Chapter 3
Anomalous dissolution behaviour of tablets prepared from sugar glass based solid dispersions

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3.1. Summary

In this study, anomalous dissolution behaviour of tablets consisting of sugar glass dispersions was investigated. The poorly aqueous soluble diazepam was used a lipophilic model drug. The release of diazepam and sugar carrier was determined to study the mechanisms governing dissolution behaviour. The effect of carrier dissolution rate and drug load was tested with four different sugars; in the order of decreasing dissolution rates: sucrose, trehalose, and two oligo-fructoses; inulinDP11 and inulinDP23 having a number average degree of polymerization (DP) of 11 and 23, respectively. Diazepam was incorporated in these sugar glasses in the amorphous state by means of freeze drying using water and tertiary butyl alcohol as solvents. None of the tablets disintegrated during dissolution. Dissolution of 80% of the lipophilic drug within 20 minutes, was found when diazepam and sugar dissolution profiles coincided. The sugar carrier and diazepam dissolved at the same rate, which was constant in time and fast. This condition was met for relatively slow dissolving carriers like the inulins or for low drug loads. For relatively fast dissolving carriers like sucrose or trehalose with high drug loads, release profiles of diazepam and sugar did not coincide: diazepam dissolved much more slowly than the sugars. In case of non-coinciding release profiles, diazepam release was split into three phases. During the first phase non-steady state dissolution was observed: diazepam release accelerated and a drug rich layer consisting of crystalline diazepam was gradually formed. This first phase determined the further release of diazepam. During the second phase a steady state release rate was reached: zero-order release was observed for both drug and carrier. During this phase the remaining (non-crystallised) solid dispersion is dissolved without the further occurrence of crystallization. The third phase, starting when all carrier is dissolved, involved the very slow dissolution of crystallised diazepam, which was present either as the skeleton of a tablet resulting in a zero-order release profile or as separate particles dispersed in the dissolution medium resulting in a first-order release. To understand the anomalous dissolution behaviour, a model is proposed. It describes the phenomena during dissolution of amorphous solid dispersion tablets and explains that fast dissolution is observed for low drug loads or slow dissolving carriers like inulin.

3.2. Introduction

Drug dissolution is a prerequisite for absorption from the gastro-intestinal tract. However, after oral administration dissolution of drugs poorly soluble in aqueous solutions (lipophilic drugs) is often slow and irreproducible due to the aqueous environment of the gastro-intestinal lumen. As a result, the oral bioavailability of class II drugs [1] (highly permeable over the intestinal membrane and poorly soluble) can be improved by increasing the dissolution rate of the drug [77, 83, 147, 171]. The application of dispersions is one of the strategies applied to increase

the dissolution rate of lipophilic drugs in aqueous environments. They consist of a hydrophilic carrier incorporating very small particles of the lipophilic drug, preferably in the amorphous state [32, 73, 83, 145, 172]. The expected increase in bioavailability (up to 600%) by using solid dispersions is confirmed in many in-vivo studies [2-6].

However, effects governing the dissolution rate enhancement obtained with solid dispersions remain unexplained. Publications on the fast release of drugs from solid dispersions are ubiquitous, but Craig [32] justly remarked that only few of them focus on the mechanism of release and the parameters that dominate the dissolution process. The influence of carrier is not fully understood. Moreover, the effect of drug load on the release rate of drugs from solid dispersions is ambiguous: in some studies a faster release of drug was observed upon lowering the drug load [30, 71, 72], yet in other studies a faster release of drug was seen at higher drug loads [73-75].

The first approach to explain the dissolution rate of a solid was developed by Noyes and Whitney [27]. They claimed the dissolution rate to be proportional to the difference between bulk concentration and concentration at the dissolving interface. Nernst and Brunner [76] introduced the diffusion layer model. They assumed that dissolution at the solid-liquid interface is rapid and transport of the solute to the bulk is completely determined by diffusion through a stagnant boundary layer surrounding the dissolving interface. The dissolution rate of a solid is then given by:

$$\frac{dm}{dt} = A\frac{D}{\delta}\left(C_s - C_{bulk}\right) \qquad \text{(eq.1)}$$

in which *dm/dt* is the dissolution rate ($kg \cdot s^{-1}$), A represents the area available for dissolution, D the diffusivity of the dissolving compound in the solvent, δ the thickness of stagnant boundary layer, C_s is the equilibrium solubility and C_{bulk} is the concentration in the bulk.

