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Characterization and dissolution of fenofibrate solid dispersion systems

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Summary

In this study, solid dispersion systems of the sparingly water soluble drug, fenofibrate, in PEG 6000 and PVP were prepared and characterized. The effect of particle size of solid dispersions on the dissolution rate was also examined in ethanolic media at two stirring rates. DSC studies showed that fenofibrate was able to dissolve in the melt of PEG 6000 but not in PVP. Also, no transformation of the crystalline form of fenofibrate during the preparation of solid dispersions in these two carriers was observed using various methods. Furthermore, there was no indication of complex formation between fenofibrate and PEG 6000 from equilibrium solubility experiments. An enhancing effect of increasing the proportion of PEG 6000 was achieved only for large particles when using a medium containing 60% ethanol with stirring at 100 rpm. However, in the same medium but with stirring at 50 rpm, the dissolution rate was reduced with the decreasing particle size. As expected, the decrease in drug solubility in the medium containing 40 or 50% of ethanol slowed down the dissolution rate of fenofibrate from the PEG 6000 solid dispersions, and the dissolution rate was also dependent on the particle size. The dissolution rate of fenofibrate from the physical mixture was slower than that from the solid dispersion, and decreased with increasing proportion of PEG 6000 incorporated and with decreasing particle size. No evidence of a storage effect was obtained.

Introduction

When a sparingly soluble drug is to be formulated with a faster release rate, adequately dispersion of the drug in water-soluble carriers as a solid dispersion system is achievable. This concept was introduced by Sekiguchi and Obi (1961). The case of solid dispersions in this context has been reviewed thoroughly (Chiou and Riegelman, 1970, 1971a,b; Chiou, 1977; Ford, 1986). However, it has frequently been observed that an increase in the amount of drug incorporated results in a reduced dissolution rate. This is normally ascribed to the formation of a coarser particular dispersion of the drug. Recently, Nyström et al. (1988) reported that the reduced dissolution

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rate of the dispersion prepared by the melting method containing a higher concentration of carrier corresponded to a reduction in the dissolution rate of the carrier. A similar situation was found in an ordered mixture system where the enhancement of drug dissolution rate was observed only when using soluble carriers, but not insoluble carriers (De Viliers et al., 1989). Sallam et al. (1988) also reported that the effect of the solubility characteristics of the excipients of an interactive mixture was particularly significant on the dissolution rate.

Although the use of water-soluble carrier in a solid dispersion system may increase drug solubility to some extent, the provision of sink conditions is still necessary in dissolution testing in order to characterize the factors affecting drug release. Several methods have been suggested to maintain sink conditions. Using a flow-through type dissolution apparatus to minimize the saturation of a low solubility drug in the medium is one such method (Jachowicz, 1987a,b). Employing a drug amount that does not exceed 5% of the drug solubility in the medium is another way to maintain sink conditions (Sjökvist et al., 1989). The addition of a cosolvent which increases the drug solubility in the aqueous based dissolution medium is also possible to provide sink conditions (Nicklasson et al., 1984; Gould et al., 1987).

The situation was considered where a cosolvent, added to enhance drug solubility and thus provide sink conditions for a drug, also resulted in a decrease in the solubility and hence dissolution rate of a water-soluble carrier present in a solid dispersion system. The dissolution rate theory for such a polyphase mixture has been investigated by Higuchi et al. (1965). A theoretical consideration was further derived by Corrigan (1991). The aim of this study was to characterize the preparation of a solid dispersion using polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP) as water-soluble carriers. The effects of dissolution medium, particle size, and stirring rate were also examined. Hopefully, the DSC and dissolution studies of fenofibrate solid dispersions in PEG 6000 or PVP could be discussed from the above points of views, and an optimal formulation could be obtained.

Experimental

Materials

Fenofibrate was supplied by Val. Chim. (lot EV531, France). Tween 80 and polyethylene glycol 4000 and 6000 (PEG 4000 and 6000) were purchased from E. Merck Co. Polyvinylpyrrolidone K-30 (PVP K-30) was obtained from BASF Co. (lot no. 12-5424). Ethanol (95%) was provided by Taiwan Tobacco & Wine Monopoly Bureau. All the other materials used were either pharmaceutical or reagent grade.

Methods

Preparation of physical mixtures

Fenofibrate and PEG 6000 or PVP were weighed accurately in several proportions (2:1, 1:1, 1:2, 1:5, and 1:10). The mixtures were triturated thoroughly with a mortar for 5 min, and then powdered and sieved into three size fractions (< 180, 180–425, and > 425 μm).

