Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 349 (2008) 66–73
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Unexpected differences in dissolution behavior of tablets prepared from solid dispersions with a surfactant physically mixed or incorporated

H. de Waard *, W.L.J. Hinrichs, M.R. Visser, C. Bologna, H.W. Frijlink

Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands

Received 19 April 2007; received in revised form 17 July 2007; accepted 20 July 2007
Available online 24 July 2007

Abstract

In a previous study, it was shown that the incorporation of poorly soluble drugs (BCS class II) in sugar glasses could largely increase the drug's dissolution rate [van Drooge, D.J., Hinrichs, W.L.J., Frijlink, H.W., 2004b. Anomalous dissolution behaviour of tablets prepared from sugar glass-based solid dispersions. J. Control. Release 97, 441–452]. However, the application of this technology had little effect when high drug loads or fast dissolving sugars were applied due to uncontrolled crystallization of the drug in the near vicinity of the dissolving tablet. To solve this problem a surfactant, sodium lauryl sulphate (SLS), was incorporated in the sugar glass or physically mixed with it. Diazepam and fenofibrate were used as model drugs in this study. The dissolution behavior of tablets prepared from solid dispersions in which SLS was incorporated was strongly improved. Surprisingly, the dissolution rate of tablets prepared from physical mixtures of SLS and the solid dispersion was initially fast, but slowed down after about 10 min. The solid dispersions were characterized by DSC to explain this unexpected difference. These measurements revealed the existence of interaction of SLS with both the drug and the sugar in the solid dispersion when SLS was incorporated. It is hypothesized that due to this interaction, the dissolution of SLS was slowed down by which a high solubility of the drug in the near vicinity of the dissolving tablet is maintained during the whole dissolution process. Therefore, uncontrolled crystallization is effectively prevented.

Keywords: Sugar glass; Poorly soluble drug; High drug load; Crystallization; Sodium lauryl sulphate

1. Introduction

Combinatorial chemistry and High Throughput Screening are modern techniques in drug research. Many of the drugs, evolving from these techniques, can be categorized as class II drugs according to the Biopharmaceutics Classification System (Lipinski et al., 2001). These drugs are poorly water soluble, but once they are dissolved they are easily absorbed over the gastro-intestinal membrane (Amidon et al., 1995; Lobenberg and Amidon, 2000). Therefore, the bioavailability after oral administration can be improved by enhancement of the dissolution rate (Curatolo, 1998).

One of the approaches to enhance the dissolution rate is the use of fully amorphous solid dispersions (Law et al., 2003; Leuner and Dressman, 2000). A solid dispersion for such application is a system composed of a hydrophilic matrix in which a poorly soluble drug is dispersed. The enhanced dissolution rate of drugs from these solid dispersions is mainly based on four different mechanisms (Corrigan, 1985; Craig, 1990, 2002): (1) wetting of the drug is improved by direct contact of the drug with the hydrophilic matrix, (2) the saturation concentration around small particles is higher than around large particles (Kelvin law (Keck and Muller, 2006)), (3) the surface area is increased and (4) the drug has higher energy in the amorphous state than in the crystalline state, through which the saturation concentration is increased (Hancock and Parks, 2000; Huang and Tong, 2004; Rodriguez-Spong et al., 2004).

In a previous study (van Drooge et al., 2004b), we have investigated the dissolution behavior of tablets prepared from fully amorphous solid dispersions. These solid dispersions were composed of different types of sugar glasses in which diazepam was incorporated. It was found that when the drug load was low and/or the sugar did not dissolve too fast, the dissolution rate of the drug was high. However, when the drug load was high and/or the sugar dissolved fast, the dissolution was slow and incomplete. It was proposed that in these cases high concentrations of

* Corresponding author. Tel.: +31 50 363 2397; fax: +31 50 363 2500.
E-mail address: h.de.waard@rug.nl (H. de Waard).

0378-5173/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2007.07.023

the drug could be found in the direct vicinity of the dissolving tablet. The high concentrations of the drug result in uncontrolled formation of large drug crystals. Due to the crystalline nature and the low specific surface area, the crystals subsequently dissolve slowly. These binary solid dispersions can, therefore, not always be used to improve the dissolution rate of class II drugs.

To increase the dissolution rate from these solid dispersions, the uncontrolled crystallization in the near vicinity of the dissolving tablet should be prevented. Incorporation of a surfactant in the tablet could be an option to achieve this. Incorporation of a surfactant in a solid dispersion to improve the dissolution rate is extensively described in literature (Alden et al., 1992; Morris et al., 1992; Mura et al., 2005; Najib et al., 1986; Okonogi and Puttipipatkhachorn, 2006; Sjökvist et al., 1991, 1992; Wulff et al., 1996). The increased dissolution rate was ascribed to the formation of a solid solution instead of a solid dispersion, which increases the dissolution rate. However, the slow dissolution rate from the sugar glass-based solid dispersions is not caused by a poor solubility of the drug in the carrier but by a too high concentration of drug in the near vicinity of the dissolving tablet. To solve this, both physically mixing a surfactant with the solid dispersion or incorporating a surfactant in the solid dispersion could be an option to improve the dissolution rate because it may create a micro-environment around the dissolving tablet with a high solubility for the drug.

In this study, we investigated whether physical mixing of a surfactant with the solid dispersion was an effective method to increase the dissolution rate or whether the surfactant should be incorporated in the solid dispersion. Diazepam and fenofibrate were used as model drugs, whereas inulin and trehalose were used as model sugars and sodium lauryl sulphate (SLS) was used as surfactant. Furthermore, the solid dispersions were characterized by differential scanning calorimetry (DSC).

2. Materials and methods

2.1. Materials

Diazepam and SLS were provided by BUFA B.V. Uitgeest, The Netherlands. Fenofibrate, trehalose, tertiary butyl alcohol (TBA) and Anthrone reagent were obtained from Sigma–Aldrich Chemie B.V. Zwijndrecht, The Netherlands. Inulin, type HD0391111 (having a number average degree of polymerization of 11) was a gift from Sensus, Roosendaal, The Netherlands. Concentrated sulphuric acid was provided from Merck B.V. Darmstadt, Germany. Demineralized water was used.