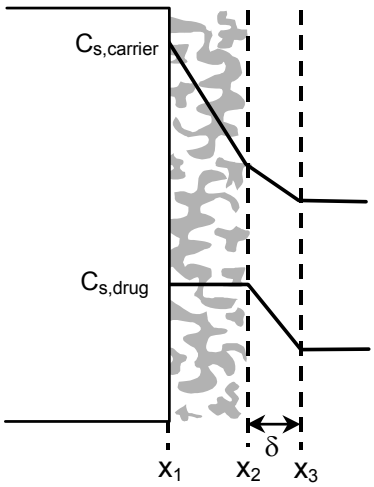

Figure 1: Concentration profiles of drug and carrier during dissolution of a binary mixture according to Higuchi et al.[82]

However, the dissolution rate of a two component system can be more complex. Higuchi et al. [82] investigated a uniform, intimate, non-disintegrating mixture of two dissolving compounds both in crystalline state. One of the compounds (e.g. the carrier: *C*) generally dissolves faster, resulting in a porous layer consisting of the other compound (e.g. the lipophilic drug: *D*) (see figure 1). Higuchi et al. investigated the effect of this layer and the composition of the mixture on the dissolution rate of the fast dissolving component *C*. In fact the deceleration of the dissolution of *C* was discussed while dissolution of *D* was assumed to remain unchanged. They considered only the steady state release portion of the problem and assumed that in the porous layer the concentration of *D* is equal to its solubility ($C_{Drug} = C_{s,Drug}$). This implies that no supersaturation of *D* occurs in the liquid compartment of the porous layer. It also implies a constant flux of *D* to the bulk, since the thickness of the stagnant boundary layer δ will be constant [82]. Although solid dispersions consist of a two component system, the Higuchi model apparently fails for these systems, since a rapid release of the lipophilic component is often observed. For three reasons the dissolution of amorphous solid dispersions can not be described in this way. Firstly because accelerated dissolution is obtained from non-disintegrating solid dispersion tablets when compared to crystalline mixtures. Therefore, supersaturation of *D* must be present during dissolution of a solid dispersion. A second complication is that in general the extent of supersaturation can change in time. Whereas thirdly, when the supersaturation is too large due to fast dissolution of the carrier, crystallization of the lipophilic drug at the tablet surface may occur. It has been observed that crystallization can influence dissolution behaviour of solid dispersions [71, 72, 83-85]. Both supersaturation and crystallization kinetics will affect dissolution behaviour. It was stated that non-steady state dissolution (yielding sigmoidal release) during the first part of dissolution, in fact largely determines the dissolution rate especially when a large solubility difference exists between carrier and drug [82, 84]. However, non-steady state release behaviour was assumed to be negligible in Higuchi's description

This study focuses on the mechanisms of dissolution of fully amorphous solid dispersions. In this study tablets are investigated to monitor the in-vitro dissolution of solid dispersions. They consist of two non-interacting, non-complexing compounds that largely differ in solubility: a sugar as carrier and diazepam as a model drug. Four different sugars with different dissolution rates were used and various drug loads were tested. To obtain insight in the dissolution mechanism, both diazepam and sugar release profiles were monitored during dissolution experiments.

3.3. Materials

The following materials were used as supplied: tertiary butanol (TBA), Anthrone reagent, trehalose and sucrose. Two inulins, type TEX!803 and HD001111, having a number average degree of polymerization of 23 (inulinDP23) and 11 (inulinDP11) respectively, were a gift from Sensus, Roosendaal, The Netherlands.

Diazepam was provided by BUFA B.V. Uitgeest, The Netherlands. The water used was demineralised in all cases.

3.4. Methods

3.4.1. Determination of solubilities

An excess of the sugar of interest was added to demineralised water of 37°C. The suspensions were stirred continuously in a closed vessel while keeping the temperature at 37°C. After 2 weeks equilibration, the suspensions were centrifuged and the supernatant was collected and stored in a closed beaker at 45°C to prevent crystallization. Samples were diluted and the sugar concentration was determined by means of the Anthrone assay (see below).
Diazepam solubility was determined in water and in saturated sugar solutions to evaluate whether the sugars used in this study had a solubilizing effect on diazepam. An excess of diazepam was added to water and to saturated sugar solutions. The suspensions were stirred continuously in a closed vial while keeping the temperature at 37°C. After about 2 weeks, the suspensions were centrifuged (3000 rpm) and the diazepam concentration of the supernatant was measured (see below).

