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Research paper

Strongly enhanced dissolution rate of fenofibrate solid dispersion tablets by incorporation of superdisintegrants

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ABSTRACT

In this study, it was shown that the incorporation of superdisintegrants in solid dispersion tablets containing a high drug load can strongly enhance the dissolution rate of the highly lipophilic drug fenofibrate. In addition, the dissolution rate was more increased when the superdisintegrant was incorporated in the drug containing solid dispersions than when it was physically mixed with the solid dispersions. The dissolution rate enhancement strongly depended on the type of superdisintegrants and increased in the order Polyplasdone® XL-10 < Polyplasdone® XL ≪ Ac-Di-Sol® ≈ Primojel®. The dissolution behavior also depended on the type of hydrophilic carriers. Solid dispersion tablets based on inulin 4 kDa, polyethylene glycol 20 K and polyvinylpyrrolidone K30 showed a much faster dissolution than those based on mannitol and hydroxypropyl-β-cyclodextrin. Finally, inulin 4 kDa-based solid dispersion tablets showed excellent storage stability, while polyethylene glycol 20 K-and polyvinylpyrrolidone K30-based solid dispersion tablets did not.

1. Introduction

Solid dispersion technology can be applied to increase the dissolution rate of highly lipophilic drugs thereby improving their bioavailability [1–4]. Usually, solid dispersions are two-component systems consisting of a hydrophilic carrier in which the drug is incorporated. The drug incorporated in the hydrophilic carrier may be molecularly dispersed or may occur as nanocrystals or amorphous nanoparticles. The improved dissolution rate of the drug can be ascribed to (i) an increased solubility of the drug because of its amorphous state or small particle size (Kelvin's law) [5–8] (ii) an increasing surface area available for drug dissolution because of the small size of the drug particles [9,10] and (iii) an improved wetting of the drug caused by the hydrophilic carrier [11,12].

In a previous study, we investigated the dissolution behavior of solid dispersion tablets in which lipophilic drugs were incorporated in saccharide carriers. The dissolution of solid dispersion tablets was rapid when the carrier did not dissolve very slow or very fast and when a drug was incorporated in the carrier at a relatively low drug load. Obviously, when the carrier dissolves slowly, the drug will also dissolve slowly. However, the slow dissolution rate of the drug when using fast dissolving carriers and/or formulations with high drug loads was considered less obvious. We hypothesized that during dissolution of these tablets, the concentration of the drug in the near vicinity of the tablets became so high that uncontrolled crystallization of the drug occurred. Consequently, large drug crystals are formed which will dissolve slowly. This hypothesis was tested by analysis of remnants of the tablets which were taken out of the dissolution vessel after 2 h of dissolution. Indeed, these remnants consisted of pure drug which was fully crystalline [13]. Therefore, we investigated the effect of incorporating a surfactant, sodium lauryl sulphate (SLS), in solid dispersions on the dissolution behavior. It was expected that during dissolution, the high surfactant concentration in the near vicinity of the dissolving tablet would increase the drug solubility and thereby prevent crystallization of the drug. Indeed, it was found that the incorporation of SLS in solid dispersions strongly improved the dissolution rate of solid dispersions with a high drug load [14]. However, the amount of SLS incorporated in such solid dispersions had to be rather high which may lead to gastrointestinal tract irritation.

Another interesting method to improve the dissolution of solid dispersion tablets with a high drug load might be the incorporation of superdisintegrants in the solid dispersions because superdisintegrants do not irritate the gastrointestinal tract and can be used at low amounts in the formulations. We speculate that by the incorporation of superdisintegrants, the tablets will rapidly

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disintegrate which prevents crystallization of the drug. Therefore, in the present study, we have investigated the effects of the following variables on dissolution behavior of solid dispersion tablets containing superdisintegrants: (i) the way to incorporate superdisintegrants in solid dispersion tablets, (ii) the type of superdisintegrants incorporated in solid dispersion tablets, and (iii) the type of hydrophilic carriers. In addition, the storage stability of some selected solid dispersion tablets was investigated. Fenofibrate was used as a model drug. Sodium starch glycolate (Primojel®), croscarmellose sodium (Ac-Di-Sol®) and two types of crosslinked PVP (Polyplasdone® XL and XL-10) were used as superdisintegrants. Inulin 4 kDa, polyvinylpyrrolidone (PVP) K30, polyethylene glycol 20 kDa (PEG 20 K), mannitol and hydroxypropyl-beta-cyclodextrin (HP-β-CD) were used as hydrophilic carriers.

2. Materials and methods

2.1. Materials

The following materials were used as supplied: fenofibrate and HP-β-CD from Sigma–Aldrich Chemie GmbH, Steinheim, Germany; inulin 4 kDa from Sensus, Roosendaal, the Netherlands; crosslinked PVP (Polyplasdone® XL and XL-10) from ISP, Wayne, USA; PVP K30 and SLS from BUFA B.V. Uitgeest, the Netherlands; PEG 20 K and tertiary butyl alcohol (TBA) from Fluka Chemie GmbH, Steinheim, Germany; mannitol (Pearlitol® SD) from Roquette, Lestrem, France; sodium starch glycolate (Primojel®) from DMV International, Veghel, the Netherlands; and croscarmellose sodium (Ac-Di-Sol®) and microcrystalline cellulose (Avicel® PH-102) from FMC Biopolymer, Philadelphia, USA. Lipanthyl® tablets (145 mg fenofibrate tablets, Lot no. 12178, Expiry 12/2011) were purchased from Laboratoires Fournier S.A., Dijon Cedex, France. Demineralized water was used in all experiments.

2.2. Methods

Three different types of formulations were prepared: (1) solid dispersions composed of drug and carrier in which superdisintegrants were incorporated; (2) solid dispersions composed of drug and carrier physically mixed with superdisintegrants; and (3) physical mixtures of drug, carrier and superdisintegrant.

