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The preparation of agglomerates containing solid dispersions of diazepam by melt agglomeration in a high shear mixer

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Abstract

The aim of this study was to prepare by melt agglomeration agglomerates containing solid dispersions of diazepam as poorly water-soluble model drug in order to evaluate the possibility of improving the dissolution rate. Lactose monohydrate was melt agglomerated with polyethylene glycol (PEG) 3000 or Gelucire® 50/13 (mixture of glycerides and PEG esters of fatty acids) as meltable binders in a high shear mixer. The binders were added either as a mixture of melted binder and diazepam by a pump-on procedure or by a melt-in procedure of solid binder particles. Different drug concentrations, maximum manufacturing temperatures, and cooling rates were investigated. It was found to be possible to increase the dissolution rate of diazepam by melt agglomeration. A higher dissolution rate was obtained with a lower drug concentration. Admixing the binders by the melt-in procedure resulted in similar dissolution rates as the pump-on procedure. The different maximum manufacturing temperatures and cooling rates were found to have complex effects on the dissolution rate for formulations containing PEG 3000, whereas only minor effects of the cooling procedure were found with Gelucire 50/13. Gelucire 50/13 resulted in faster dissolution rates compared to PEG 3000.

Keywords: Melt agglomeration; High shear mixer; Polyethylene glycol; Diazepam; Solid dispersion; Dissolution rate

1. Introduction

Despite many years of extensive research the commercial application of solid dispersions in pharmaceutical products has been very limited. The reason for this may be problems with the method of preparation, the reproducibility of physicochemical properties, the formulation into dosage forms, the scale up of the manufacturing method and/or the stability (Serajuddin, 1999; Breitenbach, 2002).

Solid dispersions are prepared either by a fusion, solvent or solvent-fusion method. Traditionally, when the fusion method has been applied, solid dispersions have been prepared in small scale using high temperatures to melt the carrier in which the drug is dispersed and then solidifying the mixture on an ice bath (Serajuddin, 1999; Leuner and Dressman, 2000). The solidified dispersion is then pulverised and sieved. This method, which is difficult to apply in a large pharmaceutical scale, usually produces materials that are soft, tacky and have poor flow properties and compressibility (Ford and Rubinstein, 1980). It is desirable to improve the flow properties and the compressibility of solid dispersion material to improve

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the processing of the material. A feasible method for this could be melt agglomeration, where the carrier acts as a meltable binder.

Previous studies have shown that solid dispersion can be combined with the melt agglomeration method (Kinget and Kemel, 1985) resulting in an enhanced drug dissolution (Ford and Rubinstein, 1980; Gupta et al., 2001; Passerini et al., 2002).

Polyethylene glycols (PEGs) of different molecular weight have commonly been used as meltable binders in melt agglomeration of immediate-release granules. Furthermore, PEGs have been extensively used as carriers in solid dispersion systems. Another family of carriers is Gelucire®, which is made up of glycerides and fatty acid esters of PEGs. Gelucire has been shown to further increase the dissolution rate of poorly water-soluble drugs compared to PEGs probably due to surface active and self-emulsifying properties (Dordunoo et al., 1991; Damian et al., 2000).

Diazepam is a poorly water-soluble (0.05 mg/ml) (Nunez and Yalkowsky, 1998) benzodiazepine. Previous studies with solid dispersions of diazepam and PEG of different molecular weights have shown an enhancement of the dissolution rate of diazepam compared to the pure drug (Geneidi and Hamacher, 1980; Rabasco et al., 1991). Studies have also indicated that diazepam could be prepared either as a solid dispersion or a solid solution depending on the concentration of drug incorporated in the carrier (Ginés et al., 1990).

The aim of the present study was to improve the dissolution rate of a poorly water-soluble model drug (diazepam) by melt agglomeration in a high shear mixer using PEG 3000 and Gelucire® 50/13 as meltable binders. The effect of diazepam concentration, type of binder, maximum manufacturing temperature, and cooling rate on the dissolution rate was investigated.

2. Materials and methods

2.1. Materials

Lactose, 450 mesh (α-lactose monohydrate, DMV, The Netherlands) was used as a filler. Diazepam (Unikem, Denmark) was used as a poorly water-soluble model drug. Gelucire® 50/13 (solid beads) (mixture of glycerides and PEG esters of fatty acids, Gattefossé, France) or PEG 3000P (powder) (Clariant, Germany) was used as meltable binder.

2.2. Methods

2.2.1. Primary characterisation of materials

The particle size distributions by volume of the lactose and the diazepam were determined in triplicate by a Malvern Mastersizer S laser diffraction particle sizer (Malvern Instruments, UK), applying a dry powder feeder with a pressure of 3 bar. The median particle diameter and the span were found to be 13 μm and 2.3 for the lactose and 16 μm and 3.4 for the diazepam. The span is the difference between the diameters at the 90 and the 10 percentage points relative to the median diameter.

