Increasing the Solubility Characteristics of Fenofibrate with Cyclodextrin*

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Abstract. The incidence of genetic lipoprotein disorders, or hyperlipoproteinaemia, is currently increasing. Examinations were carried out on the hyperlipoproteinaemic drug fenofibrate, and various cyclodextrin derivatives were applied to increase the solubility of this drug. Numerous products with several compositions (drug : CD mole ratio = 2 : 1, 1 : 1, 1 : 2 or 1 : 3) were studied and three preparation methods (powder mixing, kneading and precipitation) were used. In vitro drug liberation and membrane diffusion examinations revealed compositions suitable for the preparation of a capsule dosage form (1 : 2 and 1 : 3 physical mixtures).

Key words: Cyclodextrins, DIMEB, fenofibrate, mixing, kneading, precipitation, increase of solubility characteristics, membrane diffusion.

1. Introduction

In order for a therapeutic effect to be attained, a drug should be liberated from the dosage form, dissolved in the interstitial fluid and be absorbed. There are a number of drugs which dissolve only slightly or are insoluble in water or in gastric juice. Various efforts have been made in pharmaceutical technology to influence and regulate the solubility and absorption of such drugs, including the selection of suitable auxiliary materials which promote the bioavailability of slightly soluble drugs.

Both in scientific research and in the pharmaceutical industry, increasing interest is currently being shown in the cyclodextrins (CDs), which form inclusion complexes with suitable guest molecules. This complexation increases the solubility and rate of dissolution of these drugs [1–3].

CDs are cyclic non-reducing oligosaccharides containing 6, 7 or 8 glycopyranose units (α-, β- or γ-CD) [1–4]. The difference in surfacial functional groups results in different derivatives.

CDs are used in several fields: the pharmaceutical industry, the food industry, cosmetics, the tobacco industry and agrochemistry [1, 2, 4]. They are also of use in spectroscopy and chromatography [5]. Numerous scientific teams throughout

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* Dedicated to Dr. Béla Selmeczi, university professor, with the best wishes for his 65th birthday.
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the world work with CDs. Many experiments have been performed with CDs in our department, in which products were used in different dosage forms, e.g. in tablets: nitroglycerine, furosemide, paracetamol, iomeglamic acid and nitrazepam; in suppositories: diazepam, nitrazepam and metronidazole; and in oral liquid preparations: papaverine and phenobarbital sodium [6–26].

Publications relating to 20 drug–CD derivatives can be found since 1990 in this Journal. Those dealing with doxorubicin and daunorubicin [27], chloronitrobenzene derivatives [28], coronene [29], tenoxicam [30], ephedrine [31], terfenadine [32], and β- and γ-CD are of special interest to us.

Fenofibrate (procetophen) is one of the most effective hyperlipoproteinaemic drugs. It is a derivative of clofibrate first prepared in Furnier-Dijon (France), in 1973, with advantageous properties in decreasing the lipid level [33]. Lipanthyl® capsule, a Hungarian registered preparation, contains 100 mg of fenofibrate. A review of the literature connected with fenofibrate revealed only pharmacological and clinical publications.

Studies on the lipoprotein fractions in human experiments demonstrated that fenofibrate significantly decreases the low and very low density (LDL and VLDL) lipid levels, while it increases the high density (HDL) fraction [34–37].

As fenofibrate dissolves only slightly in water, our aim was to increase its solubility by using CDs.

2. Experimental

2.1. MATERIALS

Fenofibrate (**F**): Isopropyl{2-[4-(4-chlorobenzoyl)-phenoxy]-2-methylpropionate}, Chemical Works of Gedeon Richter Ltd. (Budapest, Hungary); α, β- and γ-CD, methyl-β-CD (**Me-β-CD**), dimethyl-β-CD (**DIMEB**), hydroxyethyl-β-CD (**HE-β-CD**) and hydroxypropyl-β-CD (**HP-β-CD**), Chinoin-Sanofi Chemical and Pharmaceutical Works Ltd. (Budapest, Hungary).