2.2.1. Superdisintegrants incorporated in solid dispersions

Solid dispersions were prepared by lyophilization as described before [15]. Briefly, fenofibrate was dissolved in pure TBA at a concentration of 12.5 mg/ml. Inulin 4 kDa, PVP K30, PEG 20 K, HP-β-CD or mannitol was dissolved in demineralized water at a concentration of 8.33 mg/ml. The superdisintegrants were dispersed in the aqueous solutions at a concentration of 0.696 mg/ml. Subsequently, these two solutions were mixed at a TBA/water ratio of 4/6 (v/v). The final concentrations of drug, carrier and superdisintegrant in the water/TBA mixture were 5, 5 and 0.42 mg/ml, respectively. Immediately after mixing, the solution was frozen in liquid nitrogen and then lyophilized. The formed solid dispersions all consisted of 48% w/w fenofibrate, 48% w/w carrier and 4% w/w superdisintegrant.

In a typical lyophilization cycle, the frozen solution was placed on the shelf of a Christ model Alpha 2–4 lyophilizer (Salm and Kipp, Breukelen, the Netherlands) with a condenser temperature of −53 °C. Lyophilization was performed according to a two-step procedure. First, the pressure was set at 0.220 mbar and the shelf temperature at −35 °C for one day. Subsequently, the pressure was decreased to 0.05 mbar, while the shelf temperature was gradually increased to 20 °C. This condition was maintained for another day. After removing the samples from lyophilizer, they were placed in a desiccator over siliga gel for at least one day before performing further experiments.

2.2.2. Superdisintegrants physically mixed with solid dispersions

For solid dispersions composed of drug and carrier physically mixed with superdisintegrants, only Primojel® and inulin 4 kDa were used as superdisintegrant and carrier, respectively. First, solid dispersions that consisted of 50% w/w fenofibrate and 50% w/w inulin 4 kDa were prepared by lyophilization as described above. Thereafter, Primojel® and solid dispersions were gently mixed by using a spatula and a mortar. The final powder mixture was composed of 48% w/w fenofibrate, 48% w/w inulin 4 kDa and 4% w/w Primojel®. A solid dispersion without superdisintegrant at a drug load of 50% w/w was used as a control. The samples were stored at the same conditions as described in Section 2.2.1.

2.2.3. Preparation of fully physical mixture

For fully physical mixtures, only Primojel® and inulin 4 kDa were used as superdisintegrant and carrier, respectively. Fenofibrate, inulin 4 kDa and Primojel® were gently mixed by using a spatula and a mortar. The powder mixture consisted of 48% w/w fenofibrate, 48% w/w inulin 4 kDa and 4% w/w Primojel®. The samples were stored at the same conditions as described in Section 2.2.1.

2.2.4. Differential scanning calorimetry (DSC)

A differential scanning calorimeter (DSC Q2000, TA Instruments, Ghent, Belgium) was used to determine the degree of drug crystallinity in solid dispersions. About 2–4 mg of sample in an open aluminium standard pan was heated at a scanning rate of 20 °C/min from a temperature −50 to 220 °C under a nitrogen gas flow. The heat of fusion of crystallized drug in solid dispersions was calculated from the peak area of the melting endotherm. The heat of fusion of pure crystalline drug was measured in a separate experiment. The ratio of the two fusion enthalpies was used to calculate the extent of relative drug crystallinity in solid dispersions. All experiments were conducted at least in duplicate. Calibrations of temperature and heat flow were carried out with indium.

2.2.5. X-ray powder diffraction (XRPD)

Samples were analyzed using an X'Pert PRO MPD diffractometer (PANalytical, Almelo, the Netherlands) with a copper anode (Cu Kα radiation, λ = 0.15405 nm, 40 kV, 40 mA). The diffraction pattern was measured with a step size of 0.008° and a dwell time of 45 s at each step between 4 and 50 2θ at ambient temperature.

2.2.6. Tableting

All powder combinations were compressed to flat and round tablets using an ESH compaction apparatus (Hydro Mooi, Appingedam, the Netherlands). Tablets containing 48 mg fenofibrate were prepared at a maximum force of 5 kN which was reached in 2.5 s. Weight and diameter of the these tablets were 100 mg and 9 mm, respectively. Tablets containing the 145 mg drug were prepared at a maximum force of 10 kN which was reached in 2.5 s. Weight and diameter of the these tablets were 302 mg or 640 mg and 13 mm, respectively. The 302 mg tablets were prepared from an inulin 4 kDa-based solid dispersion with Primojel® incorporated (145 mg fenofibrate, 145 mg inulin 4 kDa and 12 mg Primojel®). The 640 mg tablets were prepared from both the same amount and the same type of solid dispersions which was physically mixed with 338 mg Avicel® PH-102.

2.2.7. Disintegration test

The disintegration time of the tablets was determined in 900 ml of 0.5% w/v SLS at 37 °C using a USP disintegration test apparatus without disc (Erweka Apparatebau-GmbH, Heusenstamn Kr. Offenbach/Main, Germany). The samples were tested in triplicate.

2.2.8. Dissolution experiments

Dissolution of samples was carried out by using a USP dissolution apparatus II (Rowa Techniek B.V., Leiderdrop, The Netherlands) with a paddle at 100 rpm and 37 °C. The dissolution medium was continuously circulated through UV-spectrophotometer flow cells (Ultraspec III, Pharmacia LKB) at 20 ml/min using a peristaltic pump (Ismatec, Zurich, Switzerland). The samples were filtered through 0.35 μm filter prior to analysis. Concentration of fenofibrate in dissolution medium was measured every 2 min for 2 h at a wavelength of 290 nm. Measurements were conducted in triplicate. To maintain sink condition during dissolution test, one liter of demineralized water containing 0.5% w/v SLS and 1.5% w/v SLS was used as dissolution medium for the tablets containing 48 mg and 145 mg fenofibrate, respectively.