The BET multipoint surface area of the lactose, determined in duplicate by a Gemini 2375 Surface Area Analyser (Micromeritics, USA), was 0.94 m^2/g.

The pycnometric densities of the lactose, the diazepam, the solid Gelucire 50/13, and the solid PEG 3000 were determined by an Accupyc 1330 gas displacement pycnometer (Micromeritics, USA) using helium purge. Analyses were performed in duplicate. Before the analysis, the Gelucire beads were milled in a coffee mill (Braun AG 4041, Spain) for 3 s followed by a 3-s pause to prevent melting of the Gelucire. This procedure was repeated until the beads were milled for 60 s in total. The pycnometric densities of the lactose and the diazepam were found to be 1.539 and 1.361 g/cm^3, respectively. The poured and tapped densities of the lactose were determined in duplicate according to the test of apparent volume (European Pharmacopoeia, 2002) and found to be 0.45 and 0.56 g/cm^3, respectively.

The melting range and the peak temperature of the PEG 3000 and the Gelucire 50/13 were estimated in triplicate by a Perkin-Elmer DSC 7 differential scanning calorimeter (Perkin-Elmer, USA) as previously described (Seo and Schæfer, 2001). DSC scans were also done for binary mixtures of PEG 3000:diazepam and Gelucire 50/13:diazepam between 25 and 160 °C at a heating rate of 10 °C/min. The mixtures were prepared by manually mixing with different ratios of diazepam. For each mixture, analyses were performed in duplicate.

The densities of the melted binders were estimated at 60 and 80 °C as previously described (Eliasen et al., 1998). The analyses were performed in triplicate.

The viscosities of the melted binders were estimated in duplicate by a Rotovisco RV 20 (Haake, Germany) as previously described (Schæfer and Mathiesen, 1996). The analyses were performed at 60 and 80 °C.

All data on material properties presented here are the mean value of the repeated estimations.

2.2.2. Agglomeration equipment

The agglomeration experiments were performed in a water-jacketed 10-l high shear mixer (PMA1 Pellet Processor, Aeromatic-Fielder, UK) (Seo and Schæfer, 2001). During the process, the power consumption of the impeller motor, the impeller speed, and the product temperature were recorded. A metal tube (inner diameter 2.7 mm) placed in one of the openings in the mixer lid was used to add the mixture of melted binder and diazepam. The distance between the inner wall of the mixer bowl and the orifice of the tube was 3.7 cm. The orifice of the tube was mounted 18.7 cm above the bottom of the mixer bowl. A peristaltic pump (Cole Parmer model no. 7553-77, USA) and a plastic tube were used to feed the mixture from a beaker to the metal tube. The plastic tube was electrically heated to 70 °C with a heating device (Hillesheim, Germany). A hotplate (IKA Labortechnik type RET B, Germany) was used to heat the beaker.

2.2.3. Agglomeration procedure

The load of the mixer was 1250 g of lactose in all the experiments. The lactose was heated either by the preheated jacket of the bowl together with frictional heat caused by the impeller rotation or solely by the frictional heat. A binder concentration of 22.0% m/m of the amount of lactose was applied in all experiments. The binders were added by two different procedures, pump-on or melt-in.

When the pump-on procedure was applied, the prescribed amount of diazepam was manually dissolved or dispersed in the accurate amount of melted binder. The mixture of melted binder and diazepam was kept at 70 °C until the addition was initiated. This was done when the product temperature had reached 55 °C for experiments with Gelucire 50/13 and 63 °C for experiments with PEG 3000. These temperatures correspond to a temperature of 5 °C above the melting range for each binder. During the addition, the impeller speed was 900 rpm. The mixture of melted binder and the diazepam was continuously mixed during the addition and the addition rate was kept at 50 ± 7 g/min. The start of massing time was defined as the time when the addition of the melted binder and the diazepam was completed. For experiments with PEG 3000, the impeller speed was either lowered to 800 rpm or kept constant at 900 rpm during the massing. For Gelucire 50/13, the impeller speed was either lowered to 800 rpm or increased to 1000 rpm.

When the melt-in procedure was applied, the prescribed amounts of solid binder, diazepam, and lactose were added to the preheated mixer bowl and dry mixed at either 900 rpm (PEG 3000) or 1000 rpm (Gelucire 50/13). The dry mixing continued until the melting of the binder was observed as an inflection point in the power consumption of the impeller motor. This inflection point was defined as the start of massing time. During massing, the impeller speed was kept unchanged.