The solvents used (acetone, ethanol, etc.) are official in *Pharmacopoeia Hungarica VII* [38].

2.2. APPARATUS

USP rotating-basket dissolution apparatus [39], type DT; kneading mixer, type LK5 (Erweka Apparatebau GmbH, Heusenstamm, Germany), Spektromom 195 (MOM, Budapest, Hungary) and Specord UV-VIS (C. Zeiss, Jena, Germany) spectrophotometers, Sartorius membrane diffusion apparatus (Sartorius-Membranfilter GmbH, Göttingen, Germany).

TABLE I. Influence of CD derivatives on the UV spectrum of fenofibrate.

1.	Fenofibrate (F)	100% =	1.00
2.	F + α-CD		2.28
3.	F + β-CD		0.43
4.	F + γ-CD		5.57
5.	F + Me-β-CD		30.00
6.	F + DIMEB		97.14
7.	F + HP-β-CD		11.71
8.	F + HE-β-CD		8.00

2.3. PRELIMINARY EXPERIMENTS

The effects of the different CD derivatives on the solubility of the active agent were determined: a mixture of 0.10 g of fenofibrate and 0.30 g of CD derivative diluted to 20.0 g with water was stirred for 15 min with a magnetic mixer. Suspension systems were filtered through filter paper and, after suitable dilution, the UV spectra were recorded (Specord UV-VIS). A system without CD was used as a control. DIMEB had the highest influence on the solubility of the active agent (Table I): the solubility was increased by a factor of 97.

This derivative was used for the further examinations.

The absorption maximum of the active agent was determined (292 nm). The calibration plot revealed that the absorption obeys the Bouguer–Lambert–Beer law in the concentration interval 0–20 μg/g, with an extinction coefficient (ϵ) value of 40.97.

2.4. PREPARATION OF PRODUCTS

Products were prepared in four different mole ratios (drug : CD mole ratio = 2 : 1, 1 : 1, 1 : 2 or 1 : 3).

Physical mixtures: the ground components were mixed in a mortar and sieved through a DIN 0.315 mm sieve.

Kneaded products: physical mixtures of the drug and DIMEB were mixed (ERWEKA LK5) in the same quantity of ethanol + water (1 : 1). 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).

Precipitated products: hot (50 °C) saturated acetone solutions of fenofibrate and DIMEB were mixed and the clear, yellow solution was cooled with ice to 2 °C with continuous stirring (1 °C/min). The precipitated product was filtered off, dried, ground, sieved (DIN 0.315 mm) and homogenized.

Products were stored under normal conditions at room temperature in closed glass containers.

2.5. MEMBRANE DIFFUSION EXPERIMENTS

Stricker's SARTORIUS instrument was used [40–41]. Measurements were performed on 100.0 mL of artificial gastric juice (pH = 1.1 ± 0.1) and artificial plasma (pH = 7.5 ± 0.1). 50 mg of active agent, or product containing 50 mg of active agent, was in the donor phase in all cases. The temperature was 37.5 ± 1.5 °C. During the examination, 5.0 mL samples were taken five times (after 30, 60, 90, 120 and 150 min) and their active agent contents were determined spectrophotometrically (Spektromom 195) after dilution. The amount of diffused active agent and the diffusion constant K_d were calculated.

$$K_d = \frac{c_{II_2} - c_{II_1}}{T_2 - T_1} \cdot \frac{1}{C_{I_0}} \cdot \frac{V_{II_0}}{F} \quad [\text{cm min}^{-1}]$$

where c_{IIx} is the corrected drug concentration in II phase to point of time T_x (mg/mL); V_{II_0} is the volume of the aqueous phase II at point of time T_0 (100 mL); F is the surface of membrane (cm^2); T_x is the time (min); c_{I_0} is the theoretical initial drug concentration in the phase I (mg/mL).