2.2. Methods

2.2.1. Preparation of solid dispersions

Solid dispersions were prepared by a freeze drying method as described previously (van Drooge et al., 2004a). In short, the drug (diazepam or fenofibrate) was dissolved in TBA, 25 mg/ml, while the sugar (inulin or trehalose) and SLS if applicable were dissolved in water at different concentrations. After heating both solutions to 40 °C, they were mixed at a TBA/water ratio of 4/6 (v/v) (in all cases 1.6 ml TBA solution with 2.4 ml aqueous solution) in a 20 ml vial. Immediately after mixing, the vials were immersed in liquid nitrogen until the mixture was completely frozen. Subsequently, the frozen solutions were placed in a Christ Epsilon 2–4 lyophiliser (Salm en Kipp, Breukelen, The Netherlands) with a condenser temperature of −85 °C. For the primary drying, the shelf temperature was set at −35 °C and a pressure of 0.220 mbar for 1 day and for the secondary drying the pressure was decreased to 0.030 mbar and the shelf temperature was gradually raised to 20 °C, which was done in another 24 h. After the samples were removed from the freeze dryer, they were stored in a vacuum desiccator over silica gel at room temperature (van Drooge et al., 2004a,c).

The composition of the solid dispersions and physical mixtures, are listed in Tables 1 and 2. Physical mixtures of SLS and solid dispersions without SLS incorporated were prepared using a spatula and mortar.

Table 1
Freeze dried formulations with diazepam as model drug

Code	Drug diazepam	Matrix		Surfactant SLS
		Inulin	Trehalose	
10D/90T/0S	10		90	
10D/90T/10S	10		90	10
20D/80T/0S	20		80	
20D/80T/20S	20		80	20
5D/45I/5S	5	45		5
10D/40I/5S	10	40		5
10D/90I/0S	10	90		
10D/90I/2.5S	10	90		2.5
10D/90I/5S	10	90		5
10D/90I/10S	10	90		10
15D/35I/5S	15	35		5
20D/30I/5S	20	30		5
20D/80I/0S	20	80		
20D/80I/2.5S	20	80		2.5
20D/80I/5S	20	80		5
20D/80I/10S	20	80		10
20D/80I/20S	20	80		20
30D/70I/10S	30	70		10
40D/60I/10S	40	60		10

Amounts of the different contents correspond to the weight ratios in the powder.

Table 2
Freeze dried formulations with fenofibrate as model drug

Code	Drug fenofibrate	Matrix		Surfactant SLS
		Inulin	Trehalose	
10F/90T/0S	10		90	
10F/90T/10S	10		90	10
20F/80T/0S	20		80	
20F/80T/20S	20		80	20
10F/90I/0S	10	90		
10F/90I/10S	10	90		10
20F/80I/0S	20	80		
20F/80I/20S	20	80		20

Amounts of the different contents correspond to the weight ratios in the powder.

2.2.2. Differential scanning calorimetry

DSC was used to determine the degree of crystallinity (D_{crys}) of the drug in the solid dispersions, which was defined as the ratio between the heat of fusion (ΔH_{sd}) of the solid dispersion and the heat of fusion of the drug as received (ΔH_{dr}) multiplied by fraction drug (f) in the mixture (see Eq. (1)).

$$D_{crys} = f\frac{\Delta H_{sd}}{\Delta H_{dr}}100\% \quad (1)$$

To determine the degree of crystallinity of diazepam, the scanning calorimeter (DSC2920, TA Instruments, Ghent, Belgium) was functioning at a heating rate of 20 °C/min, from 20 to 300 °C, after a preheating step of 10 min at 70 °C to evaporate the residual water. The sample was placed in an open aluminium pan. Indium was used for calibrating. From the DSC thermograms obtained by this method, also the temperature and the enthalpy of an endothermic event caused by SLS were acquired.

Modulated DSC (MDSC) was used to determine the glass transition temperature (T_g) of the pure drugs and matrices and the degree of crystallinity of fenofibrate. The heating rate was 2 °C/min, from −40 to 140 °C, with a modulation amplitude of 0.318 °C every minute. The T_g of the pure drugs was measured by melting and quench cooling the sample in the pan preceding the MDSC-measurement. The glass transition temperatures were taken as the inflection point of the transition.

Furthermore, DSC was used to study the effect of SLS and/or diazepam on the glass transition temperature of the maximally freeze concentrated fraction (T_g'). The following solutions were evaluated: (1) solutions of 150 mg/ml inulin in water containing different concentrations SLS (0–33 mg/ml) mixed with pure TBA (ratio water/TBA 6/4) and (2) the same SLS/inulin solutions mixed with 25 mg/ml diazepam dissolved in TBA (ratio water/TBA 6/4). The mixtures were analyzed immediately after mixing. The liquid samples (50–60 mg) were positioned in an open aluminium cup. The scanning calorimeter was functioning at a heating rate of 20 °C/min, from −60 to 40 °C.

Finally, the DSC was used to determine the enthalpy and the temperature of the endothermic peak of SLS. Samples of the same composition as the samples described in the previous paragraph were prepared and freeze dried. The obtained samples were placed in an open aluminium pan. The scanning calorimeter was functioning at a heating rate of 20 °C/min, from 20 to 300 °C, after a preheating step of 10 min at 70 °C to evaporate the residual water.

2.2.3. Tabletting

All formulations were compressed to 9 mm tablets having a weight of approximately 55 or 100 mg. In cases SLS was present in the 100 mg tablets, the tablet weight was increased by the amount of SLS, to keep the absolute amount of drug and sugar constant. This means for example that a tablet of formulation 10D/90T/10S in Table 1 had a weight of 110 mg and consisted of 10 mg diazepam, 90 mg trehalose and 10 mg SLS. The maximum compaction load was 5 kN and the speed of compaction was 5 kN/s. All tablets were processed on an ESH compaction apparatus (Hydro Mooi, Appingedam, The Netherlands) and the 9 mm die was lubricated with magnesium stearate. After tabletting, the tablets were stored in a vacuum desiccator over silica gel at room temperature for at least 1 day before further processing.