2.2.9. Stability study

Solid dispersion tablets were stored under closed vial conditions in climate chambers at 40 °C, 75% relative humidity (RH) and 20 °C, 45% RH for 3 months. The dissolution behavior of these tablets was evaluated in triplicate.

2.2.10. Comparison of dissolution profiles

Dissolution profiles were compared by using similarity factor (f_2), which is defined by the following equation [16]:

$$f_2 = 50\log\{[1 + 1/n\sum n_{t=1}(R_t - T_t)^2]^{-0.5} \times 100\}$$

where n is the number of dissolution sampling times, and R_t and T_t are the percentage of tablet dissolved at each time point for the reference and test products, respectively. An f_2 value larger than 50 indicates that the two dissolution profiles are similar.

3. Results

3.1. DSC studies

The melting point and the melting enthalpy of crystalline fenofibrate were 81.0 °C and 91.0 J/g, respectively. The glass transition (T_g) of amorphous fenofibrate was −19.6 °C. The degree of relative crystallinity of fenofibrate in all formulations except for the PEG 20 K-based solid dispersion is presented in Table 1. The relative degree of crystallinity of the drug in the PEG 20 K-based solid dispersion could not be determined because its corresponding physical mixture did not give an appropriate thermogram. The thermogram lacked the melting peak of fenofibrate most likely because the drug dissolved in PEG K20 after the carrier was molten (at 60 °C). In all other solid dispersions, except for the mannitol-based solid dispersion, about 66–73% of fenofibrate was crystalline. The extent of relative drug crystallinity in the mannitol carrier was approximately 83%. Moreover, besides the endothermic peak of fenofibrate, the thermogram of the mannitol-based solid dispersion showed an endothermic peak at 164.8 °C which can be ascribed to crystalline mannitol. In none of the thermograms of the solid dispersions the T_g of fenofibrate was found. These results indicate that fenofibrate in these solid dispersions was partially present as crystals and partially molecularly distributed.

Table 1
Degree of relative fenofibrate crystallinity in various formulations (physical mixture and solid dispersion are abbreviated as PM and SD, respectively).

Formulation	Relative crystallinity of fenofibrate (%) mean ± s.d.
Way in which Primojel® was incorporated in inulin 4 kDa-based formulations	
Primojel® incorporated in SD	70.83 ± 3.01
Primojel® physically mixed with SD	73.24 ± 0.91
Fully PM	99.91 ± 2.28
No Primojel® incorporated in SD	72.90 ± 3.36
Type of superdisintegrants incorporated in inulin-based SDs	
Primojel®	70.83 ± 3.01
Ac-Di-Sol®	70.34 ± 0.70
Polyplasdone® XL	70.50 ± 0.89
Polyplasdone® XL-10	73.32 ± 4.13
Type of carriers incorporated in the solid dispersion. Primojel® was incorporated in all solid dispersions	
Inulin 4 kDa	70.83 ± 3.01
PEG 20 K	N/A[a]
PVP K30	73.28 ± 0.26
HP-β-CD	66.56 ± 1.31
Mannitol	83.48 ± 0.79

[a] Could not be determined by differential scanning calorimetry.

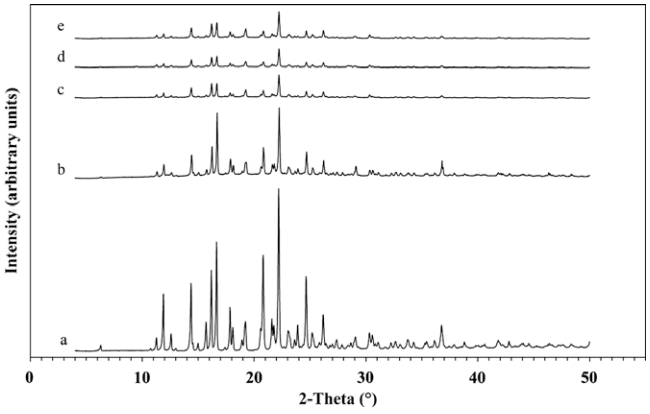

Fig. 1. X-ray powder diffraction patterns of (a) fenofibrate, (b) fully physical mixture of fenofibrate, inulin 4 kDa and Primojel®, (c) solid dispersion (SD) of fenofibrate and inulin 4 kDa physically mixed with Primojel®, (d) SD of fenofibrate, inulin 4 kDa and Primojel® and (e) SD of fenofibrate and inulin 4 kDa without Primojel®.

3.2. XRPD studies

Fig. 1 shows the X-ray powder diffraction patterns of pure fenofibrate, inulin 4 kDa-based solid dispersion in which Primojel® was incorporated, inulin 4 kDa-based solid dispersion which was physically mixed with Primojel®, its corresponding fully physical mixture and inulin 4 kDa-based solid dispersion without Primojel®. The X-ray powder diffraction pattern of pure fenofibrate showed peaks which are consistent with the results obtained by Heinz et al. [17]. The typical peak intensities of fenofibrate in the fully physical mixture were higher than those of the inulin 4 kDa-based-based solid dispersions with Primojel® incorporated or physically mixed and the inulin 4 kDa-based solid dispersion without Primojel®. In addition, the X-ray powder diffraction pattern of all solid dispersions in which different superdisintegrants were incorporated showed the typical diffraction pattern of crystalline fenofibrate (Fig. 2). X-ray diffraction patterns of Primojel®, Ac-Di-Sol®, Polyplasdone® XL and XL-10 indicate that these superdisintegrants were amorphous. Finally, X-ray powder diffraction patterns of solid dispersions composed of fenofibrate, Primojel® and different carriers, pure carriers and pure fenofibrate are presented in Fig. 3. The pure carriers HP-β-CD, PVP K30 and inulin 4 kDa showed no diffraction peaks, indicating that they were amorphous, while PEG 20 K- and mannitol did show diffraction peaks, indicating that these carriers were (partially) crystalline. HP-β-CD-, PVP K30- and inulin 4 kDa-based solid dispersions only showed the typical peaks of crystalline fenofibrate. X-ray powder diffraction patterns of PEG 20 K- and mannitol-based solid dispersions, however, showed diffraction peaks which were the same as those of the pure carriers and fenofibrate. In conclusion, during