For both procedures, a sample of approximately 90 g was withdrawn with a beaker immediately after completed massing, and the sample was poured directly into liquid nitrogen to be flash-cooled. Approximately half of the remaining part of the agglomerates was transferred to a preheated fluidised bed granulator, Glatt GPCG-1 (Glatt, Germany) in order to allow the agglomerates to be cooled down more slowly in a controlled way. The initial inlet air temperature of the fluidised bed granulator was set to either 70 or 100 °C, and the fluidising air flow rate was set to 100 m^3/h, giving rise to maximum product temperatures of approximately 60 or 85 °C, respectively. After addition of the agglomerates to the fluidised bed granulator, cooling was started by setting the inlet air temperature at 30 °C. The fluidisation was stopped when the product temperature had reached 32 °C for Gelucire 50/13 and 45 °C for PEG 3000. These temperatures were chosen to ensure a complete solidification of the binders and correspond to a temperature 2 °C below the melting range of each binder.

2.2.4. Agglomerate characterisation

2.2.4.1. Size distribution. The amount of agglomerates >4 mm was determined using either manual sieving (nitrogen cooled agglomerates) or vibration

sieving (fluidised bed cooled agglomerates) for ~10 s on a Jel-Fix 50 (J. Engelsmann, Germany). The agglomerate size distribution of the agglomerates <4 mm was determined by sieve analysis. A series of 14 ASTM standard sieves in the range of 75–2000 μm was vibrated for 10 min at a low vibration level. For the nitrogen cooled agglomerates, the total fraction <4 mm was sieve analysed. For the fluidised bed cooled agglomerates, a sample of approximately 80 g prepared with a Laborette 27 automatic rotary sample divider (Fritsch, Germany) was analysed.

The geometric weight mean diameter (d_{gw}) and the geometric standard deviation (s_g) were calculated from the sieve analysis data. The yield was calculated as the total amount of agglomerates emptied from the bowl of the high shear mixer expressed as the percentage of the amount of material added to the bowl. The size fraction 900–1000 μm to be used for the measurements in Sections 2.2.4.2–2.2.4.5 was prepared by vibration at low vibration level for 10 min.

2.2.4.2. In vitro dissolution studies. In vitro dissolution tests were performed 7 days after manufacturing of the agglomerates. The tests were carried out in triplicate in an Erweka DT 70 dissolution tester (Erweka, Germany) at 37 °C using paddles rotating at 100 rpm. Agglomerate samples of an amount containing approximately 6.8 mg diazepam were used. Additionally, the dissolution profile was measured for a sample of an aqueous suspension containing approximately 6.8 mg of pure diazepam. 900 ml of 0.2 M phosphate buffer (pH 6.8) were used as dissolution medium. 10 ml samples were withdrawn at 1, 3, 5, 7, 10, 15, 20, and 30 min. Fresh and tempered dissolution medium was added each time to maintain a constant volume. The samples were immediately filtered through a membrane filter (cellulose acetate, pore size 0.45 μm), and the diazepam content was determined by UV-measurement at 241 nm using a Perkin-Elmer spectrometer (UV-Vis spectrometer, type Lambda 14P, Perkin-Elmer, USA) equipped with a 1.0 cm cuvette.

2.2.4.3. Determination of drug content. The analysis of the diazepam content in the agglomerate size fraction 900–1000 μm was carried out in duplicate by dissolving agglomerate samples corresponding to approximately 0.8 mg of diazepam in 0.1 M hydrochloric acid, and the amount of drug was spectrophotometrically determined at 241 nm.

2.2.4.4. Image analysis. The agglomerates were placed on an illuminated desk. Photos were taken with a digital camera (MTI CCD72EX, DAGE-MTI, USA) connected to a 60-mm lens (Mikro-Nikkor, Nikon, Japan) (magnification: 1 pixel = 10 μm). Image analyses were performed on the photos using imaging processing and analysis software (Global Lab Image/2, Data Translation Inc., USA). Approximately 80 agglomerates were used for each analysis. The shape of the agglomerates was characterised by the two-dimensional shape factor, e_R, devised by Podczeck and Newton (1994).

2.2.4.5. Scanning electron microscope (SEM) micrographs. Micrographs of selected agglomerates were taken by a SEM (Jeol JSM 5200, Japan). Prior to microscopy, the samples were coated with gold/palladium by sputtering for 150 s (Biorad, E5200 Auto Sputter Coater, UK).

2.2.5. Experimental design

Lactose was agglomerated by the pump-on procedure with mixtures of either melted PEG 3000/diazepam or melted Gelucire 50/13/diazepam. Two different concentrations of diazepam were applied for each binder, 15 or 30% (m/m of the amount of binder) diazepam was used with PEG 3000 and 30 or 40% diazepam was used with Gelucire 50/13. The settings of the impeller speed and the circulator temperature were chosen to give either a low maximum product temperature during the process (approximately 60 °C) or a high maximum product temperature (approximately 75–85 °C).

