cyclodextrins and their Inclusion Complexes*, Akadémia Press, Budapest (1982).
23. J. Szejtli: *Cyclodextrins in Pharmacy*, Chinoin, Budapest (1985).
24. J. Szejtli: *Proceedings of the Ist Intern. Symp. on Cyclodextrins*, Akadémia Press, Budapest (1982).

25. J. L. Atwood, J. E. D. Davis, and T. Osa: *Proceedings of the 2nd Intern. Symp. on CDs*, D. Reidel, Dordrecht (1984).
26. Royal Society of Chem.: *Abstracts of the 3rd Intern. Symp. on CDs*, Lancaster, U.K. (1986).
27. G. Kedvessy: *Pharm. Ind.* **47**, 99 (1985).
28. B. W. Müller and U. Brauns: *Pharm. Ind.* **48**, 1427 (1986).
29. M. Kata and G. Kedvessy: *Pharm. Ind.* **49**, 98 (1987).
30. USP XXI. U.S. Pharmacopeial Convention, Inc., Rockville (1985).
31. *Pharmacopoeia Hungarica, Ed. VII*, Medicina, Budapest (1986).