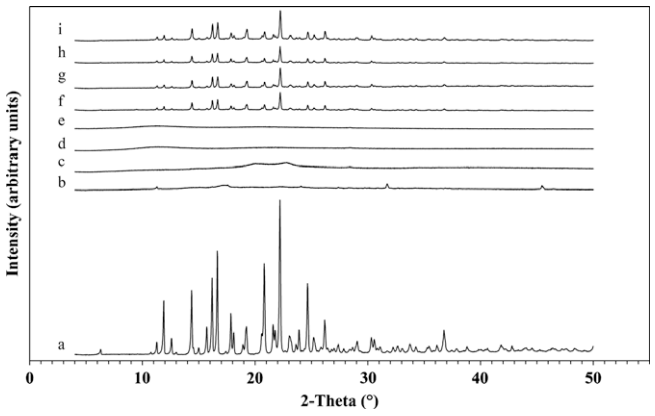

Fig. 2. X-ray powder diffraction patterns of (a) fenofibrate, (b) Primojel®, (c) Ac-Di-Sol®, (d) Polyplasdone® XL, (e) Polyplasdone® XL-10, (f) solid dispersion (SD) of fenofibrate, inulin 4 kDa and Primojel®, (g) SD of fenofibrate, inulin 4 kDa and Ac-Di-Sol®, (h) SD of fenofibrate, inulin 4 kDa and Polyplasdone® XL and (i) SD of fenofibrate, inulin 4 kDa and Polyplasdone® XL-10.

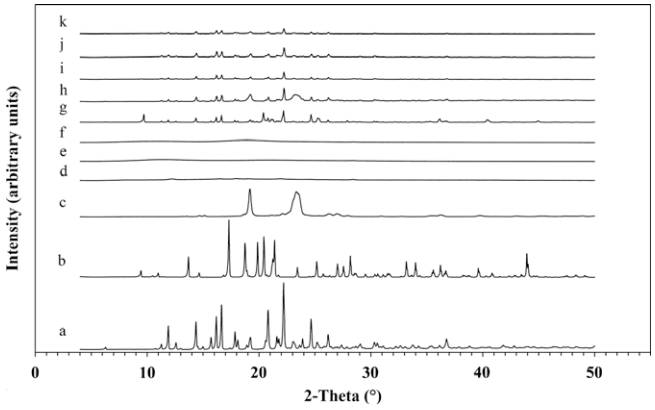

Fig. 3. X-ray powder diffraction patterns of (a) fenofibrate, (b) mannitol, (c) PEG 20 K, (d) inulin 4 kDa, (e) PVP K30, (f) HP-β-CD, (g) solid dispersion (SD) of fenofibrate, Primojel® and mannitol, (h) SD of fenofibrate, Primojel® and PEG 20 K, (i) SD of fenofibrate, Primojel® and inulin 4 kDa, (j) SD of fenofibrate, Primojel® and PVP K30 and (k) SD of fenofibrate, Primojel® and HP-β-CD.

manufacturing of all solid dispersions, fenofibrate at least partially crystallized. In addition, the carriers PEG 20 K and mannitol also crystallized, while the other carriers were amorphous. These findings are consistent with the DSC results.

3.3. Disintegration studies

The disintegration time of the various tablet formulations in 0.5% w/v SLS is shown in Table 2. The inulin 4 kDa-based solid dispersion tablets without Primojel® incorporated showed an extremely slow disintegration of about 100 min. When Primojel® was either incorporated in the inulin 4 kDa-based solid dispersions or physically mixed with the inulin 4 kDa-based solid dispersions, the disintegration time was strongly reduced to 10–11 min. Remarkably, the fully physical mixture tablets composed of inulin 4 kDa, Primojel® and fenofibrate disintegrated even faster, with disintegration time of 8 min. When different superdisintegrants were incorporated in inulin 4 kDa, tablets containing Primojel® and Ac-Di-Sol® gave more or less the same disintegration times. In contrast, tablets with Polyplasdone® XL and XL-10 incorporated gave disintegration times of about 24 and 31 min, respectively. Furthermore, when different carriers in which Primojel® was incorporated were used, disintegration time of tablets containing

Table 2
Disintegration time of physical mixture tablets and various solid dispersion tablets in 0.5% w/v SLS (physical mixture and solid dispersion are abbreviated as PM and SD, respectively).

Formulation	Disintegration time (min) mean ± s.d.
Way in which Primojel® was incorporated in inulin 4 kDa-based formulations	
Primojel® incorporated in SD	10.35 ± 0.25
Primojel® physically mixed with SD	11.16 ± 0.47
Fully PM	8.23 ± 0.44
No Primojel® incorporated in SD	101.55 ± 1.33
Type of superdisintegrants incorporated in inulin-based SDs	
Primojel®	10.35 ± 0.25
Ac-Di-Sol®	12.07 ± 0.57
Polyplasdone® XL	24.02 ± 0.50
Polyplasdone® XL-10	30.59 ± 0.29
Type of carriers incorporated in the solid dispersion. Primojel® was incorporated in all solid dispersions	
Inulin 4 kDa	10.35 ± 0.25
PEG 20 K	9.07 ± 0.32
PVP K30	10.41 ± 0.20
HP-β-CD	4.37 ± 0.22
Mannitol	1.41 ± 0.26

the carriers inulin 4 kDa, PEG 20 K and PVP K30 were about 9–11 min. Disintegration of tablets prepared from mannitol- and HP-β-CD-based solid dispersions was extremely fast with disintegration time of about 2 and 4 min, respectively.