Additional experiments were performed using the melt-in procedure. 15% diazepam was applied in experiments with PEG 3000 and 30% was applied in experiments with Gelucire 50/13. For both binders, the high maximum product temperature level was used.

The experiments were carried out in duplicate. The results shown in this paper are mean values of the repeated experiments. The range of the results is indicated as '±' in Table 2 and as error bars in Figs. 3 and 4.

3. Results and discussion

3.1. Binder properties

It is seen from Table 1 that Gelucire 50/13 has a lower density as well as a lower viscosity compared to PEG 3000.

It was found by DSC measurements that the two binders differed in melting behaviour. PEG 3000 had a narrow melting range, while Gelucire 50/13 had a wider two-peak melting range. Gelucire 50/13 consists of mixtures of glycerides and PEG esters of fatty acids, and segregation of the glycerides might cause the two-peak melting range (Sutananta et al., 1994).

The solubility of lactose in PEG 3000 as well as Gelucire 50/13 was found to be less than 0.1% m/m at 70 °C based on visual observation.

3.2. Phase diagram

The scans from the DSC measurements on physical mixtures of diazepam and binder were used to construct phase diagrams (Fig. 1).

The phase diagrams were used to choose the diazepam concentrations in the agglomeration experiments. 15 or 30% m/m of diazepam were chosen for the experiments with PEG 3000, and 30 or 40% m/m of diazepam were chosen for the experiments with Gelucire 50/13. The phase diagrams indicate that for each binder the lower concentration is likely to result in a solid solution and the higher in a solid dispersion (Damian et al., 2000; Kapsi and Ayres, 2001).

3.3. Agglomerate size, size distribution, and shape

Experiments performed with Gelucire at a low temperature had to be excluded since it was impossible to obtain agglomerates at a maximum product temperature of 60 °C. A high impeller speed and a long massing time were found to be prerequisites for obtaining rounded agglomerates with Gelucire 50/13. These conditions resulted in so much frictional heat that the product temperature could not be maintained at 60 °C by cooling of the mixer bowl.

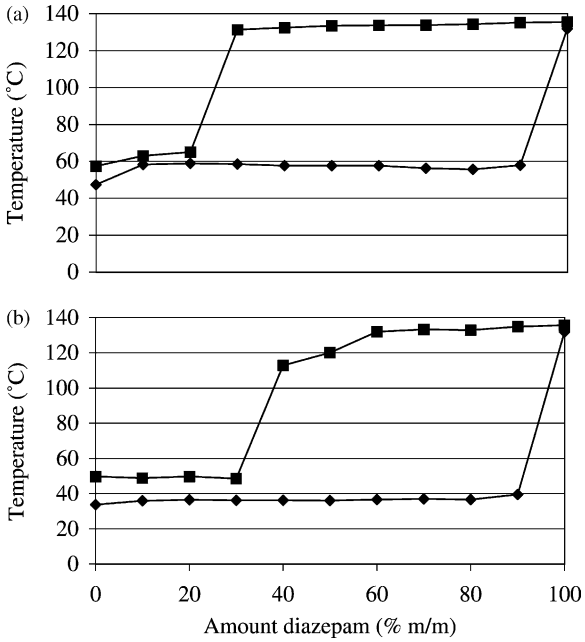

Fig. 1. Phase diagrams of binary mixtures of diazepam and binder. (a) PEG 3000 and (b) Gelucire 50/13. Start of melting (◆) and end of melting (■).

The massing time needed to produce agglomerates of similar size is seen to be shorter for PEG 3000 than for Gelucire 50/13 when the pump-on procedure was used (Table 2). The shorter massing time for PEG 3000 results in a lower maximum product temperature when a high maximum temperature was intended.

Generally, the yield for all experiments was found to be within the range of 90–95%. Gelucire 50/13

Table 1
Physical properties of the binders

Type of binder	Pycnometric density (g/cm^3)	Density (melted) (g/cm^3)		Melting temperature (°C)		Viscosity (mPa s)	
		60 °C	80 °C	Range	Peak	60 °C	80 °C
PEG 3000	1.238	1.09	1.08	47–58	56	306	172
Gelucire 50/13	1.116	1.00	0.99	34–50	44	70	40

Table 2
Effects of type of binder, amount of diazepam, maximum product temperature, and cooling procedure (fluidised bed or nitrogen) on the amount of agglomerates >4 mm, agglomerate size (d_{gw}) and size distribution (s_g), and the shape factor (e_R) of the agglomerates