2.2.4. Dissolution

Dissolution was performed on a USP dissolution apparatus II, Rowa Techniek. The paddle speed was 100 rpm and all experiments were done in triplicate. The temperature was kept at 37 °C and the volume of the dissolution medium was 1000 ml. Experiments were performed in pure water or in a 0.5% (w/v) SLS solution.

To study dissolution behavior, generally sink conditions are applied (Gibaldi and Feldman, 1967). By definition sink conditions are met when the amount of drug to be dissolved does not exceed 5% of the drug solubility in the dissolution medium (Sheu et al., 1994). Since diazepam has a solubility of 62.5 mg/l in pure water (Mithani et al., 1996), this means that strict sink conditions are not applied for the diazepam tablets. On the other hand, the saturation concentration is not reached at complete dissolution. Therefore, this condition will be referred to as pseudo-sink conditions. When the tablets containing fenofibrate were dissolved in pure water, even the saturation concentration of fenofibrate (0.1–0.3 mg/l (Granero et al., 2005; Law et al., 2003)) was exceeded. This means that non-sink conditions were applied. Therefore, dissolution experiments were performed using a 0.5% (w/v) SLS containing medium. The solubility of fenofibrate in this medium instead of pure water was increased 2000-fold (Granero et al., 2005). Therefore, in this medium sink conditions were applied. It was assumed that the SLS which dissolved from the tablets had hardly any influence on the final solubility of the drug in the bulk of the dissolution medium, since the final concentration is only 0.002% (w/v) and the solubility of the drug is only substantially increased when the critical micelle concentration (0.2%, w/v SLS) is exceeded (Mura et al., 1999; Sjökvist et al., 1991; Weintraub and Gibaldi, 1969). The concentration of diazepam and fenofibrate in water was measured spectrophotometrically (Ultrospec III, Pharmacia LKB) at a wavelength of 230 and 290 nm, respectively.

To monitor the dissolution of the sugar, samples were taken at different time intervals. The sample size was 1 ml for samples taken from the dissolution medium consisting of pure water and 0.5 ml for samples taken from the SLS-medium. The latter samples were diluted with 0.5 ml water. Subsequently, the concentration of the samples was determined using the Anthrone assay (Scott and Melvin, 1953): the samples were vortexed with 2.00 ml Anthrone reagent (0.1%, w/v) in concentrated sulphuric acid. As a result of the mixing enthalpy, the temperature of the samples strongly increased. After cooling to room temperature (45 min), the samples were analyzed with a spectrophotometer (ThermoSpectronic, Unicam UV 500) at 630 nm.

3. Results and discussion

3.1. Physicochemical characteristics of the drugs, matrices and solid dispersions

The physicochemical properties of the used drugs and matrices are shown in Table 3. None of the solid dispersions

Table 3
Physical properties of drugs and sugars used ($n = 2$–4; mean ± S.D.)

	T_m (°C)	ΔH_{fus} (J/g)	T_g (°C)	Solubility (mg/l)
Diazepam	133.2 ± 0.3	91.5 ± 4.3	46.6 ± 0.6	65.2[a]
Fenofibrate	82.5 ± 0.7	91.7 ± 2.7	−21.3 ± 0.3	0.1–0.3[b]
Inulin	–	–	131.6 ± 0.2	–
Trehalose	–	–	121.5 ± 0.8	–

[a] Mithani et al. (1996).
[b] Law et al. (2003) and Granero et al. (2005).

containing diazepam as drug showed a melting endotherm, which implies that the drug was fully amorphous. Solid dispersions containing fenofibrate showed a melting endotherm at approximately 83 °C indicating that (a part of) the fenofibrate is present in its crystalline form. The amount of crystalline fenofibrate was 50–70% when fenofibrate was dispersed in inulin and 40–80% when it was dispersed in trehalose. It is thought that due to the low T_g of fenofibrate (−21.3 °C; see Table 3) crystallization occurred during the secondary drying step.

The thermogram of pure SLS showed an endothermic peak at approximately 200 °C. When cooling an exothermal peak at about 185 °C of the same enthalpy was detected (see Fig. 1a). Upon reheating the same sample again, a peak at 200 °C appeared. Apparently a reversible transformation occurred. This peak was found to be the result of a solid–solid transition upon visual inspection of the heated material, which usually means that the substance exhibits polymorphism.

The endothermic peak of SLS at 200 °C clearly changed when SLS was incorporated in solid dispersions. In Fig. 1b, the enthalpy of the SLS peak, corrected for the amount of inulin, is plotted as function of the SLS/inulin ratio. For samples without diazepam no change in enthalpy was found when the ratio SLS/inulin decreased from 1.0 to 0.5. However, when this ratio was further decreased, a decrease in enthalpy was found. Furthermore, the temperature of the peak maximum was evaluated (Fig. 1c). When the ratio SLS/inulin decreases, a decrease in temperature was found at all ratios. Additionally, the T_g' of solutions containing different SLS/inulin ratios was determined (Fig. 2). A decrease in T_g' was found when the fraction SLS was increased. These results clearly indicate an interaction between SLS and inulin, both in the solid and dissolved state. A further change of the endothermic peak of SLS was observed when the samples contained also diazepam. At all SLS/inulin ratios, the enthalpy (Fig. 1b) and temperature (Fig. 1c) of the peak decreased with respect to the corresponding samples without diazepam. These results show that besides the interaction between SLS and inulin also an interaction between SLS and diazepam exists in the solid state.