TABLE 1

Formulations of fenofibrate solid dispersions

Carriers	Drug/carrier ratio	Preparation method
PEG 6000	2:1	melting, solvent (methanol, ethanol)
	1:1	melting, solvent (methanol, ethanol)
	1:2	melting, solvent (methanol, ethanol)
	1:5	melting, solvent (ethanol)
	1:10	melting, solvent (ethanol)
PEG 4000	1:1	melting
	1:5	melting
PEG 6000 + Tween 80	1:1	
1% (w/w)		melting
5% (w/w)		melting
PVP K-30	2:1	solvent (ethanol)
	1:1	solvent (ethanol)
	1:2	solvent (ethanol)
	1:5	solvent (ethanol)
	1:10	solvent (ethanol)

Preparation of solid dispersions

Solid dispersions containing different weight ratios of fenofibrate to carrier were prepared by either the melting or solvent method as described below and the samples were stored in a desiccator until used.

Melting method

Fenofibrate and PEG 6000 or 4000 were accurately weighed according to the weight ratios of the formulations listed in Table 1. The mixtures was melted at 85°C in a water bath. When completely dissolved, the melt was poured on a stainless steel plate and cooled to ambient temperature. It was then stored in vacuo overnight before being pulverized. The resulting powder was sieved to obtain three size fractions (< 180, 180–425, and > 425 μm).

Solvent method

The solid dispersions with PEG 6000 or PVP were also prepared by dissolving the mixture of fenofibrate and carrier at the weight ratio shown in Table 1 in a minimal volume of ethanol or methanol. The solvent was then evaporated at 50°C in a hot-air oven. The residue was further dried in vacuo overnight. The mass was then crushed, powdered, and sieved into three size fractions (< 180, 180–425, and > 425 μm).

DSC characterization

Samples with approximately equal amounts of drug were examined using a differential scanning calorimeter (Dupont, DSC-10). A heating rate of 10°C/min was employed from 30 to 300°C in an atmosphere of nitrogen with the sample kept in aluminum pans. Indium was used as the calibration standard. The results presented were the mean of three determinations.

Particle size characterization

A Coulter Multisizer II (Coulter Electronics Ltd) with 280 and 560 μm apertures was used to determine the size distribution of the drug particles. A saturated medium with fenofibrate was prepared by adding excess fenofibrate in 0.9% NaCl solution containing 0.2% Tween 80. After an appropriate period of agitation, the suspension was then filtered through a 0.45 μm membrane. It was employed as the medium for the measurement of particle size. The mean values and the particle distributions for three size fractions of fenofibrate were thus confirmed.

Solubility measurement

The solubility of fenofibrate in a range of water/ethanol mixtures was determined by adding an excess amount of drug to the mixture. The content of the suspension was equilibrated by stirring for at least 24 h at 37°C in a thermostatically controlled water bath. The suspension was then filtered and the supernatant was analyzed spectrophotometrically at a wavelength of 290 nm after appropriate dilution. The average of triplicates was reported. The effect of PEG 6000 (0–5% w/v) concentration on the solubility of fenofibrate in three ethanol/water media (40, 50 and 60% v/v) was also examined following the same procedure as above. The solubility of fenofibrate/PEG 6000 solid dispersions in these media containing 40, 50, and 60% v/v of ethanol was determined as above.

Dissolution studies

The dissolution profiles of fenofibrate from the solid dispersions (an amount equivalent to 100 mg of fenofibrate was used) with three size fractions were determined using the paddle method (USP XXI) in 900 ml of 40, 50, and 60% (v/v) ethanolic solution at a temperature of 37°C. Two paddle speeds of 50 and 100 rpm were also employed to examine their effects. Samples were taken at appropriate time intervals, suitably di-

TABLE 2

The solubilities of fenofibrate in ethanolic solutions with various concentration of PEG 6000

PEG 6000 concentration (% w/v)	Ethanol content (% v/v)		
	40	50	60
0	254.8 ± 13.9 [a]	1112.2 ± 32.9	4478.8 ± 56.0
1	262.3 ± 34.6	1131.3 ± 46.7	4484.6 ± 66.2
2	264.4 ± 41.4	1162.4 ± 34.3	4498.4 ± 46.6
3	284.6 ± 43.9	1172.4 ± 22.6	4508.8 ± 36.5
4	286.1 ± 16.8	1175.2 ± 32.9	4518.8 ± 36.3
5	294.8 ± 33.9	1212.5 ± 42.3	4578.4 ± 46.6

[a] Mean ± S.D. (μg/ml, $n = 3$)

luted and assayed for fenofibrate with the measurement of UV absorption at 290 nm. An equal volume of fresh medium was added to maintain a constant volume. The dissolution studies were either performed until all the solids were completely dissolved or stopped at 24 h if the duration of dissolution was longer. For the latter cases, the residues were collected and the amount of fenofibrate in the residues was determined by the same method. The mean of three replicates was reported for each time point.