Binder	Amount diazepam (% m/m)	Massing time (min)	Maximum temperature (°C)	Agglomerates >4 mm (%)	Fluidised bed			Nitrogen		
					d_{gw} (μm)	s_g	e_R	d_{gw} (μm)	s_g	e_R
PEG 3000[a]	15	5 ± 1	61.9 ± 0.3	20.7 ± 1.9	1008 ± 134	1.7 ± 0.1	0.137 ± 0.069	943 ± 27	2.0 ± 0.1	−0.021 ± 0.005
PEG 3000[a]	15	11 ± 1	79.6 ± 0.5	10.5 ± 1.6	798 ± 6	1.9 ± 0.1	0.367 ± 0.005	1242 ± 61	1.7 ± 0.0	0.038 ± 0.025
PEG 3000[b]	15	19 ± 1	77.1 ± 0.6	4.8 ± 0.2	702 ± 20	1.3 ± 0.0	0.239 ± 0.004	1184 ± 17	1.6 ± 0.0	0.004 ± 0.005
PEG 3000[a]	30	6 ± 1	61.6 ± 0.5	24.1 ± 1.3	1107 ± 47	1.6 ± 0.0	0.099 ± 0.006	1052 ± 4	2.0 ± 0.1	0.000 ± 0.031
PEG 3000[a]	30	7 ± 0	74.9 ± 0.2	12.3 ± 0.9	677 ± 15	1.9 ± 0.0	0.287 ± 0.013	1068 ± 11	1.9 ± 0.1	−0.018 ± 0.003
Gelucire 50/13[a]	30	23 ± 2	85.0 ± 0.2	1.4 ± 0.2	877 ± 104	1.3 ± 0.0	0.401 ± 0.033	1012 ± 67	1.4 ± 0.0	0.166 ± 0.035
Gelucire 50/13[b]	30	20 ± 0	84.9 ± 0.5	1.6 ± 0.2	950 ± 23	1.3 ± 0.0	0.337 ± 0.002	1214 ± 14	1.5 ± 0.1	0.244 ± 0.005
Gelucire 50/13[a]	40	25 ± 1	84.4 ± 1.2	2.7 ± 1.5	812 ± 13	1.4 ± 0.1	0.364 ± 0.007	963 ± 22	1.5 ± 0.1	0.071 ± 0.019

[a] Binder addition by the pump-on procedure.
[b] Binder addition by the melt-in procedure.

is seen to give rise to a lower amount of agglomerates >4 mm compared to PEG 3000 (Table 2). Furthermore, a high maximum product temperature is seen to reduce the amount of agglomerates >4 mm. Both effects can be explained by a lower binder viscosity, which causes a better distribution of the binder. Adding the PEG 3000 by the melt-in procedure is seen to result in a lower amount of agglomerates >4 mm compared to the pump-on procedure, probably due to a better distribution of the binder.

Cooling the agglomerates in liquid nitrogen is seen to result in larger agglomerates compared to agglomerates cooled in the fluidised bed (Table 2). Micrographs of fluidised bed cooled agglomerates (Fig. 2a) show single and almost spherical agglomerates and a few agglomerates consisting of clusters of small agglomerates, whereas micrographs of nitrogen cooled agglomerates mainly show agglomerates that consist of clusters of small agglomerates (Fig. 2b). By fluidisation the tendency for the wetted agglomerates to stick together is reduced, probably because the agglomerates are moving during cooling. This is seen for all experiments except for experiments with PEG 3000 at a low maximum temperature where fluidised bed cooling increases the size instead. This was due to a less efficient fluidisation since the agglomerates contained a high amount of larger agglomerates before the start of cooling.

Table 2 shows that Gelucire 50/13 gives rise to a narrower agglomerate size distribution compared to PEG 3000. The shape factor describes the deviations from the ideal round shape and the surface irregularities (Podczeck and Newton, 1994). The ideal value for the shape factor is 1.0. However, a value of 0.6 is often accepted to indicate spherical agglomerates with a smooth surface (Podczeck and Newton, 1995). Fluidised bed cooling results in higher values of the shape factor (Table 2) indicating that the agglomerates are rounder and of a more regular surface structure. Cooling in nitrogen gives rise to low or even negative values of the shape factor indicating very irregular agglomerates. This is in accordance with the sticking together seen in Fig. 2b. Performing the melt agglomeration at the higher maximum product temperature causes a slightly higher value of the shape factor due to less sticking together.