2.6. DISSOLUTION STUDIES

In the USP rotating-basket dissolution apparatus, 100 mg of pure fenofibrate, or product containing 100 mg of drug, was examined in 900.0 g of distilled water, and capsules (industrial and CD-containing ones) were examined in enzyme-free artificial gastric juice at 37 ± 1 °C. The basket was rotated at 100 rpm. Sampling was performed after 5, 10, 15, 30 and 60 min (and after 90 min in the case of capsules). The sample volume was 5.0 mL. The withdrawn sample was replaced by fresh dissolution medium. The fenofibrate contents of the samples after dilution were determined spectrophotometrically at 292 nm (Spektromom 195).

3. Results

3.1. DISSOLUTION STUDIES

The amount of fenofibrate dissolved in distilled water during 60 min is less than 0.5%.

The *physical mixtures* yielded a higher dissolution of active agent as compared to fenofibrate. The sequence of solubility increase depended on the quantity of the auxiliary material: the rate of dissolution increased with increase of the CD content of the products. The highest value for physical mixtures was obtained for the 1 : 3 composition, which gave a 10% fenofibrate solution, i.e. a more than a 21-fold solubility increase relative to the pure active agent. Maximum dissolution was reached at 15 min, and this value did not change later (saturation) (Figure 1).
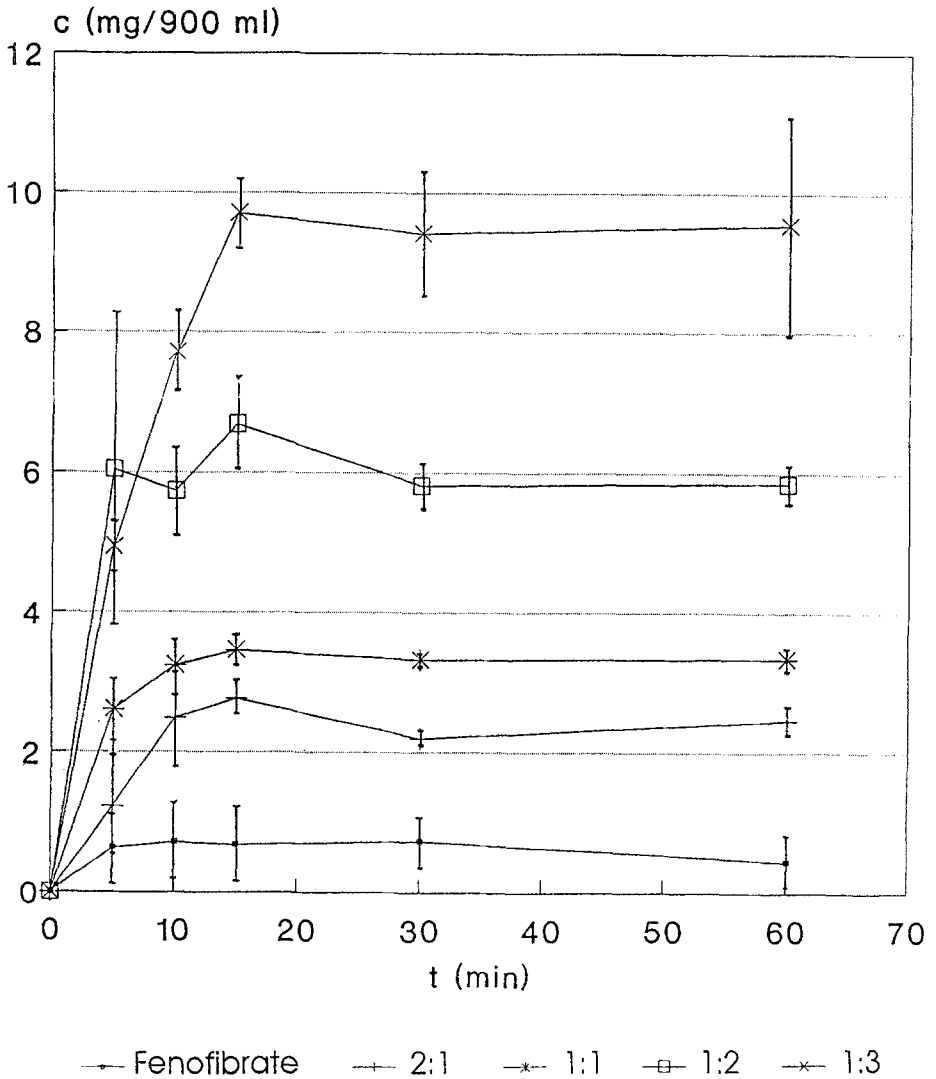
Fig. 1. Influence of the drug : DIMEB ratio on the rate of dissolution of physical mixtures (at 37 °C, from 100 mg pure drug).