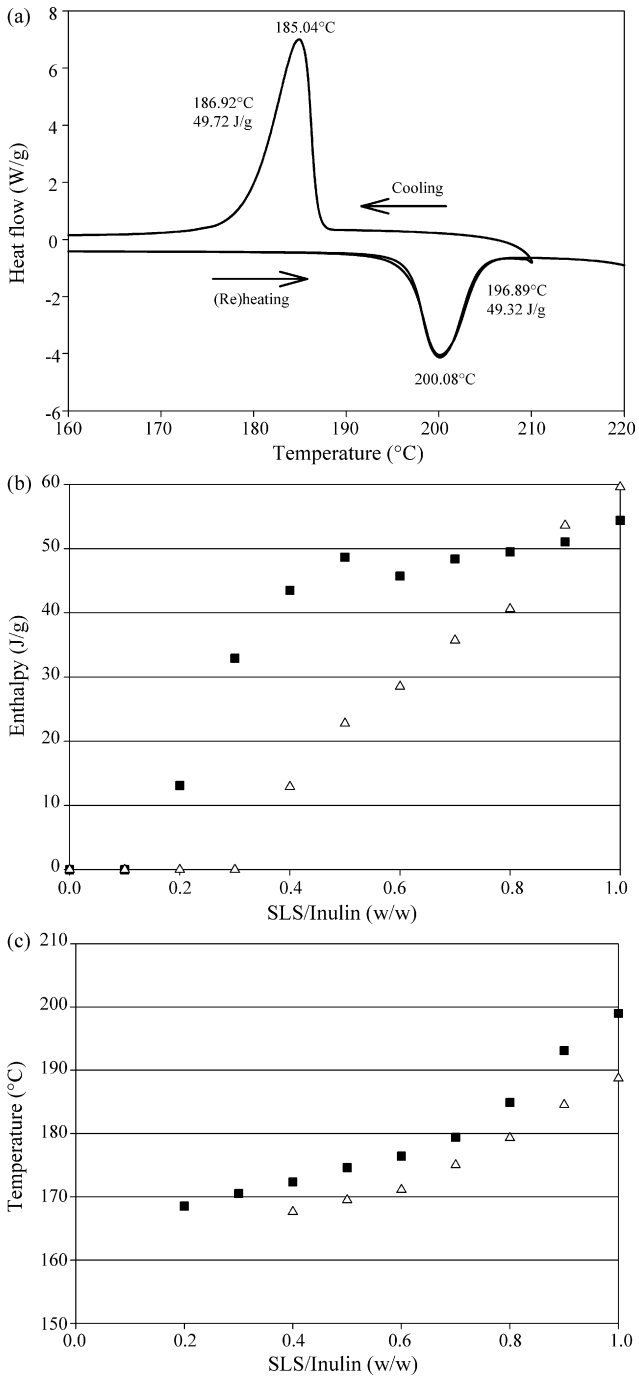

Fig. 1. (a) DSC thermogram of SLS. Sample was heated, cooled and heated. (b) Influence of the ratio SLS/inulin on the enthalpy of the endothermic peaks of SLS. The values were corrected for the amount of inulin and diazepam if applicable in the sample. Samples without diazepam (■) and with diazepam (△) (10%, w/w in inulin) were tested. (c) Influence of the ratio SLS/inulin on the temperature at which maximum of the endothermic peak of SLS was found. Samples without diazepam (■) and with diazepam (△) (10%, w/w in inulin) were tested.

3.2. Effect of SLS on the dissolution rate of diazepam at pseudo-sink conditions

In Fig. 3a, the results of the dissolution experiments of diazepam containing tablets (tablet mass 100 mg plus the mass of SLS; drug load 10 and 20 mg) at pseudo-sink conditions (pure water) are summarized. Without SLS, the dissolution of diazepam from the trehalose based tablets was very slow. According to van Drooge (van Drooge et al., 2004b), the slow dissolution of the drug is caused by the very fast release of trehalose from the dissolving tablet. This phenomenon was ascribed to crystallization of the drug in the near vicinity of

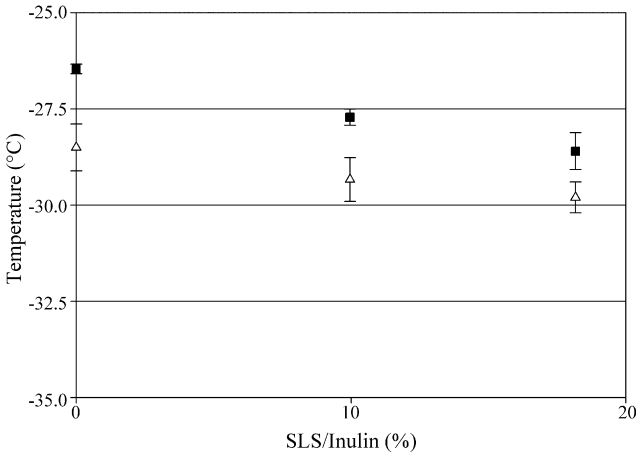

Fig. 2. Temperature of the T_g' as function of the ratio SLS/inulin. Different samples are shown: (1) SLS/inulin in pure water with the addition of TBA (■) and (2) SLS/inulin in pure water with the addition of 25 mg/ml diazepam in TBA (△). Values of 11 and 18% SLS for both solutions (with and without diazepam) are significantly different from 0% SLS ($P < 0.05$).

the dissolving tablet caused by a too high supersaturation. In contrast, dissolution of diazepam (10%, w/w) from inulin based tablets showed a release of 80% within 20 min. Because inulin dissolves slower than trehalose, release of the sugar does not result in a too high concentration of the drug in the near vicinity of the dissolving tablet and crystallization does not occur. However, when the drug load in the inulin based tablet was increased to 20% (w/w) again a low dissolution rate was found. Apparently at this higher drug load also uncontrolled crystallization occurred.