3.4. Dissolution studies

First, the effect of the presence and the way of incorporation of Primojel® on the dissolution behavior of tablets containing inulin 4 kDa as carrier was investigated (Fig. 4). As expected, dissolution of solid dispersion tablets without Primojel® was extremely slow. Only about 7% of the drug was dissolved within 20 min and about 55% after 2 h. After this dissolution test, the remnants of the tablets were analyzed by DSC and appeared to consist of fully crystalline fenofibrate. Dissolution of fully physical mixture tablets was faster than that of the solid dispersion tablets without Primojel®. The dissolution of drug was initially rapid but then slowed down. After 2 h, only about 65% of the drug was dissolved. When Primojel® was incorporated in the solid dispersion tablets, the drug dissolved very fast and over 80% of the drug was released within 20 min. The drug was completely dissolved within 30 min. Finally, when Primojel® was physically mixed with the solid dispersion, about 80% of the drug was dissolved within 36 min and the drug was completely dissolved within 1 h. When the dissolution profile of

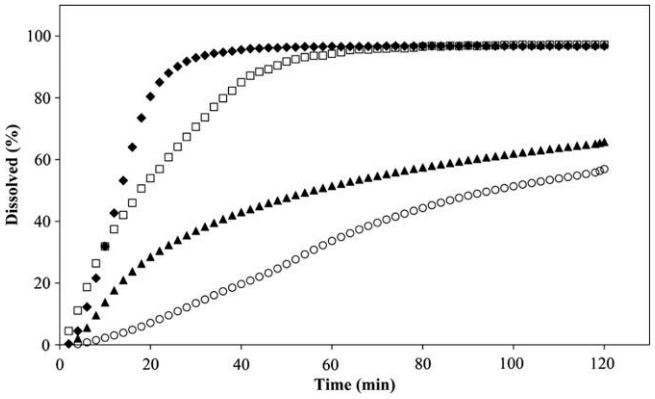

Fig. 4. Dissolution of fenofibrate from inulin 4 kDa-based tablets in which Primojel® was incorporated in different ways. (♦, Primojel® incorporated in solid dispersion by freeze drying; □, Primojel® physically mixed with solid dispersion; ▲, fully physical mixture; and ○, solid dispersion without Primojel®).

Table 3
Similarity factor (f_2) for dissolution profiles of different formulations (physical mixture and solid dispersion are abbreviated as PM and SD, respectively).

Formulation	Inulin 4 kDa-based SD with Primojel® incorporated (containing 48 mg fenofibrate)	Inulin 4 kDa-based SD without superdisintegrant[a]	Lipanthyl® tablet (containing 145 mg fenofibrate)
Way in which Primojel® was incorporated in inulin 4 kDa-based formulations (containing 48 mg fenofibrate)			
Primojel® incorporated in SD	____	13	____
Primojel® physically mixed with SD	43	____	____
Fully PM	21	____	____
No Primojel® incorporated in SD[a]	13	____	____
Type of superdisintegrants incorporated in inulin-based SDs (containing 48 mg fenofibrate)			
Ac-Di-Sol®	*51*	12	____
Polyplasdone® XL	21	32	____
Polyplasdone® XL-10	18	38	____
Type of carriers incorporated in the SD. Primojel® was incorporated in all SDs (containing 48 mg fenofibrate)			
PEG 20 K	47	____	____
PVP K30	38	____	____
HP-β-CD	23	____	____
Mannitol	19	____	____
Inulin 4 kDa-based SD with Primojel® incorporated (containing 145 mg fenofibrate)	____	____	33
PM of inulin 4 kDa-based SD with Primojel® incorporated and Avicel® PH-102 (containing 145 mg fenofibrate)	____	____	*71*

[a] Inulin 4 kDa-based solid dispersion without superdisintegrant containing 50 mg fenofibrate.

tablets composed of inulin 4 kDa-based solid dispersion with Primojel® incorporated is compared to those tablets composed of inulin 4 kDa-based solid dispersion with Primojel® physically mixed, the corresponding fully physical mixture and inulin 4 kDa-based solid dispersion without superdisintegrant, all f_2 values were less than 50, indicating the dissimilar dissolution profiles (Table 3). Because the results above indicated that solid dispersion tablets in which Primojel® was incorporated was the best formulation strategy to increase dissolution rate of fenofibrate, the dissolution behavior of solid dispersion tablets with different types of superdisintegrants incorporated in the solid dispersion were evaluated. As can be seen in Fig. 5 and Table 3, Ac-Di-Sol® had a similar effect on the dissolution behavior as Primojel® ($f_2 > 50$). In the cases of two types of Polyplasdone®, however, dissolution of fenofibrate was slow. Tablets with Polyplasdone® XL incorporated gave a slightly faster drug dissolution than tablets with Polyplasdone® XL-10 incorporated. About 80% of the drug was dissolved within 84 min and 102 min for Polyplasdone® XL and XL-10 incorporated, respectively. In both cases, at 2 h the dissolution of drug was about 90%. Consequently, it can be concluded that superior dissolution behavior was achieved when Primojel® or Ac-Di-Sol® was incorporated in inulin 4 kDa-based solid dispersions instead of the two types of Polyplasdone®.

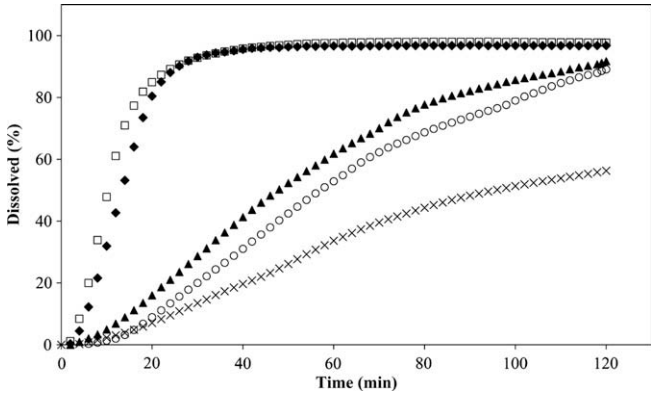

Fig. 5. Dissolution of fenofibrate from inulin 4 kDa-based solid dispersion tablets. Various superdisintegrants were incorporated in the solid dispersions (♦, Primojel®; □, Ac-Di-Sol®; ▲, Polyplasdone® XL; ○, Polyplasdone® XL-10; and ×, solid dispersion tablet without superdisintegrant).