On dissolution of the *kneaded products*, as for the physical mixtures, the sequence of solubility increase depended on the composition. The best results were obtained for the 1 : 3 composition. The degree of solubility increase was the same as for the physical product with the same components (about 21-fold). There were significant differences for the 1 : 1 and 1 : 2 compositions. The dissolution of the kneaded products was better, the dissolution rate was slower than that of the physical mixtures, with the maximum being reached at about 30 min (Figure 2).
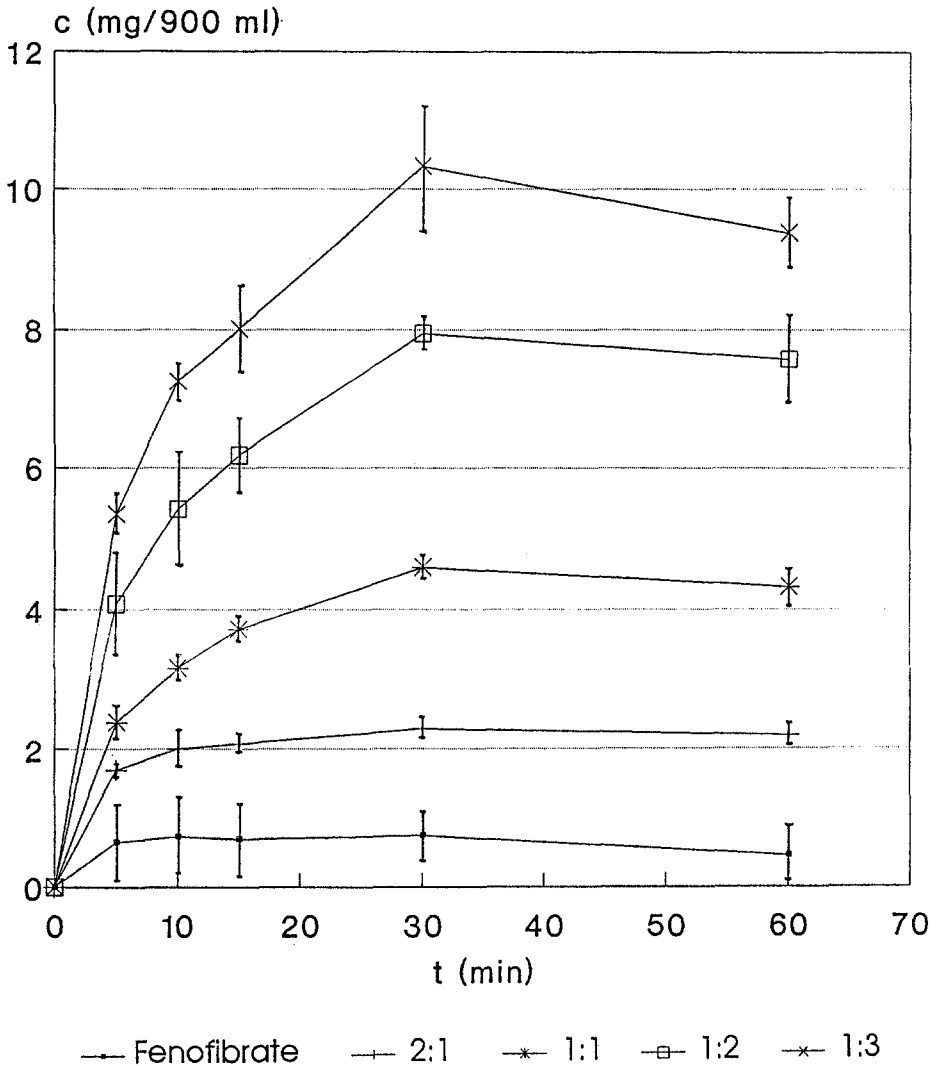
Fig. 2.   Influence of the drug: DIMEB ratio on the rate of dissolution of kneaded products (at 37 °C, from 100 mg pure drug).