The dissolution rate of diazepam from tablets of inulin as well as trehalose sugar glasses increased tremendously when SLS is incorporated in the solid dispersion. The time to dissolve 80% of the dose (t_{80}) seems to be independent of the type of sugar. Even from tablets containing 20 mg diazepam 80% of the drug dissolved within 5 min, while the t_{80} of binary solid dispersion tablets was not reached within 60 min. Apparently, incorporation of SLS in the solid dispersion results in an effective prevention of diazepam crystallization during dissolution.

In contrast, when the SLS was added by physical mixing, instead of incorporation in the solid dispersion the dissolution rate was unexpectedly low: the t_{80} of the drug was still more than 60 min. Although the dissolution of diazepam from these tablets was initially faster than from tablets consisting of solid dispersions without SLS, it was substantially slower than from tablets consisting of solid dispersions with SLS incorporated (see Fig. 3b for a typical example). In addition after a few minutes, the dissolution rate strongly decreased. The typical change in the slope of the curve suggests that the diazepam crystallized in the near vicinity of the dissolving tablet, forming large crystals with a small surface area (van Drooge et al., 2004b). It can, therefore, be concluded that in contrast to the solid dispersions with SLS incorporated, crystallization of diazepam was not effectively prevented by physical mixing of SLS with the solid dispersion. However, crystallization was delayed compared to tablets without SLS.

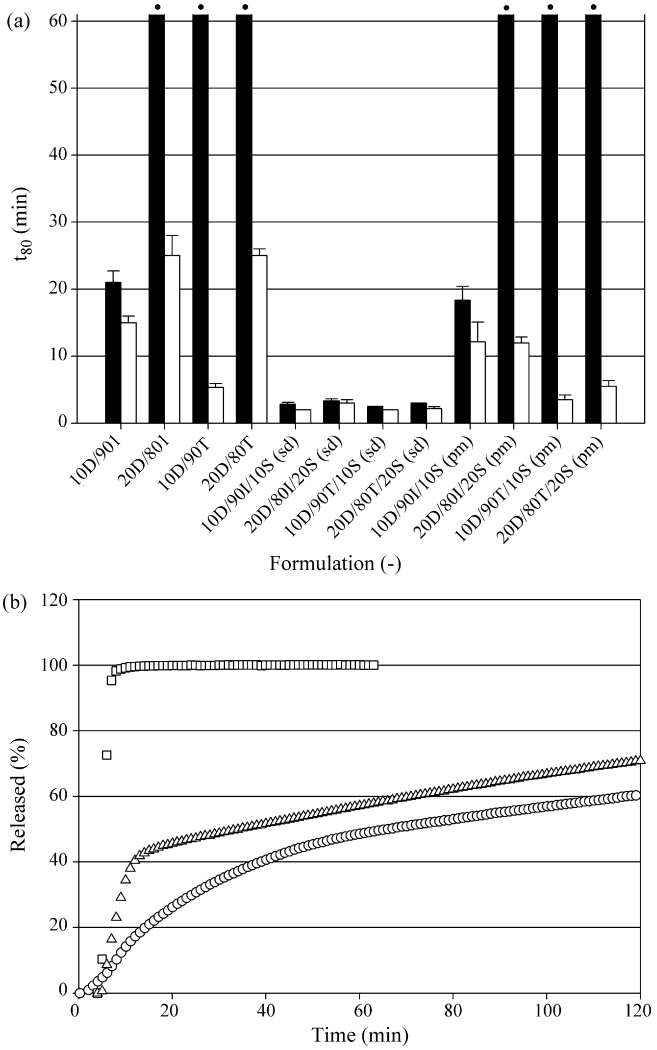

Fig. 3. (a) The time required to dissolve 80% of the drug (■) and the sugar (□) at pseudo-sink conditions (pure water) of tablets containing diazepam as model drug. The formulations corresponding to the columns marked with a dot have not reached the t_{80} within 60 min (tablet weight is 100, 110 or 120 mg; $n = 3$; mean ± S.D.). (b) Dissolution profiles of tablets containing diazepam (10 mg) as model drug. Tablets without SLS (◯), with SLS incorporated in the solid dispersion (□) and SLS added by physical mixing with the solid dispersion (△) are shown (tablet weight is 100 or 110 mg; $n = 3$; mean).

3.3. Effect of SLS on the dissolution rate of fenofibrate at sink and non-sink conditions

The dissolution rate of fenofibrate was examined at sink (0.5%, w/v SLS) and non-sink (pure water) conditions. In Fig. 4, the results of the dissolution of fenofibrate at sink conditions are summarized. The differences in t_{80} values between the different formulations were not as prominent as found for diazepam. However, as discussed in the material en methods section, the dissolution behavior of the diazepam tablets were studied at pseudo-sink conditions (pure water), while for the fenofibrate tablets sink conditions (0.5%, w/v SLS) were used. The results indicate that the solubility of fenofibrate at these sink conditions was increased to a level that a distinction between the different formulations cannot be made.

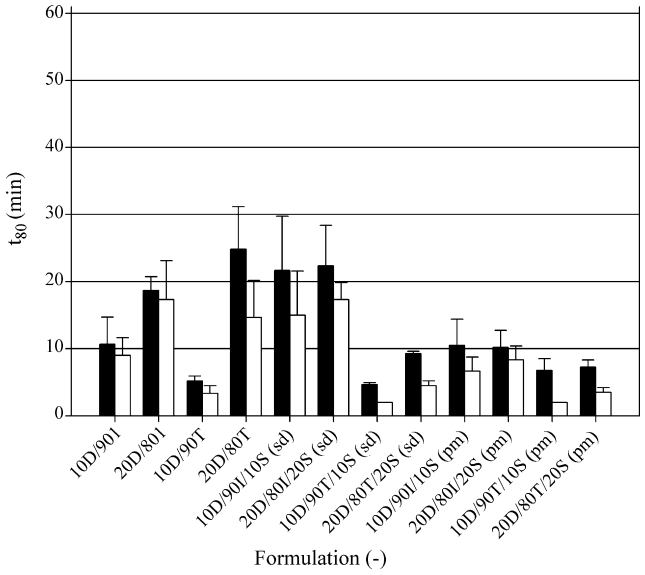

Fig. 4. Summary of the time required to dissolve 80% of the drug (■) and the sugar (□) of tablets containing fenofibrate as model drug. Dissolution was performed at sink conditions (0.5%, w/v SLS). Columns exceeding the borders of the graph have not reached the t_{80} within 60 min (tablet weight is 100, 110 or 120 mg; $n = 3$; mean ± S.D.).