Results and Discussion

The effect of ethanol on the solubility of fenofibrate was examined. The results reveal that the solubility of fenofibrate in these ethanolic media follows a log-linear relationship and increases exponentially with the volume fraction (f) of ethanol as expressed by Eqn 1. The best estimates of the water solubility of fenofibrate (C_0) and the so-called solubilizing power (σ) of ethanol were 1.34 μg/ml and 0.056, respectively.

$$\log C_s = \log C_0 + \sigma \cdot f \quad (1)$$

The effect of the addition of PEG 6000 on the solubility of fenofibrate in the mixture of water and ethanol was studied and the results are listed in Table 2. An apparent trend toward slightly increasing solubility of fenofibrate with increase in the proportion of PEG 6000 added is observed. However, the extent is not profound enough to propose the formation of a complex between fenofibrate and PEG 6000. As indicated by Table 3, the equilibrium solubility of fenofibrate/PEG 6000 solid dispersions in the mixture of water and ethanol also shows only a minor increase in fenofibrate solubility with increase in the proportion of PEG 6000 incorporated. In order to characterize the factors affecting the dissolution of fenofibrate from the solid dispersions, three media with 40, 50, and 60% volume fractions of ethanol in water were selected. The three media afford the 900 ml of dissolution medium with the ability to dissolve 0.255 ± 0.032, 1.11 ± 0.10, and 4.48 ± 0.35 mg/ml of fenofibrate, respectively.

TABLE 3

The solubilities of fenofibrate / PEG 6000 solid dispersions [a] at various ratios in ethanolic solutions

Fenofibrate/ PEG 6000 ratio	Ethanol content (% v/v)		
	40	50	60
1:0	254.8 ± 13.9 [b]	1112.2 ± 32.9	4478.8 ± 56.0
2:1	253.8 ± 33.9	1132.1 ± 22.3	4499.4 ± 67.1
1:1	262.8 ± 24.5	1146.3 ± 42.3	4503.3 ± 66.4
1:2	264.3 ± 34.3	1145.6 ± 52.5	4534.5 ± 54.4
1:5	265.3 ± 41.5	1152.2 ± 32.6	4528.8 ± 62.5
1:10	275.4 ± 32.5	1165.1 ± 42.2	4674.4 ± 57.3

[a] Prepared with the melting method.
[b] Mean ± S.D. (μg/ml, $n = 3$)

This means that the 100 mg dosing amount of fenofibrate will reach different extents of saturation in these three media.

Solid dispersion is one of the most frequently used methods to improve the dissolution rate of water-insoluble drugs. In this study, the solid dispersions of fenofibrate in PEG 6000 and PVP were prepared by various methods. Their charac-

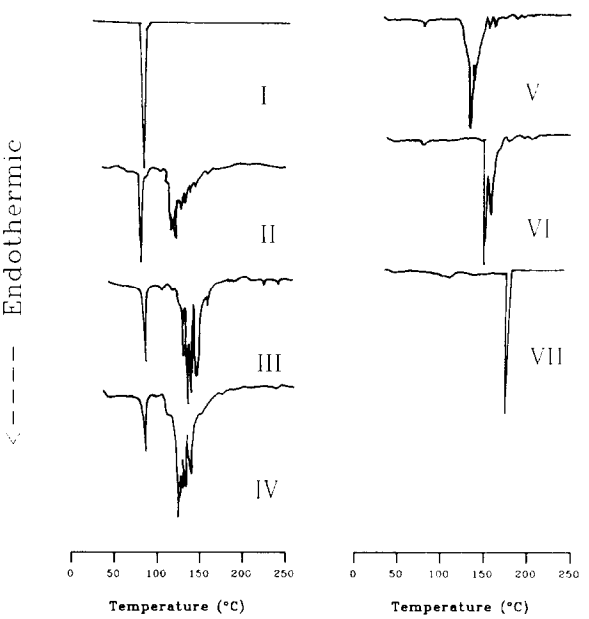

Fig. 1. DSC thermograms for fenofibrate solid dispersions in PVP prepared by the solvent method at different ratios. (I) 1:0; (II) 2:1; (III) 1:1; (IV) 1:2; (V) 1:5; (VI) 1:10; (VII) 0:1.