The highest dissolution was found for the *precipitated products* (Figure 3), and especially for the 1 : 3 composition. The maximum was measured at 15–30 min, which probably means oversaturation. The excess amount later recrystallizes and the system stabilizes. This is supported by the small scattering values. This is shown by the saturation concentration values in Figures 1 and 2. This phenomenon can also be seen for other products, e.g. the 2 : 1 physical mixture.

    To summarize, the degree of dissolution depends on the quantity of auxiliary material; increasing the CD ratio increases the amount of material dissolved. The rate of dissolution depends on the preparation methods. There was a higher rate
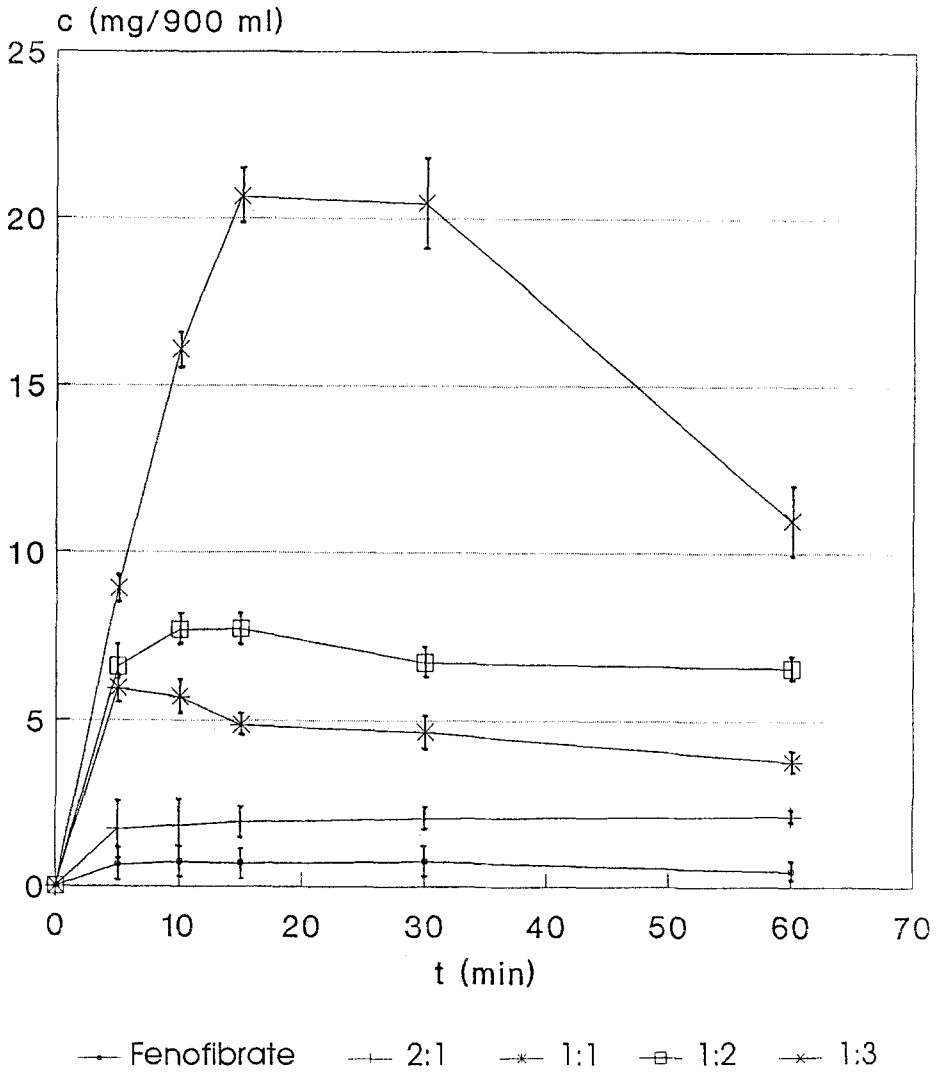
c (mg/900 ml)