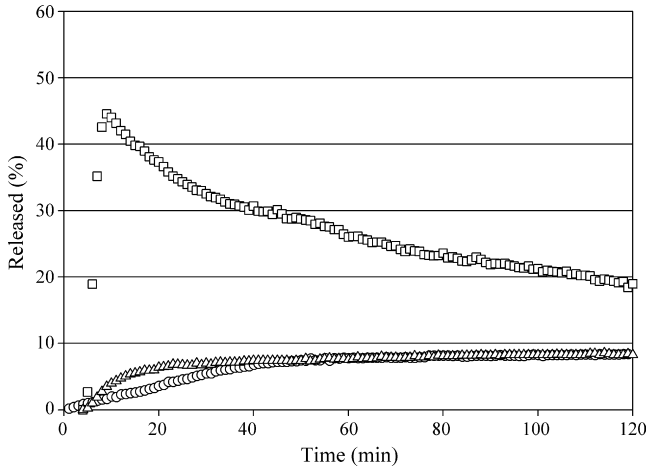

Fig. 5. Dissolution profiles of tablets containing fenofibrate (10 mg) as model drug. Dissolution was performed at non-sink conditions (pure water). Tablets without SLS (◯), with SLS incorporated in the solid dispersion (□) and SLS added by physical mixing with the solid dispersion (△) are shown (tablet weight is 100 or 110 mg; $n = 3$; mean).

In contrast to sink conditions, a clear effect of SLS was observed at non-sink conditions. A tablet prepared from a solid dispersion of fenofibrate and inulin at a drug load of 10 mg, slowly dissolved with a maximum release of 8% of the drug after 2 h (Fig. 5). However, in this case still more fenofibrate dissolved (0.8 mg/l) than was expected from the saturation concentration (0.1–0.3 mg/l). Again unexpected, SLS physically mixed with the solid dispersion had hardly any affect on the dissolution behavior. In contrast, when SLS was incorporated in the solid dispersion a strong effect was seen: an initial rapid release followed by a decrease of dissolved drug. The decrease in the amount of dissolved drug can be ascribed to the solubility of fenofibrate in pure water. In this particular case a maximum of 45% of the dose was dissolved in 1-l water, which corresponds to 4.5 mg/l. Since the solubility of fenofibrate is 0.1–0.3 mg/l, a concentration of 15–45 times the saturation concentration was reached. In vitro supersaturation is followed by a decrease in the amount dissolved drug due to crystallization. However, it can be envisaged that in vivo the drug will be absorbed before crystallization can occur, resulting in increased bioavailability (Chen et al., 2004; Pan et al., 2000).

The maximum dissolved fraction of the drug and the t_{80} for the sugar are summarized in Table 4. The tablets consisting of solid dispersions without SLS or with SLS added by physical mixing showed for both drug loads a lower fraction drug maximally dissolved when trehalose instead of inulin was used. This can be ascribed to the higher dissolution rate of trehalose, as mentioned earlier. However, when SLS was incorporated in the solid dispersion at a drug load of 10% (w/w) the fraction drug maximally dissolved from the inulin based tablet was much higher than from the trehalose based tablet while the dissolution rate of both sugars was similar. Therefore, this should be caused by another property of the oligosaccharide inulin in comparison to the disaccharide trehalose, i.e. a higher viscosity in the near vicinity of the dissolving tablet.

3.4. Influence of varying the drug load and SLS content

To further evaluate the effects of incorporation of SLS in solid dispersions on the dissolution behavior, the amount of drug in the solid dispersions was increased. In these experiments only diazepam and inulin were used as model drug and sugar. In order

Table 4
Fraction fenofibrate maximally dissolved within 2 h and time needed to dissolve 80% of the sugar at non-sink conditions (pure water)

Fenofibrate content per tablet (mg)	Method of addition of SLS	Fraction drug maximally dissolved within 2 h (%)		t_{80} Of the sugar (min)	
		Inulin	Trehalose	Inulin	Trehalose
10	–	8 ± 0	5 ± 1	25 ± 6	11 ± 3
	P.M.	8 ± 0	7 ± 1	10 ± 2	3 ± 0
	S.D.	42 ± 2	19 ± 2	2 ± 0	2 ± 1
20	–	3 ± 0	1 ± 0	28 ± 7	16 ± 1
	P.M.	4 ± 1	3 ± 0	9 ± 2	4 ± 1
	S.D.	11 ± 2	11 ± 2	7 ± 5	5 ± 2

$n = 3$; mean ± S.D., (–) = no SLS added, P.M. = SLS added to the solid dispersion by physical mixing, S.D. = SLS incorporated in the solid dispersion by freeze drying.

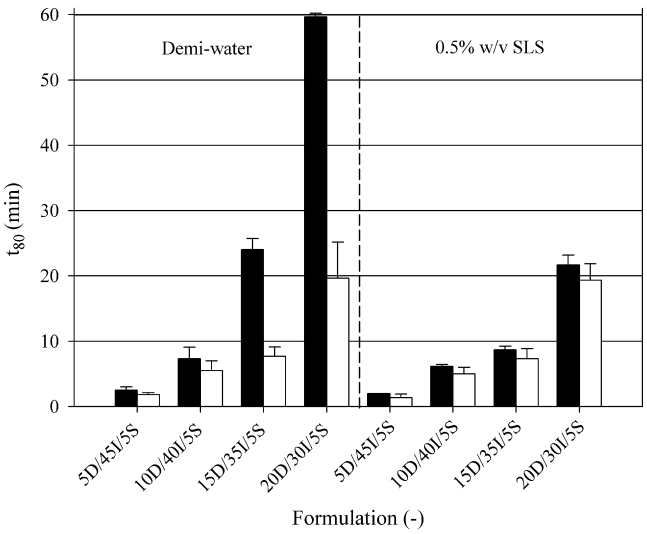

Fig. 6. Effect of increasing the drug load on the time required to dissolve 80% of the drug (■) and the sugar (□) of tablets containing diazepam as model drug. Experiments were performed at pseudo-sink conditions (pure water) as well as at sink conditions (0.5%, w/v SLS) (tablet weight is 55 mg; $n = 3$; mean ± S.D.).