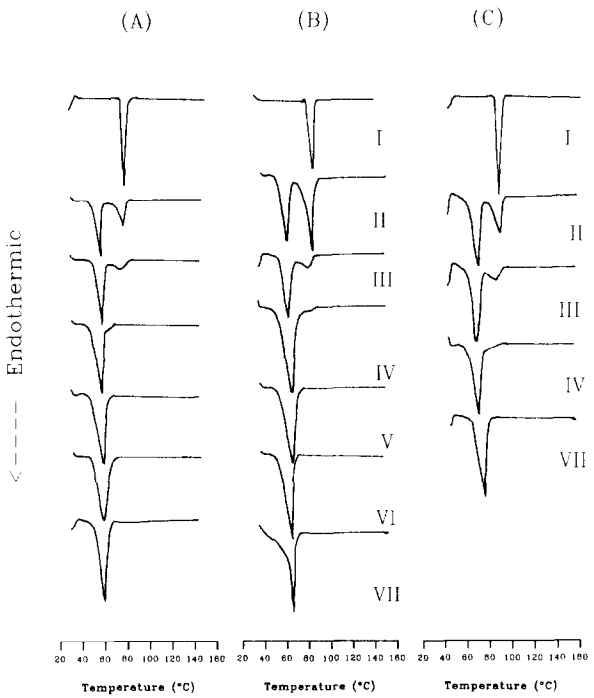

Fig. 2. DSC thermograms for fenofibrate/PEG 6000 solid dispersions prepared by (A) melting method, (B) solvent method (ethanol) and (C) physical mixtures. (I) 1:0; (II) 2:1; (III) 1:1; (IV) 1:2; (V)1:5; (VI) 1:10; (VII) 0:1.

teristics were examined with a differential scanning calorimeter. The physical mixture of PEG 6000 and fenofibrate simply obtained by trituration was also included for comparison. Fig. 1 shows the DSC scans for the PVP solid dispersions prepared by the solvent method at different drug/PVP ratios. It clearly indicates that the distinct melting peak of fenofibrate at approx. 80°C does not change with increasing PVP/drug ratio. This implies that the dispersion of fenofibrate in PVP still maintains the same crystalline form as the drug itself. Fig. 2 illustrates the DSC diagrams for the PEG 6000 physical mixtures and the solid dispersions prepared by the melting and solvent methods. Generally speaking, the melting peak of fenofibrate becomes broader as the ratio of PEG 6000 to fenofibrate increases, and then disappears when the ratio increases up to 5:1. This phenomenon is observed for all samples, irrespective of the method or solvent (the thermograms for the samples using methanol as solvent are not shown) used during preparation. Actually, distinct crystals of fenofibrate can still be seen in all the samples. Therefore, the broadening and disappearance of the melting peak of fenofibrate is probably due to the complete or partial dissolution of fenofibrate in the melt of PEG 6000. A similar phenomenon has been reported for ciprofloxacin, and the proposal as a means to prepare solid dispersions for drugs with a higher melting temperature has been suggested (Veiga et al., 1991). Eventually, the samples prepared by different methods present similar DSC diagrams, affording further evidence to support the contention that the crystal form of fenofibrate should be the same and is able to dissolve in the

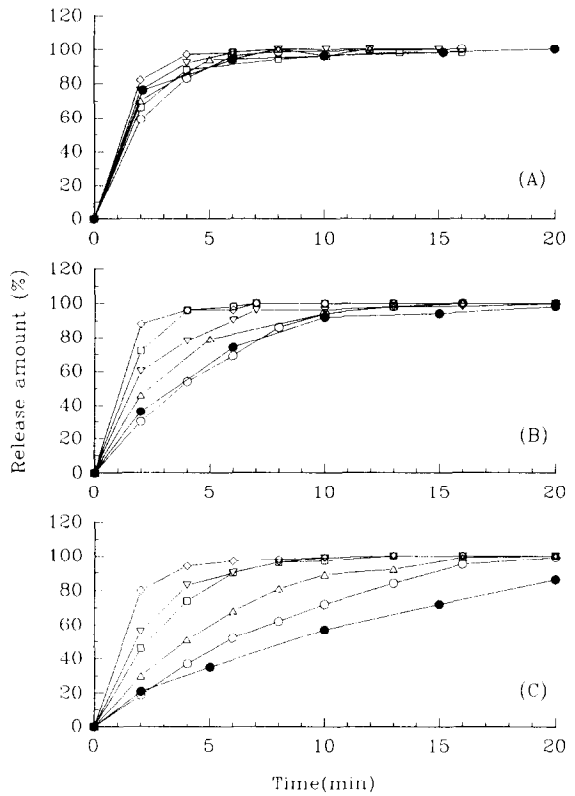

Fig. 3. Dissolution profiles of fenofibrate from PEG 6000 solid dispersions prepared with the melting method in 60% ethanolic medium stirred at 100 rpm: (A) <180 μm, (B) 180–425 μm, and (C) >425 μm ($n=3$). Fenofibrate/PEG 6000 = 1:0 (●); 2:1 (○); 1:1 (△); 1:2 (□); 1:5 (▽); 1:10 (◇).