Fig. 3.   Influence of the drug : DIMEB ratio on the rate of dissolution of precipitated products (at 37 °C, from 100 mg pure drug).

of dissolution for physical mixtures and precipitated products, and a lower one for kneaded products. There was no significant difference in the amount of dissolved drug between the same compound products made by different preparation methods.

TABLE II. Membrane diffusion examination of fenofibrate + DIMEB products (2.5 h).

Products	1 : 2			1 : 3		
	Diffused amount of drug			Diffused amount of drug		
	mg	S	K_d (cm/min)	mg	S	K_d (cm/min)
Physical mixtures	5.85	±0.53	$1.951 \cdot 10^{-3}$	3.91	±0.29	$1.304 \cdot 10^{-3}$
Kneaded products	3.63	±0.49	$1.208 \cdot 10^{-3}$	3.26	±0.07	$1.211 \cdot 10^{-3}$
Precipitated products	6.73	±0.48	$2.243 \cdot 10^{-3}$	6.12	±0.42	$2.133 \cdot 10^{-3}$
Fenofibrate	2.87	±0.18	$0.957 \cdot 10^{-3}$			

S = Standard deviation.

3.2. MEMBRANE DIFFUSION EXAMINATIONS

On the basis of the dissolution experiments to determine the diffusion rate constant, the 1 : 2 and 1 : 3 products from all preparation methods were used. The results of these examinations can be seen in Table II.

There were significant differences in both the amount of diffused active agent and the diffusion rate constant between given compound products made by different preparation methods. On the other hand, there was no significant difference between the different compound products made by the same preparation method. The best results were obtained for the precipitated products. The amount of diffused active agent was twice as much as for fenofibrate itself.

The diffusion experiments and dissolution values favoured the simplest preparation method (powder mixing). For the 1 : 2 and 1 : 3 active agent : CD products, we recommend the capsule form, taking into consideration the amount of auxiliary material and the degree of dissolution increase.

3.3. CAPSULE PREPARATION

The 1 : 2 product (61.7 mg) and the 1 : 3 product (54.6 mg), taking into consideration the degree of dissolution increase, were weighed and placed in capsules similar to industrial ones. It was expected that, because of the better solubility of the decreased amount of active agent, we would get the same values as for the industrial products, as there is no solubility-increasing auxiliary material in the industrial product, but merely filling and colouring materials [42].