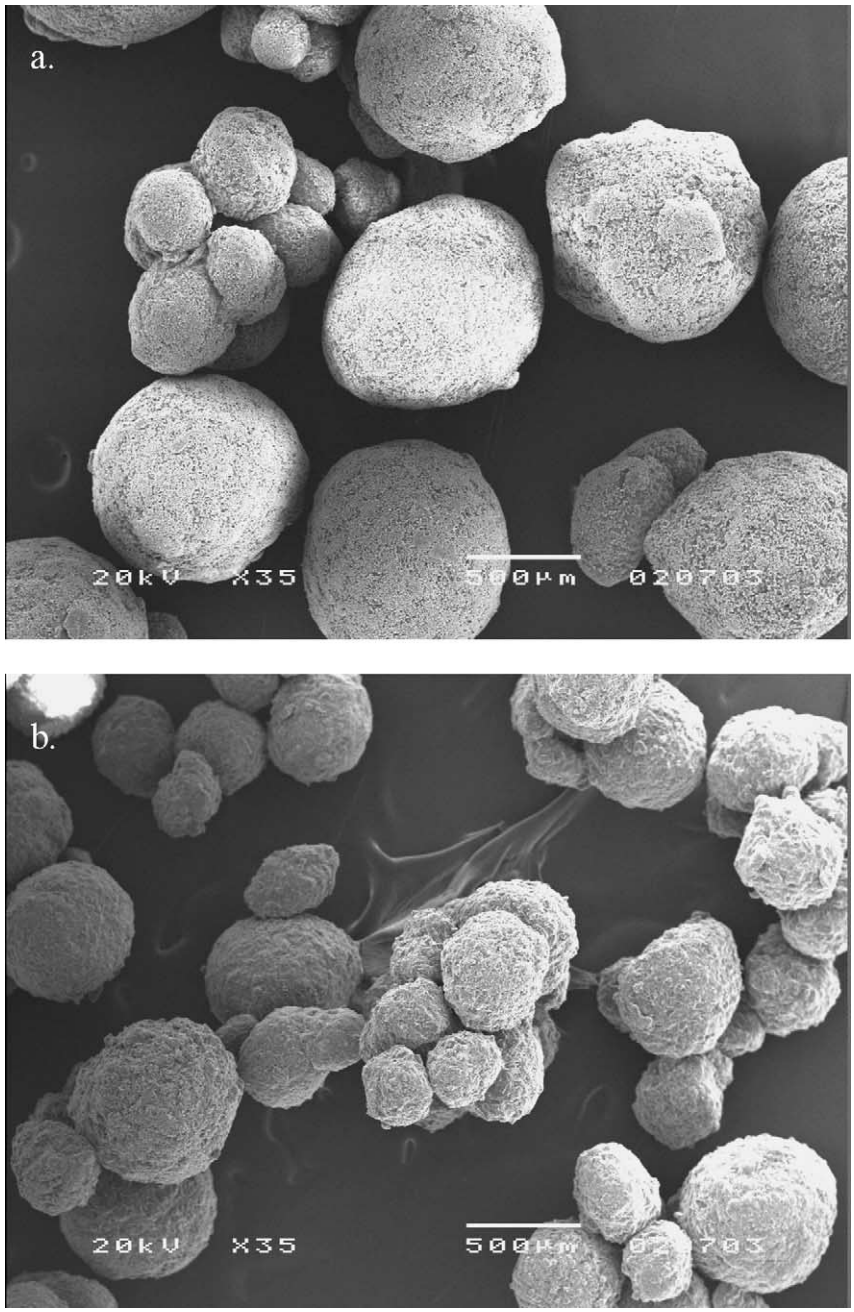

Fig. 2. SEM micrographs of agglomerates produced with PEG 3000 at a high product temperature and with 15% diazepam. Binder addition procedure: pump-on. (a) Fluidised bed cooled and (b) liquid nitrogen cooled.

3.4. Dissolution studies

Diazepam is a weak base and has consequently a pH-dependent aqueous solubility. The solubility increases at decreasing pH (Mason et al., 1981; Nunez and Yalkowsky, 1998). The 0.2 M phosphate buffer (pH 6.8) was chosen as a dissolution medium to allow a better distinction between the different agglomerate formulations. The pH of the dissolution medium was unchanged after completed dissolution. The content of approximately 6.8 mg of diazepam in the samples used for the dissolution tests corresponds to approximately 15% of the aqueous saturation solubility at 25 °C at the pH 6.8.

The dissolution rate of pure diazepam is seen to be markedly lower than the dissolution rate of diazepam from all the agglomerates containing diazepam and PEG 3000 (Fig. 3). This is because the diazepam is dissolved or finely dispersed in the PEG 3000, which acts as a hydrophilic carrier.