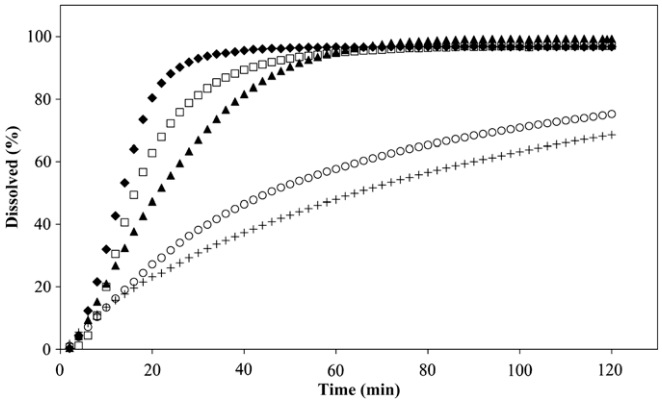

Fig. 6. Dissolution of fenofibrate from solid dispersion tablets based on various carriers. In all cases, Primojel® was incorporated in the solid dispersion (♦, Inulin 4 kDa; □, PEG 20 K; ▲, PVP K30; ○, HP-β-CD; and +, mannitol).

Also the effect of the types of carriers on the dissolution behavior was evaluated. As can be clearly seen in Fig. 6, inulin 4 kDa, PEG 20 K and PVP K30 performed better than HP-β-CD and mannitol. About 80% of the drug was dissolved from inulin 4 kDa-, PEG 20 K-, PVP K30-based tablets within 20, 30 and 40 min, respectively, while the amount of drug released from HP-β-CD- and mannitol-based tablets was only 75% and 70% after 2 h, respectively. When the dissolution profiles of the inulin 4 kDa-based solid dispersion tablets were compared with the other carrier-based solid dispersion tablets, all f_2 values were less than 50, indicating the dissimilar dissolution profiles (Table 3). The remnants of the HP-β-CD- and mannitol-based solid dispersion tablets after 2 h dissolution were analyzed by DSC. They appeared to consist of fully crystalline of drug.

In summary, tablets prepared from inulin 4 kDa-based solid dispersions with either Primojel® or Ac-Di-Sol® incorporated showed the excellent dissolution behavior. However, these tablets contained 48 mg fenofibrate while the marketed product, Lipanthyl® (tablets containing fenofibrate nanoparticles), contained 145 mg

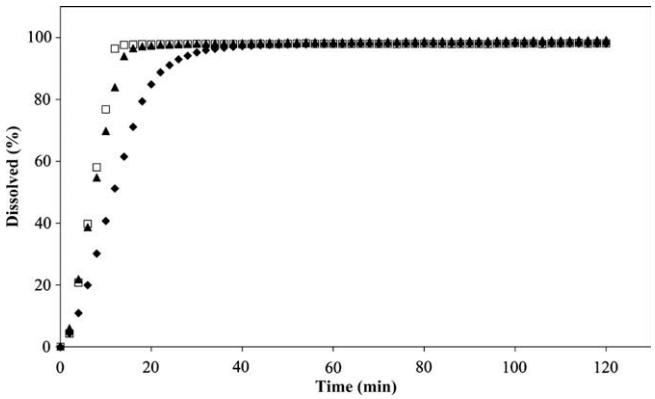

Fig. 7. Dissolution of 145 mg fenofibrate tablets (♦, inulin 4 kDa-based solid dispersion (SD) with Primojel® incorporated; ▲, physical mixture of inulin 4 kDa-based SD with Primojel® incorporated and Avicel® PH-102; and □, Lipanthyl®).

fenofibrate. Therefore, tablets containing 145 mg fenofibrate were prepared from inulin 4 kDa-based solid dispersions with Primojel® incorporated. In addition, tablets containing 145 mg fenofibrate were prepared from of a physical mixture of the same solid dispersion and Avicel® PH-102. As shown in Fig. 7, the dissolution of fenofibrate from the solid dispersion tablets without Avicel® PH-102 was slightly slower than from the Lipanthyl® tablets ($f_2 < 50$; Table 3). However, the dissolution behavior of the solid dispersion tablets with Avicel® PH-102 and that of Lipanthyl® tablets was similar ($f_2 > 50$; Table 3).

3.5. Stability studies

As described in Section 3.4, tablets prepared from inulin-based solid dispersion with either Primojel® or Ac-Di-Sol® incorporated and PEG K20 and PVP K30-based solid dispersions with Primojel® incorporated showed excellent dissolution behavior. Therefore, these tablet formulations were subjected to a stability study. The dissolution behavior of freshly prepared solid dispersion tablets were compared with those stored at 40 °C, 75% RH or 20 °C, 45% RH for 3 months.

Unexpectedly, the inulin 4 kDa-based tablets with Primojel® incorporated dissolved slightly faster after storage than when they were freshly prepared (Fig. 8a; $f_2 < 50$). However, the dissolution behavior of the inulin 4 kDa-based tablets with Ac-Di-Sol® incor-

Table 4
Similarity factor (f_2) for dissolution profiles of solid dispersion tablets freshly prepared and at storage conditions (solid dispersion is abbreviated as SD).