Dissolution was achieved both in distilled water and in artificial gastric juice (Figures 4 and 5). The capsules containing CD dissolved better than the industrial product, which contains 100 mg of fenofibrate. In both cases there was a better dissolution for the 1 : 2 product. The dissolution rate was the same for the different CD-containing products. The amount of dissolved drug was less and the dissolution rate for the industrial product was slower, especially in distilled water.
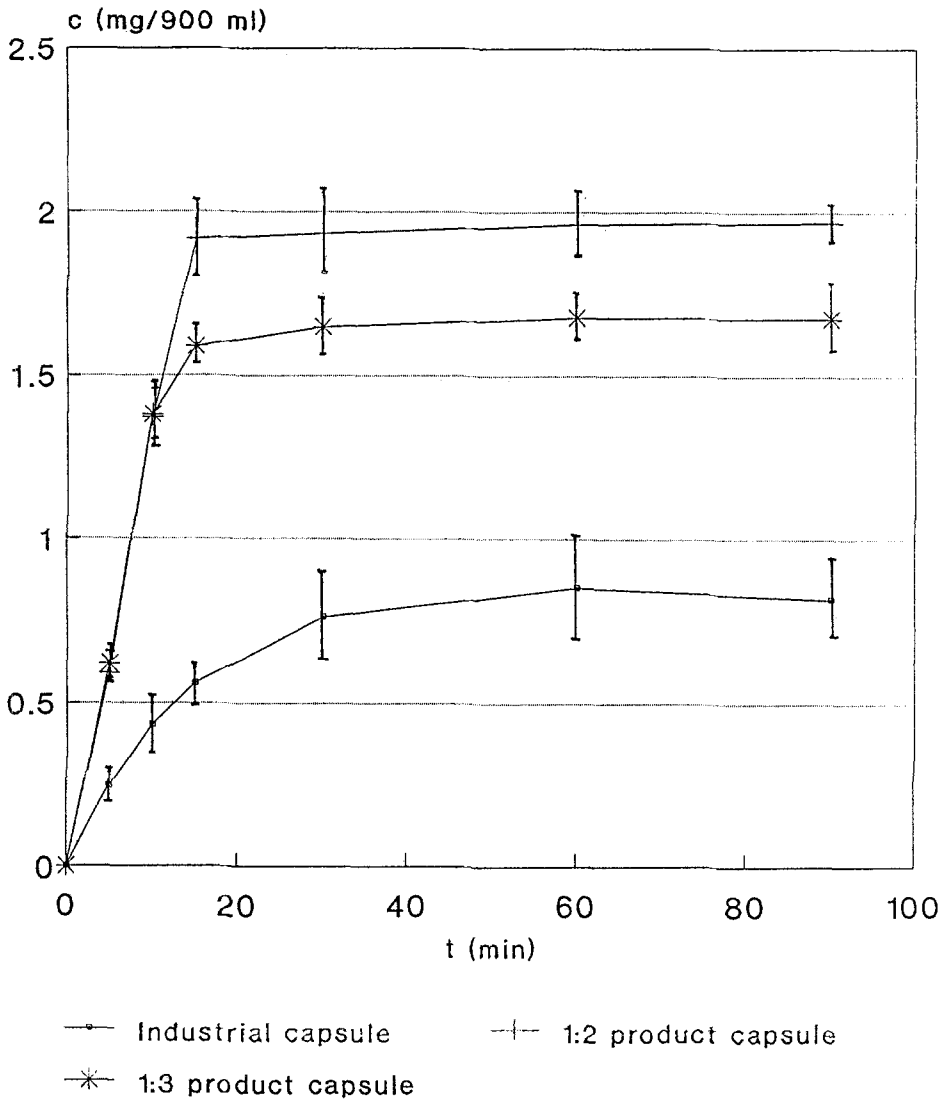
Fig. 4.   Dissolution of fenofibrate in distilled water from capsule.