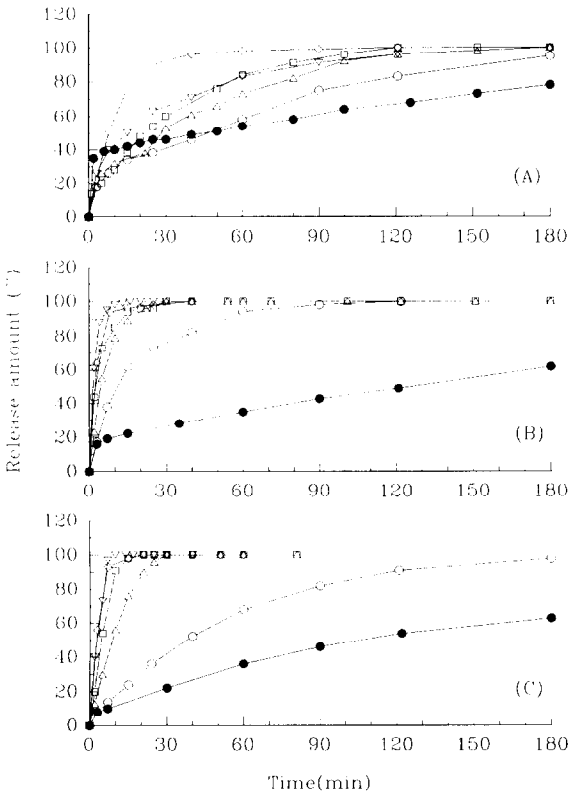

Fig. 4. Dissolution profiles of fenofibrate from PEG 6000 solid dispersions prepared with the melting method in 60% ethanolic medium stirred at 50 rpm: (A) <180 μm, (B) 180–425 μm, and (C) >425 μm ($n = 3$). Same symbols as in Fig. 3.

melt of PEG 6000. It is possible that the enhancement of the dissolution rate by PEG 6000 might arise from the reduction of particle size and/or the increase in wettability.

Dissolution tests were conducted on the solid dispersions containing different ratios of fenofibrate to PEG 6000 prepared via the melting method and the results are presented in Figs 3–8. As shown in Fig. 3, an increase in the concentration of PEG 6000 increases the dissolution rate when using 60% ethanol as the medium with stirring at 100 rpm. This effect becomes more obvious as the particle size increases. However, when dissolution was conducted in the same medium but with stirring at 50 rpm (Fig. 4), a reduced dissolution rate for particles with a size smaller than 180 μm compared to that of larger particles was noted. It was observed that a stirring rate of 50 rpm was not sufficiently rapid to maintain particles in suspension during dissolution studies, and resulting in the accumulation of particles in piles at the bottom of the dissolution tank. As a consequence, a more compact pile of particles might be formed if the size of the particles were smaller. Hence, a limited flow of the medium around and through the particle pile will slow down the dissolution rate. Nevertheless, a further increase in particle size appears to decrease the dissolution rate for all the ratios, probably due to the reduction of the surface area exposed.

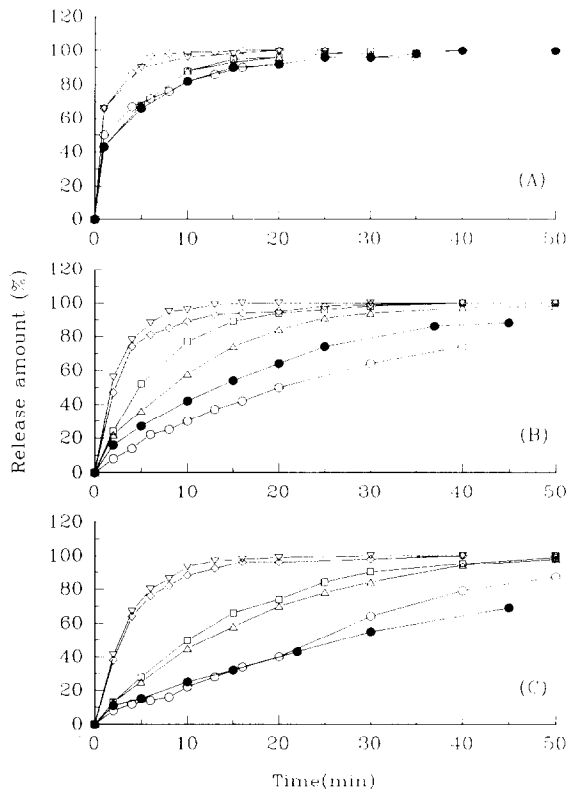

Fig. 5. Dissolution profiles of fenofibrate from PEG 6000 solid dispersions prepared with the melting method in 50% ethanolic medium stirred at 100 rpm: (A) <180 μm, (B) 180–425 μm, and (C) >425 μm ($n = 3$). Same symbols as in Fig. 3.