Increasing the diazepam concentration from 15 to 30% results in lower dissolution rate (Fig 3a). At the lower concentration, a larger part of the diazepam will be dissolved in the PEG 3000 resulting in a higher dissolution rate. This explanation is supported by the phase diagram (Fig. 1a), which shows that a solid solution cannot be obtained if the diazepam concentration exceeds 20–30%. At the higher product temperature (Fig. 3b), the effect of the diazepam concentration on the dissolution rate is less clear. For agglomerates cooled in nitrogen the same effect is seen as for agglomerates produced at the lower temperature, whereas agglomerates cooled in fluidised bed show no effect of the diazepam concentration.

No clear effect of the maximum product temperature on the dissolution rate is seen, although there seems to be an interaction between product temperature and cooling procedure (Fig. 3a and b) as will be discussed below.

The fluidised bed cooling resulted in a cooling rate of approximately 2 °C/min whereas cooling in nitrogen gave rise to an immediate cooling of the agglomerates. The dissolution rate of diazepam from agglomerates produced at the lower product temperature showed no effect of the cooling procedure (Fig. 3a). At the higher product temperature (Fig. 3b), the cooling procedure has no effect on the dissolution rate at a diazepam concentration of 30%, whereas the dissolution of diazepam was faster for agglomerates cooled in nitrogen compared to fluidised bed at a diazepam concentration of 15%. This effect of the cooling procedure was confirmed by the melt-in experiments (Fig. 3c).

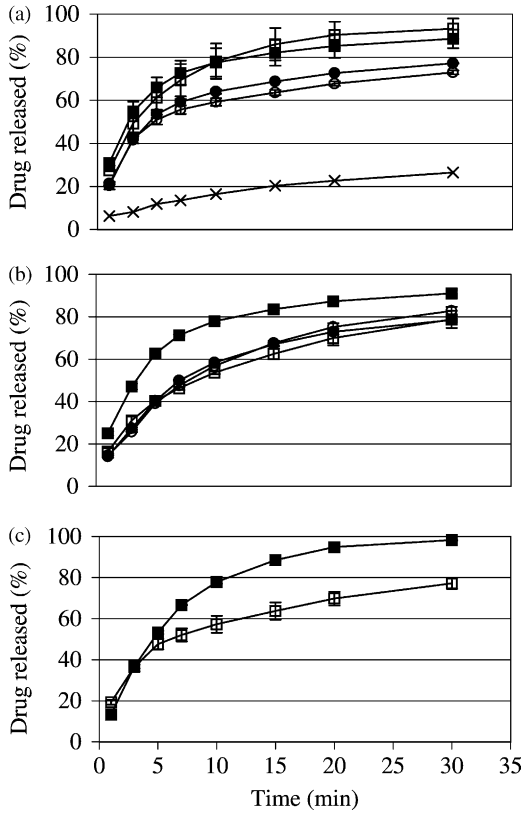

Fig. 3. Effects of drug concentration, cooling procedure, maximum product temperature, and method of binder addition on the dissolution of diazepam from agglomerates containing diazepam and PEG 3000. (a) Pump-on, product temperature approximately 62 °C; (b) pump-on, product temperature approximately 75–80 °C; and (c) melt-in, product temperature approximately 77 °C. Pure diazepam (×). 15% diazepam: fluidised bed cooled (□), liquid nitrogen cooled (■); and 30% diazepam: fluidised bed cooled (○), liquid nitrogen cooled (●).

Admixing the PEG 3000 by the melt-in procedure (Fig. 3c) results in dissolution profiles that are similar to those obtained by the pump-on procedure (Fig. 3b). This indicates that the mixing in the high shear mixer is so efficient that it is unnecessary to dissolve/disperse the diazepam in the melted PEG 3000 before the binder addition in order to obtain an optimal dissolution/dispersion of the diazepam.

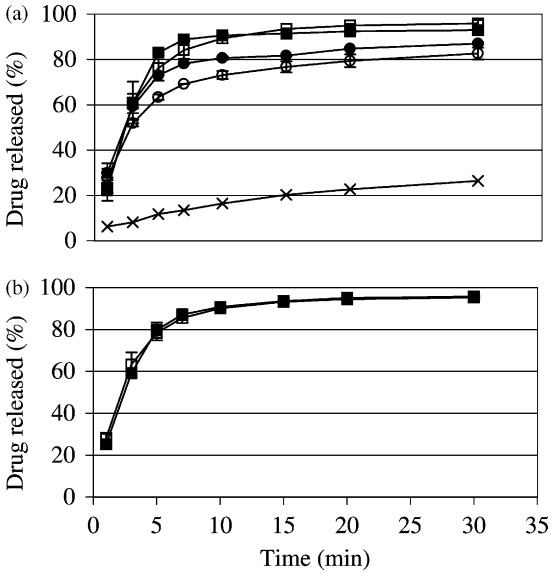

Fig. 4. Effects of drug concentration, cooling procedure, and method of binder addition on the dissolution of diazepam from agglomerates containing diazepam and Gelucire 50/13. Product temperature approximately 85 °C. (a) Pump-on and (b) melt-in. Pure diazepam (×). 30% diazepam: fluidised bed cooled (□), liquid nitrogen cooled (■); and 40% diazepam: fluidised bed cooled (○), liquid nitrogen cooled (●).