4. Discussion

The following overall conclusions may be drawn:
  - CD derivatives increase the solubility of fenofibrate;
  - on the basis of the preliminary experiments, the best solubility increase was found for DIMEB, therefore research was continued with this CD derivative;
  - dissolution of the active agent increases on increase of the CD content, and therefore the best dissolution results were obtained for the 1 : 3 active agent : CD composition;
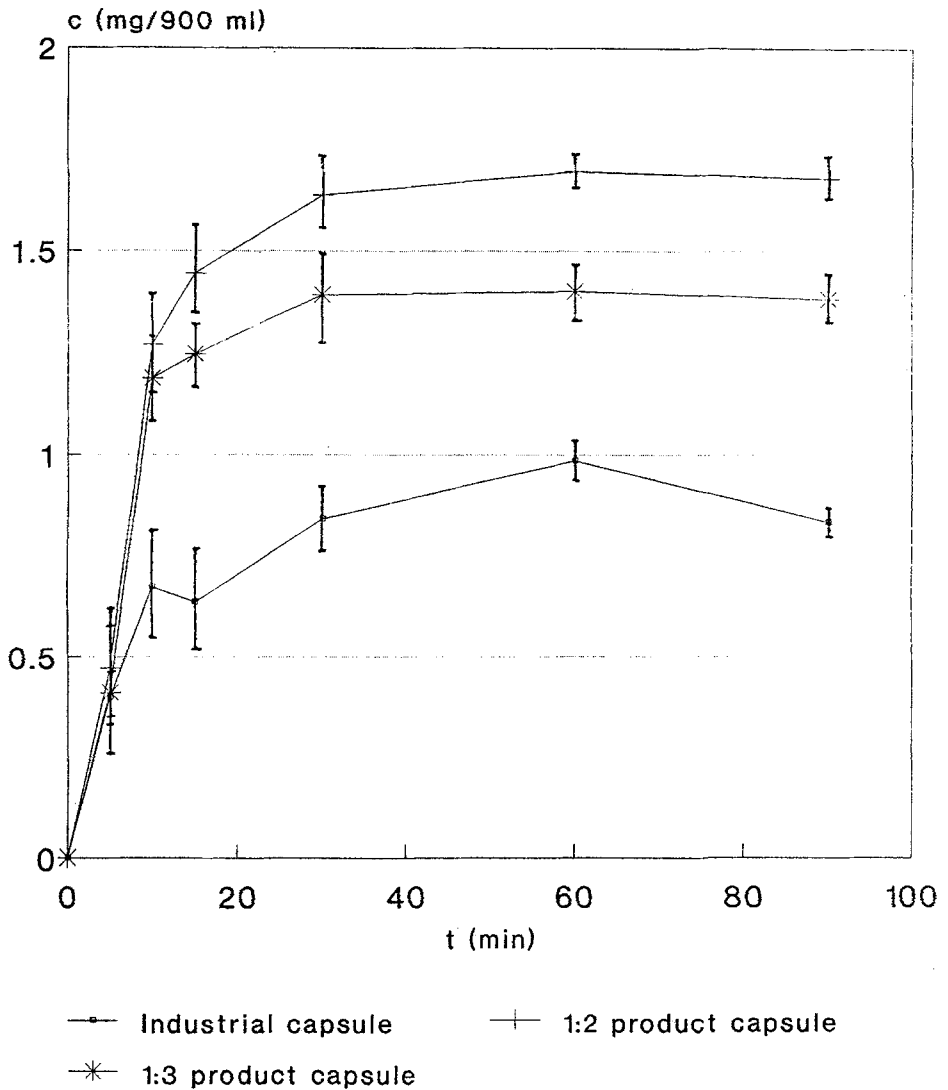
Fig. 5.   Dissolution of fenofibrate in artificial gastric juice from capsule.

— the preparation method influences slightly the dissolution of the active agent;

— on the other hand, the diffusion examinations revealed significant differences between the same compound products made by different preparation methods;

— the same preparation method influences the diffusion of fenofibrate to a small degree;

— DIMEB increased the diffusion of the active agent in all cases;

– dissolution of the capsules made from the 1 : 2 and 1 : 3 physical mixtures was better than that of the industrial products both in distilled water and in artificial gastric juice.

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