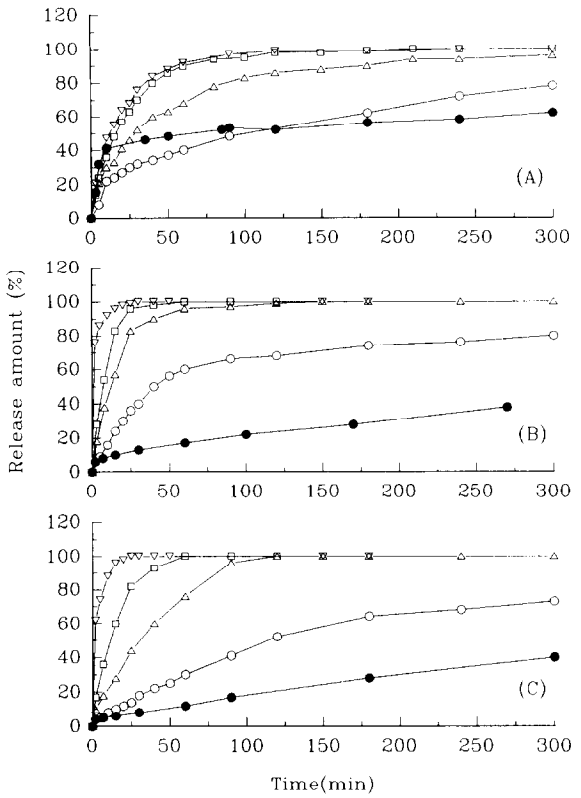

Fig. 6. Dissolution profiles of fenofibrate from PEG 6000 solid dispersions prepared with the melting method in 50% ethanolic medium stirred at 50 rpm: (A) <180 μm, (B) 180–425 μm, and (C) >425 μm ($n = 3$). Same symbols as in Fig. 3.

Figs 5–8 illustrate the dissolution profiles of three size fractions of solid dispersion particles with different ratios of fenofibrate to PEG 6000 in the 50 and 40% ethanolic media stirred at 100 and 50 rpm. A reduced dissolution rate with decreasing content of alcohol in the medium is apparent as a result of decreasing solubility. The increase in the ratio of PEG 6000 to fenofibrate enhances the dissolution rate. Moreover, the smaller size fractions give rise to a faster dissolution rate. In addition, dissolution in the 50% ethanolic medium stirred at 50 rpm reveals a similar behavior to that in the 60% ethanolic medium.

Comparisons of the dissolution rate among the solid dispersions, physical mixtures, and pure drug particles in the 60 and 40% ethanolic media stirred at 100 rpm are shown in Figs 9 and 10. In all cases, the solid dispersions produce the fastest dissolution rate. Also, in both media, the dissolution of fenofibrate from the physical mixtures with a smaller particle size is slower than from pure drug particles of the same size. Moreover, in the 60% medium, the higher proportion of PEG 6000 incorporated in the physical mixtures appears to hinder the dissolution of fenofibrate from the smaller particles. A possible reason for this might be due to the difference in the preparation method resulting in a homogeneous system for the solid dispersions, but a layer of PEG 6000 coating around fenofibrate crystals for the physical mixtures. This layer of PEG 6000 coating

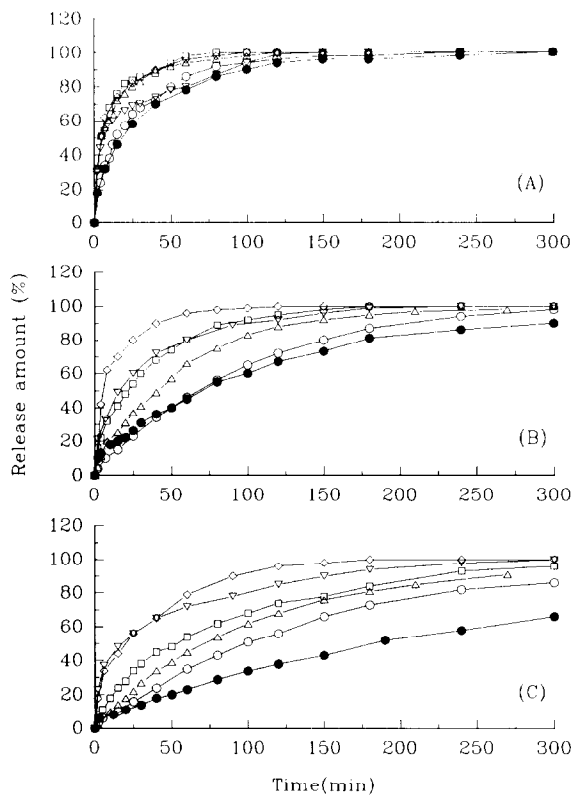

Fig. 7. Dissolution profiles of fenofibrate from PEG 6000 solid dispersions prepared with the melting method in 40% ethanolic medium stirred at 100 rpm: (A) <180 μm, (B) 180–425 μm, and (C) >425 μm ($n = 3$). Same symbols as in Fig. 3.

would be more integrated in the cases of the smaller particle size and the higher PEG 6000 proportion. Due to the lower solubility of PEG 6000 in alcohol, the dissolution of PEG 6000 in ethanolic medium would be the rate-determining step. Therefore, the dissolution of fenofibrate from the physical mixtures did not begin until that layer of the PEG 6000 coating was completely dissolved to expose the crystals of fenofibrate. However, the dissolution of fenofibrate proceeded simultaneously with that of PEG 6000 from the solid dispersions. As a result, a more integrated coating of PEG 6000 layer around the crystals in the cases of the smaller particle size and the higher PEG 6000 proportion would give a slower dissolution rate.