Formulation	Storage condition for 3 months	
Freshly prepared	40 °C, 75% RH	20 °C, 45% RH
Inulin 4 kDa-based SD with Primojel® incorporated	39[a]	40[a]
Inulin 4 kDa-based SD with Ac-Di-Sol® incorporated	68	67
PVP K30-based SD with Primojel® incorporated	33	37
PEG 20 K-based SD with Primojel® incorporated	20	23

[a] Dissolution profiles of the tablets stored at 40 °C, 75% RH and 20 °C, 45% RH showed slightly faster than that of the tablets freshly prepared.

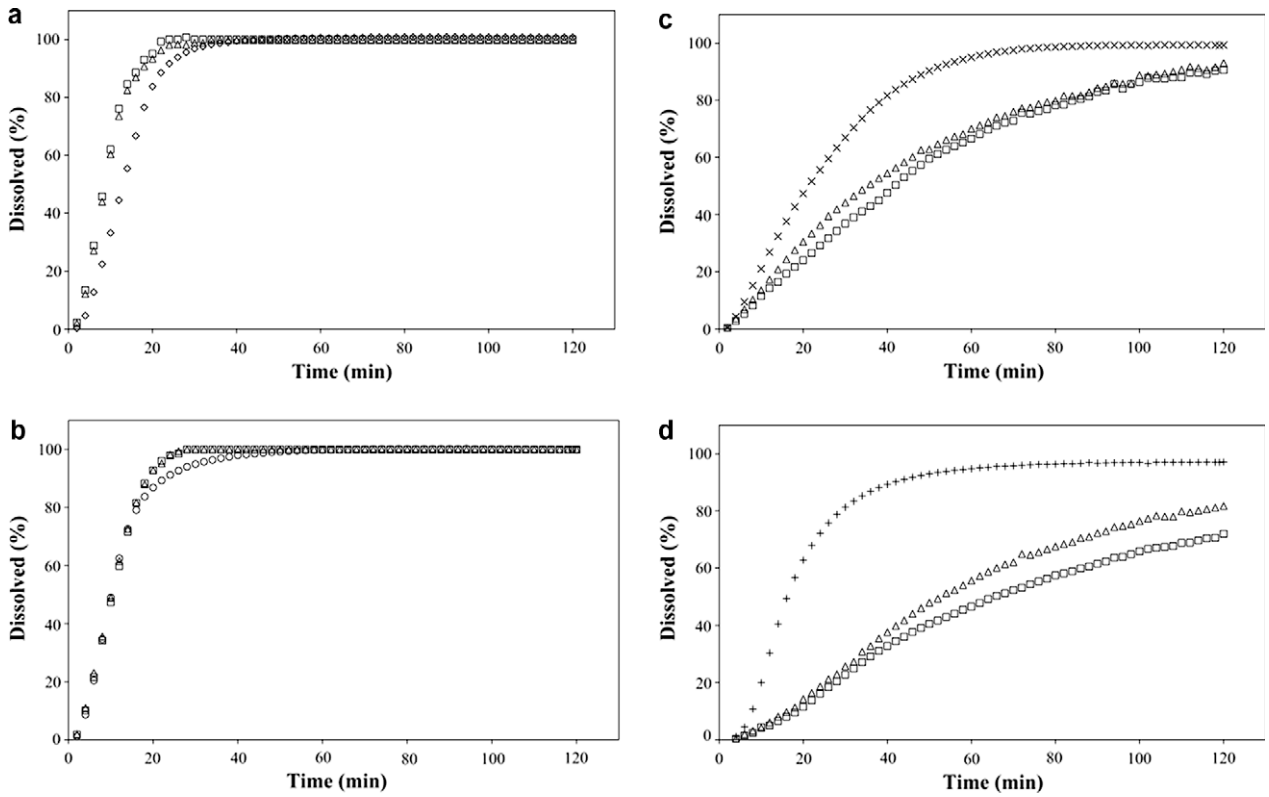

Fig. 8. (a) Effect of storage on the dissolution of fenofibrate from inulin 4 kDa-based solid dispersion tablets containing Primojel®. Primojel® was incorporated in the solid dispersion (◇, freshly prepared; Δ, stored at 20 °C, 45% RH for 3 months; and □, stored at 40 °C, 75% RH for 3 months). (b) Effect of storage on the dissolution of fenofibrate from inulin 4 kDa-based solid dispersion tablets containing Ac-Di-Sol®. Ac-Di-Sol® was incorporated in the solid dispersion (○, freshly prepared; Δ, stored at 20 °C, 45% RH for 3 months; and □, stored at 40 °C, 75% RH for 3 months). (c) Effect of storage on the dissolution of fenofibrate from PVP K30-based solid dispersion tablets containing Primojel®. Primojel® was incorporated in the solid dispersion (×, freshly prepared; Δ, stored at 20 °C, 45% RH for 3 months; and □, stored at 40 °C, 75% RH for 3 months). (d) Effect of storage on the dissolution of fenofibrate from PEG 20 K-based solid dispersion tablets containing Primojel®. Primojel® was incorporated in the solid dispersion (+, freshly prepared; Δ, stored at 20 °C, 45% RH for 3 months; and □, stored at 40 °C, 75% RH for 3 months).

porated was not affected by storage (Fig. 8b; $f_2 > 50$). Finally, the dissolution rate of the PVP K30- or PEG 20 K-based tablets was significantly decreased after storage (Fig. 8c and d; $f_2 < 50$). All f_2 values are shown in Table 4.