Using Gelucire 50/13 as the binder/carrier instead of PEG 3000 results in a higher dissolution rate at the lower as well as the higher diazepam concentration (Fig. 4). This is in accordance with previous studies showing that dispersions in Gelucire 50/13 result in a faster dissolution rate compared to PEGs of different molecular weights (Serajuddin et al., 1988) probably due to the surface activity of Gelucire 50/13, which further increases the degree of dispersion. As for the PEG 3000, a higher diazepam concentration decreases the dissolution rate (Fig. 4a). The phase diagram (Fig. 1b) indicates that a solid solution cannot be obtained if the diazepam concentration exceeds 30–40%. The effect of the cooling procedure is seen to be minor with the Gelucire 50/13. The melt-in procedure (Fig. 4b) results in similar dissolution profiles as the pump-on procedure (Fig. 4a) in accordance with the results for the PEG 3000.

The fact that a clear effect of the cooling procedure on the dissolution rate is seen only for the PEG 3000 and at a single combination of product temperature and diazepam concentration indicates a complex effect of the thermal history of the agglomerates. Several studies have shown that the preparation conditions, for example, maximum manufacturing temperature, time at maximum temperature together with the cooling rate, might have a profound effect on the structure of the prepared solid dispersion, for example, the drug particle size and the degree of crystallinity of the drug and the carrier (Craig and Newton, 1991; Lloyd et al., 1997; Naima et al., 2001; Verheyen et al., 2001). Accordingly, the dissolution rates of solid dispersions have been found to depend on the manufacturing temperature, giving faster release rates when a higher temperature was applied (Ginés et al., 1996). The cooling rate has also been shown to affect the dissolution rate. The results, however, are contradictory. For example, flash-cooled dispersions resulted in faster release compared to slow-cooled dispersions (McGinity et al., 1984). On the other hand, experiments have shown that a faster dissolution rate was obtained when slow cooling rate conditions were applied (Doshi et al., 1997).

Contrary to the above results previous studies have shown no effect of neither manufacturing temperature (Lloyd et al., 1999) nor cooling rate (Craig and Newton, 1992) on drug release. These results suggested that the systems studied had a carrier controlled dissolution. In a carrier controlled system, the dissolution rate of the dispersion is solely depending on the dissolution rate of the carrier. Manufacturing temperature and cooling rate will only be important if these conditions change the carrier and thereby the dissolution rate of the carrier. The minor effect of cooling rate on the dissolution rate in the present experiments could indicate that the diazepam–PEG 3000 and diazepam–Gelucire 50/13 agglomerate formulations are carrier controlled systems.

The interpretation of the results is difficult, however, since the dissolution rate might be affected by differences in agglomerate structure (Table 2 and Fig. 2). Agglomerates with a less spherical shape and an irregular surface, that is, a lower e_R-value, will have a larger surface area compared to agglomerates of similar size with spherical shape and regular surface. A larger surface area is expected to result in a higher dissolution rate. This might explain the faster dissolution rate that is observed for the nitrogen cooled agglomerates compared to fluidised bed cooled agglomerates (Fig. 3b and c). However, the faster dissolution rate obtained with Gelucire 50/13

compared to PEG 3000 (Figs. 3 and 4) cannot be explained by differences in surface area, because agglomerates with Gelucire are more spherical and regular than agglomerates with PEG 3000 (Table 2).

4. Conclusions

The present study has shown that it is possible to increase the dissolution rate of a poorly water-soluble drug by melt agglomeration with a hydrophilic binder in a high shear mixer. Furthermore, the study showed that it was unnecessary to dissolve/disperse the diazepam in the melted binder/carrier before the binder addition since a simple dry mixing and heating procedure resulted in the same dissolution profiles. Thus, melt agglomeration in a high shear mixer seems to be a suitable way of producing agglomerates containing solid solutions or dispersions since it will be possible to scale-up such a process.

A higher dissolution rate was obtained with a lower drug concentration indicating a higher degree of molecular dispersion at the lower concentration. Only minor effects of maximum product temperature and cooling procedure on the dissolution rate were observed. This indicates that the dissolution rate is controlled mainly by the selection of meltable binder/carrier.

Gelucire 50/13 gave rise to faster dissolution rates compared to PEG 3000. Further, the dissolution rates of the Gelucire 50/13 formulations were less sensitive to the cooling procedure compared to the PEG 3000 formulations.

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