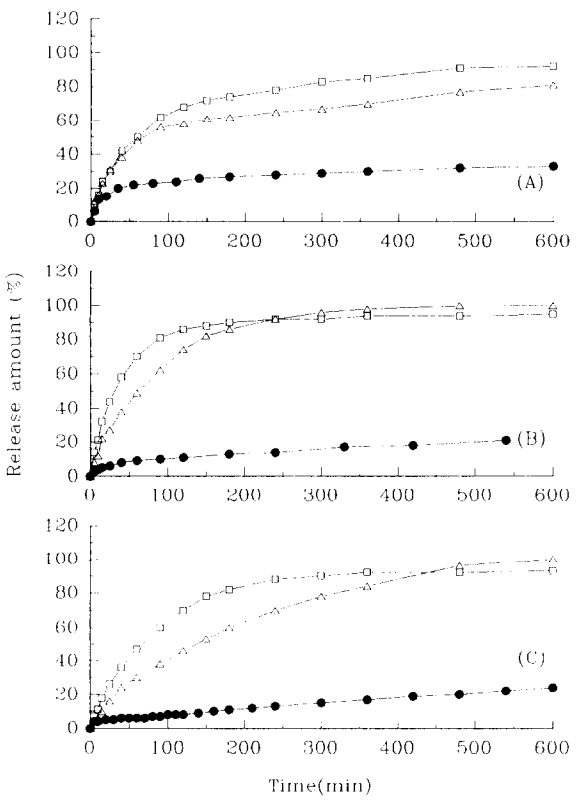

Fig. 8. Dissolution profiles of fenofibrate from PEG 6000 solid dispersions prepared with the melting method in 40% ethanolic medium stirred at 50 rpm: (A) <180 μm, (B) 180–425 μm, and (C) >425 μm ($n = 3$). Same symbols as in Fig. 3.

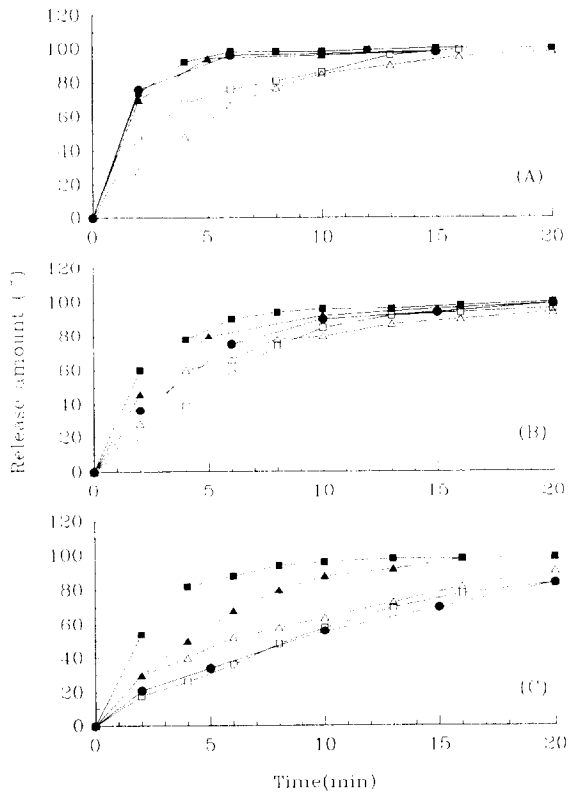

Fig. 9. Dissolution profiles of fenofibrate from PEG 6000 solid dispersions prepared with the melting method (SD) and physical mixture (PM) in 60% ethanolic medium stirred at 100 rpm: (A) <180 μm, (B) 180–425 μm, and (C) >425 μm ($n = 3$). Fenofibrate/PEG 6000 = 1:0 (●); 1:1 PM (△); 1:5 PM (□); 1:1 SD (▲); 1:5 (■).