4. Discussion

This study clearly shows that the incorporation of superdisintegrants in solid dispersion tablets can strongly increase the dissolution rate of lipophilic drugs. However, the improved dissolution behavior of the drug can only be achieved with the proper way of incorporation of the superdisintegrants in the tablets and with the proper choice of the type of superdisintegrants and carriers. As can be seen in Fig. 4, Primojel® can be used to increase the dissolution rate of fenofibrate incorporated in inulin 4 kDa-based solid dispersion tablets. In addition, the dissolution rate was more increased when Primojel® was incorporated in inulin 4 kDa-based solid dispersion than when it was physically mixed with inulin 4 kDa-based solid dispersion. This might be caused by a more homogeneous distribution of Primojel® over the tablet prepared from the inulin 4 kDa-based solid dispersion in which Primojel® was incorporated. Furthermore, application of all four superdisintegrants evaluated in this study improved the dissolution behavior of the inulin 4 kDa-based solid dispersion tablets (Fig. 5). However, the incorporation of Primojel® or Ac-Di-Sol® in the inulin 4 kDa-based solid dispersion tablets was much more effective than the incorporation of Polyplasdone® XL or XL-10. For these inulin 4 kDa-based solid dispersion tablets, the dissolution behavior can be related to their disintegration time: a shorter disintegration time leads to a higher dissolution rate. Obviously, a rapid disintegration time of inulin 4 kDa-based tablets results in an increased dissolving surface area of the drug and thereby in an increased dissolution rate. Because the mechanism by which the disintegration time is reduced by superdisintegrants is related to the swelling pressure and the hydration capacity of the superdisintegrants, these properties should be considered. According to the study of Quadir and Kolter [18], Primojel® and Ac-Di-Sol® have higher swelling pressure and hydration capacity than Polyplasdone® XL and XL-10 (Table 5). Therefore, the inulin 4 kDa-based solid dispersion tablets in which Primojel® or Ac-Di-Sol® was incorporated disintegrated faster than those in which Polyplasdone® XL or XL-10 was incorporated. Furthermore, although the swelling pressure of Primojel® is lower than that of Ac-Di-Sol®, the dissolution rate of inulin 4 kDa-based solid dispersion tablets with either of the two superdisintegrants incorporated were comparable. This result might be ascribed to the higher hydration capacity of Primojel® compared to Ac-Di-Sol®.

The type of carriers also influenced the dissolution behavior of the solid dispersion tablets (Fig. 6). Surprisingly, the disintegration time of HP-β-CD- or mannitol-based solid dispersion tablets was short but their drug releases were slow. After 2 h, the undissolved remnants of the tablets appeared to consist of fully crystalline fenofibrate. Possibly, HP-β-CD and mannitol dissolve so fast that even fast disintegration caused by the superdisintegrant could not prevent a high drug concentration in the near vicinity of the dissolving tablet resulting in uncontrolled recrystallization and formation of large crystals which obviously dissolve slowly as also observed by van Drooge et al. [13]. In contrast, due to their polymeric nature, HP-β-CD and mannitol, inulin 4 kDa, PEG 20 K and PVP K30 dissolve somewhat slower by which recrystallization of the drug was apparently prevented. Alternatively, it is also possible that during the production of HP-β-CD- and mannitol-based solid dispersions, large drug crystals were formed in the carriers which obviously also dissolve slowly. Therefore, we can conclude that fast disintegration of the solid dispersion tablets is a prerequisite for fast dissolution but it does not guarantee it.

Table 5
Swelling pressures and hydration capacities of superdisintegrants (data taken from [18]).

Superdisintegrants	Swelling pressure (kPa)	Hydration capacity (g water/g polymer)
Primojel®	158	18.3
Ac-Di-Sol®	271	12.1
Polyplasdone® XL	110	5.8
Polyplasdone® XL-10	94	4.6

In summary, incorporation of a superdisintegrant in the drug containing solid dispersion is preferred over physical mixing of a superdisintegrant with the solid dispersion, the superdisintegrant Primojel® and Ac-Di-Sol® are preferred over Polyplasdone® XL or XL-10, and the carriers inulin 4 kDa, PEG 20 K and PVP K30 are preferred over HP-β-CD and mannitol. Therefore, the inulin 4 kDa-, PEG 20 K- and PVP K30-based tablets in which Primojel® or Ac-Di-Sol® (only inulin 4 kDa-based tablets) was incorporated in the solid dispersion were selected for a storage stability study. After storage at 40 °C, 75% or 20 °C, 45% RH for 3 months, the inulin 4 kDa-based tablets showed fast dissolution indicating excellent storage stability (Fig. 8a and b) although in the case of inulin 4 kDa-based solid dispersion tablets with Primojel® incorporated showed the dissimilar dissolution profile to tablets freshly prepared.

On the other hand, the dissolution behavior of the PEG 20 K- and PVP K30-based tablets was deteriorated after storage indicating physical changes in time (Fig. 8c and d). Possibly, despite the solid nature of the carriers, there was some translational mobility in the carrier possible by which the drug particles aggregated in time. This is confirmed by Dordunoo et al. who reported that the particle size of triamterene or temazepam dispersed in PEGs increased during storage [19].

Because the marketed product Lipanthyl® contain 145 mg fenofibrate, the dissolution of 145 mg fenofibrate tablets prepared from inulin 4 kDa-based solid dispersions with Primojel® incorporated was compared to the dissolution of Lipanthyl® tablets (Fig. 7). Dissolution of tablets prepared from inulin 4 kDa-based solid dispersion with Primojel® incorporated was slightly slower than Lipanthyl® tablets. However, weight of this solid dispersion tablets was only 302 mg, while weight of Lipanthyl® tablet was 640 mg. Therefore, to produce tablets weighing the same as that of Lipanthyl® tablets, 338 mg Avicel® PH-102 was physically mixed with inulin 4 kDa-based solid dispersion. The dissolution behavior of tablets prepared from this physical mixture was comparable to that of Lipanthyl® tablets.

In conclusion, incorporation of superdisintegrant in solid dispersions to prevent crystallization of drug during dissolution can be applied for some carriers. The type of carriers has profound effect on the dissolution behavior of solid dispersion in which the superdisintegrant was incorporated. The fast dissolution behavior can be obtained by using proper choices of carriers and superdisintegrants. In this study, fenofibrate tablets with a high drug load, excellent dissolution behavior and stability can be obtained when inulin 4 kDa-based solid dispersions are used in which Primojel® or Ac-Di-Sol® is incorporated.

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