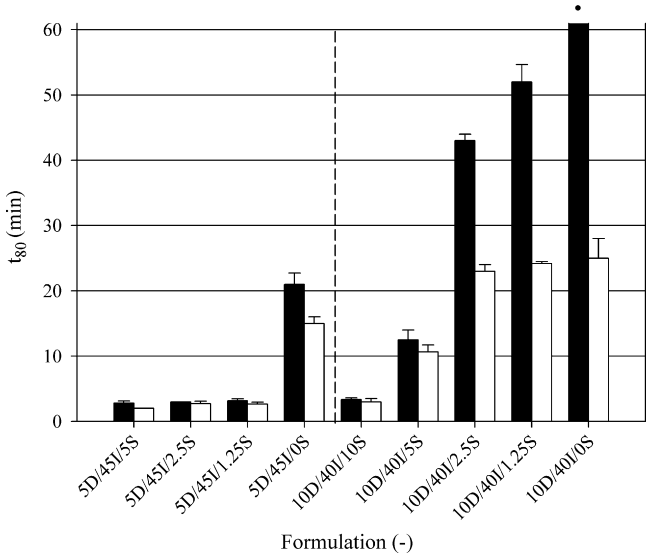

Fig. 7. Effect of decreasing the amount of SLS on the time required to dissolve 80% of the drug (■) and the sugar (□) of tablets containing diazepam as model drug. The formulation corresponding to the column marked with a dot has not reached the t_{80} within 60 min. Experiments were performed at pseudo-sink conditions (pure water) (tablet weight is 100–110 mg; $n = 3$; mean ± S.D.).

to keep the maximal concentration of diazepam in the dissolution medium at 20 mg/l, tablets of 55 mg instead of 100 mg were used. The diazepam content was gradually raised from 5 to 20 mg. The dissolution behavior in these experiments was studied at pseudo-sink conditions (pure water) as well as sink conditions (0.5%, w/v SLS).

At pseudo-sink conditions the t_{80} increased from 3 to 60 min when the drug load was increased from 5 to 20 mg (Fig. 6). This difference decreased at sink conditions to a t_{80} of 2 min for 5 mg and 22 min for 20 mg diazepam. These results confirm the idea that pseudo-sink conditions were provided when these amounts of diazepam were dissolved (see Section 2). The dissolution of inulin was similar for the corresponding formulations in the different media and, therefore, it can be concluded that the dissolution medium did not affect the dissolution rate of the matrix. Furthermore, these data indicate that even at higher drug loads (15 mg per tablet; formulation 15D35I/5S)) at pseudo-sink conditions the dissolution of diazepam can be considered rapid when SLS is incorporated.

In other experiments the concentration SLS in the solid dispersions was varied. In these experiments tablets of 100 mg plus the mass of SLS were used and only pseudo-sink conditions (pure water) were applied. When tablets containing 20 mg diazepam were tested, the t_{80} increased from 3 min (20 mg SLS) to 52 min (2.5 mg SLS) (Fig. 7). However, when the tablets contained only 10 mg diazepam no clear difference was observed when the amount of incorporated SLS was lowered from 10 to 2.5 mg, while the t_{80} increased 7-fold when no SLS at all was incorporated. These data show that for tablets containing 10 mg diazepam a small amount (2.5 mg SLS) was sufficient to increase the dissolution rate. Incorporation of more SLS did not increase the dissolution rate further. However, when the drug load was raised to 20 mg each increase in SLS content (0–20 mg) resulted in an increased dissolution rate.

4. Conclusions

In this study, it was found that the addition of SLS to formulations containing sugar glass-based solid dispersions is a suitable technology to improve the dissolution behavior of poorly soluble drugs when the drug load is high and/or the sugar dissolves very fast. However, the SLS must be incorporated in the solid dispersion to obtain the desired effect of an increased dissolution rate. Unexpectedly, physical mixing of SLS with the solid dispersion had hardly any effect on the dissolution rate.

Most likely, SLS from tablets prepared from the physical mixture was leached out rapid, and only the initial dissolution rate of the drug was increased. After that the solubility of the drug in the near vicinity of the dissolving tablet strongly decreased resulting in crystallization. In contrast, due to the interaction between SLS and the sugar and between SLS and the drug in the tablets prepared from the solid dispersion in which SLS was incorporated, the dissolution of SLS is slowed down by which a high solubility of the drug in the near vicinity of the dissolving tablet remains high during the complete dissolution process. Consequently, crystallization is effectively prevented resulting in a higher dissolution rate. Therefore, an increased in vivo bioavailability is envisaged.

References

Alden, M., Tegenfeldt, J., Sjökvist, E., 1992. Structure of solid dispersions in the system polyethylene glycol-griseofulvin with additions of sodium dodecyl sulphate. Int. J. Pharm. 83, 47–52.

Amidon, G.L., Lennernas, H., Shah, V.P., Crison, J.R., 1995. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res. 12, 413–420.

Chen, Y., Zhang, G.G., Neilly, J., Marsh, K., Mawhinney, D., Sanzgiri, Y.D., 2004. Enhancing the bioavailability of ABT-963 using solid dispersion containing Pluronic F-68. Int. J. Pharm. 286, 69–80.

Corrigan, O.I., 1985. Mechanims of dissolution of fast release solid dispersions. Drug Dev. Ind. Pharm. 11, 697–724.