The effects of the molecular weight of PEG, addition of Tween 80, and storage were also examined using the solid dispersions with carrier/fenofibrate ratios of 1:1 and 5:1 as examples. The use of PEG 4000 as a carrier seems to reveal the same effect as that of PEG 6000. The addition of Tween 80 to the 1:1 solid dispersions of PEG 6000/fenofibrate at either 1 or 5% (w/w) shows no improvement in the dissolution rate. After storage of these samples for 9 months in the desiccator at ambient temperature, no significant changes in crystalline form and dissolution rate were visible.

As shown by the Hixson-Crowell equation, a linear plot of $1 - F^{1/3}$ vs time t describes the

dissolution of spherical particles with equal size under sink conditions:

$$1 - F^{1/3} = (2DC_s t)/(d_o h) \qquad (2)$$

where F denotes the fraction to be released. According to this equation, the slope will determine the effect of particle size (d_o), drug solubility in the medium (C_s) and stirring rate (h). However, when this equation was employed to characterize the dissolution profiles of samples with a size distribution, a poor fit with the relationship was obtained, as expected. A typical plot is shown in Fig. 11. Polydispersion of the particles and low solubility of drug in the medium might

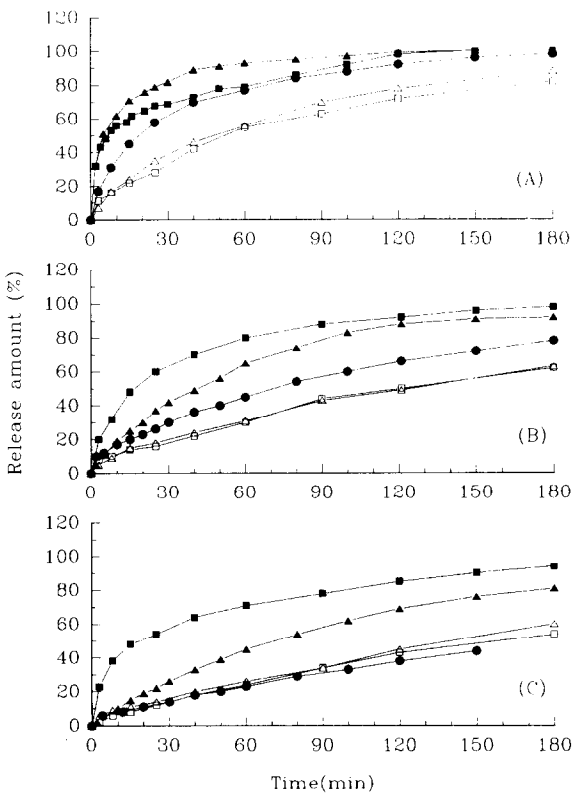

Fig. 10. Dissolution profiles of fenofibrate from PEG 6000 solid dispersions prepared with the melting method (SD) and physical mixture (PM) in 40% ethanolic medium stirred at 100 rpm: (A) <180 μm, (B) 180–425 μm, and (C) >425 μm ($n = 3$). Same symbols as in Fig. 9.

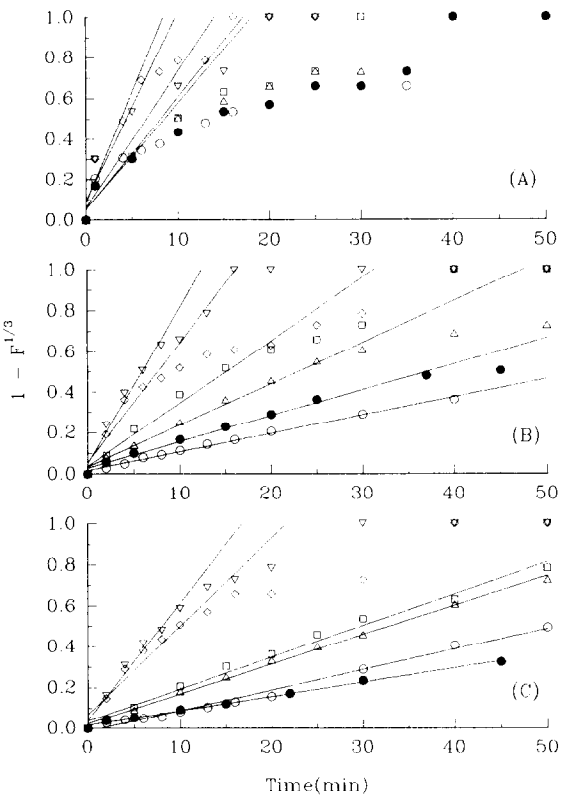

Fig. 11. Plots of the Hixson-Crowell relationship for the fenofibrate/PEG 6000 solid dispersions at different ratios in the 50% ethanolic medium stirred at 100 rpm. (A) <180 μm, (B) 180–425 μm, and (C) >425 μm. Same symbols as in Fig. 3 (lines: regression results; symbols: experimental data).

be the reasons resulting in such a deviation from that predicted by the Hixson-Crowell equation.

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