Craig, D.Q.M., 1990. Polyethylene glycols and drug release. Drug Dev. Ind. Pharm. 16, 2501–2526.

Craig, D.Q.M., 2002. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int. J. Pharm. 231, 131–144.

Curatolo, W., 1998. Physical chemical properties of oral drug candidates in the discovery and exploratory development settings. Pharm. Sci. Tech. Today 1, 387–393.

Gibaldi, M., Feldman, S., 1967. Establishment of sink conditions in dissolution rate determinations. J. Pharm. Sci. 56, 1238–1242.

Granero, G.E., Ramachandran, C., Amidon, G.L., 2005. Dissolution and solubility behavior of fenofibrate in sodium lauryl sulfate solutions. Drug Dev. Ind. Pharm. 31, 917–922.

Hancock, B.C., Parks, M., 2000. What is the true solubility advantage for amorphous pharmaceuticals? Pharm Res. 17, 397–404.

Huang, L.F., Tong, W.Q., 2004. Impact of solid state properties on developability assessment of drug candidates. Adv. Drug Deliv. Rev. 56, 321–334.

Keck, C.M., Muller, R.H., 2006. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. Eur. J. Pharm. Biopharm. 62, 3–16.

Law, D., Wang, W., Schmitt, E.A., Qiu, Y., Krill, S.L., Fort, J.J., 2003. Properties of rapidly dissolving eutectic mixtures of poly(ethylene glycol) and fenofibrate: the eutectic microstructure. J. Pharm. Sci. 92, 505–515.

Leuner, C., Dressman, J., 2000. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 50, 47–60.

Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeney, P.J., 2001. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Deliv. Rev. 46, 3–26.

Lobenberg, R., Amidon, G.L., 2000. Modern bioavailability, bioequivalence and biopharmaceutics classification system new scientific approaches to international regulatory standards. Eur. J. Pharm. Biopharm 50, 3–12.

Mithani, S.D., Bakatselou, V., TenHoor, C.N., Dressman, J.B., 1996. Estimation of the increase in solubility of drugs as a function of bile salt concentration. Pharm. Res. 13, 163–167.

Morris, K.R., Knipp, G.T., Serajuddin, A.T., 1992. Structural properties of polyethylene glycol-polysorbate 80 mixture, a solid dispersion vehicle. J. Pharm. Sci. 81, 1185–1188.

Mura, P., Faucci, M.T., Manderioli, A., Bramanti, G., Parrini, P., 1999. Thermal behavior and dissolution properties of naproxen from binary and ternary solid dispersions. Drug Dev. Ind. Pharm. 25, 257–264.

Mura, P., Moyano, J.R., Gonzalez-Rodriguez, M.L., Rabasco-Alvarez, A.M., Cirri, M., Maestrelli, F., 2005. Characterization and dissolution properties of ketoprofen in binary and ternary solid dispersions with polyethylene glycol and surfactants. Drug Dev. Ind. Pharm. 31, 425–434.

Najib, N.M., Suleiman, M., Malakh, A., 1986. Characteristics of the in vitro release of ibuprofen from polyvinylpyrrolidone solid dispersions. Int. J. Pharm. 32, 229–236.

Okonogi, S., Puttipipatkhachorn, S., 2006. Dissolution improvement of high drug-loaded solid dispersion. AAPS PharmSci. Tech. 7, E52.

Pan, R.N., Chen, J.H., Chen, R.R., 2000. Enhancement of dissolution and bioavailability of piroxicam in solid dispersion systems. Drug Dev. Ind. Pharm. 26, 989–994.

Rodriguez-Spong, B., Price, C.P., Jayasankar, A., Matzger, A.J., Rodriguez-Hornedo, N., 2004. General principles of pharmaceutical solid polymorphism: a supramolecular perspective. Adv. Drug Deliv. Rev. 56, 241–274.

Scott, T.A.J., Melvin, E.H., 1953. Determination of dextran with Anthrone. Anal. Chem. 25, 1656–1661.

Sheu, M.-T., Yeh, C.-M., Sokoloski, T.D., 1994. Characterization and dissolution of fenofibrate solid dispersion systems. Int. J. Pharm. 103, 137–146.

Sjökvist, E., Nyström, C., Alden, M., 1991. Physicochemical aspects of drug release XIII. The effect of sodium dodecyl sulphate additions on the structure and dissolution of a drug in solid dispersions. Int. J. Pharm. 69, 53–62.

Sjökvist, E., Nystrom, C., Alden, M., Caram-Lelham, N., 1992. Physicochemical aspects of drug release XIV. The effects of some ionic and non-ionic surfactants on properties of a sparingly soluble drug in solid dispersions. Int. J. Pharm. 79, 123–133.

van Drooge, D.J., Hinrichs, W.L.J., Frijlink, H.W., 2004a. Incorporation of lipophilic drugs in sugar glasses by lyophilization using a mixture of water and tertiary butyl alcohol as solvent. J. Pharm. Sci. 93, 713–725.

van Drooge, D.J., Hinrichs, W.L.J., Frijlink, H.W., 2004b. Anomalous dissolution behaviour of tablets prepared from sugar glass-based solid dispersions. J. Control. Release 97, 441–452.

van Drooge, D.J., Hinrichs, W.L.J., Wegman, K.A.M., Visser, M.R., Eissens, A.C., Frijlink, H.W., 2004c. Solid dispersions based on inulin for the stabilisation and formulation of Δ9-tetrahydrocannabinol. Eur. J. Pharm. Sci. 21, 511–518.

Weintraub, H., Gibaldi, M., 1969. Physiologic surface-active agents and drug absorption IV: effect of pre-micallar concentrations of surfactant on dissolution rate. J. Pharm. Sci. 58, 1368–1372.

Wulff, M., Alden, M., Craig, D.Q.M., 1996. An investigation into the critical surfactant concentration for solid solubility of hydrophobic drug in different polyethylene glycols. Int. J. Pharm. 142, 189–198.