3.4.2. Determination of sugar concentration

To determine the sugar concentrations the Anthrone assay was used [173]. Samples of 1.00 ml were mixed with 2.00 ml Anthrone reagent 0.1%w/v in concentrated sulphuric acid. Due to the enthalpy of mixing, the sample was heated to its boiling point. The boiling mixture was then cooled to room temperature. After 45 minutes the sample was vortexed and 200 µl of sample was analysed in a plate reader (Benchmark Platereader, Bio-Rad, Hercules, USA) at 630 nm. In every Anthrone assay run an 11 point calibration curve of the appropriate sugar in the appropriate medium was also determined (concentration range 0 to 0.100 mg/mL).

3.4.3. Determination of diazepam concentration

Concentrations of diazepam in water were determined spectrophotometrically at a wave length of 230 nm. Calibration curves were established from 0 to 0.020 mg/ml.

3.4.4. Determination of viscosity

First, Newtonian behaviour of the saturated sucrose solution was confirmed with a rotation viscosimeter operating at various rotation speeds (data not shown). Subsequently, an Ubbelohde viscosimeter (Fisher Scientific) was used to determine the relative viscosity of the saturated sugar solutions. The viscosimeter was placed in a water bath of 37°C. The viscosimeter was filled with the sugar solution and

equilibrated for about 30 minutes. The time necessary for the liquid to flow through the capillary was measured 5 times. Densities of solutions of 37°C were determined at least 5 times by weighing 5.00 mL in a closed erlenmeyer. The flow times of water and sugar solutions were used to calculate the relative viscosity according to equation 2.

$$\eta_r = \frac{\rho_{sol} t_{sol}}{\rho_w t_w} \qquad \text{(eq.2)}$$

where η_r is the relative viscosity, ρ_{sol} and ρ_w represent the densities of the sugar solutions and water respectively and t_w and t_{sol} are the times necessary to flow through the capillary for water and the sugar solutions respectively.

3.4.5. Preparation of solid dispersions

Solid dispersions were prepared as described before [174, 175]. The sugar carrier was dissolved in water and diazepam in tertiary butyl alcohol (TBA). After mixing the solutions, the mixture was immersed in liquid nitrogen until the solution was fully frozen. Placebo material was produced in the same way except that in the TBA no drug was dissolved. For lyophilization the frozen solution was placed in 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. Firstly, 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 raised to 20°C. These conditions were maintained for another day. After removing the samples from the freeze drier, they were placed in a vacuum desiccator over silica gel at room temperature for at least 1 day. This procedure results in fully amorphous sugar glass dispersions as was discussed in a previous study [174].

3.4.6. Differential Scanning Calorimetry (DSC)

To determine the degree of crystallinity of diazepam, a differential scanning calorimeter (DSC2920, TA Instruments, Gent, Belgium) operating at a linear heating rate of 10°C/min was used. The heat of fusion of crystallised diazepam was calculated from the peak area of the melting endotherm. The heat of fusion of pure crystalline drug was determined in a separate experiment. The ratio of these fusion enthalpies was used to calculate the crystallinity of diazepam. It was found that the solid dispersions used throughout this study contained all fully amorphous diazepam as indicated in figure 2. One glass transition was observed at the same temperature as the sugar carriers. However, no glass transition of diazepam was observed. Diazepam was incorporated without plasticising the sugar carriers. Apparently, diazepam does not interact with sugars in the solid state. Similar behaviour has been reported before [174].

3.4.7. Preparation of physical mixtures

Physical mixtures were prepared of crystalline diazepam with amorphous sucrose, trehalose, inulinDP11 or inulinDP23, respectively. The amorphous sugars were obtained by freeze drying from TBA/water mixtures of 40%v/v TBA, without any drug. Diazepam and amorphous sugar were gently mixed with a spatula in a mortar to yield a physical mixture of 10%w/w drug. After that the mixtures were stored in a desiccator over silicagel.

3.4.8. Tabletting

In order to prevent moisture induced crystallization of sucrose and trehalose during compaction [129], dry material was taken from the desiccator and processed as rapidly as possible. Solid dispersions or physical mixtures were compressed to 9 mm tablets of about 100mg on a ESH compaction apparatus (Hydro Mooi, Appingedam, The Netherlands). The maximum force of 5kN was reached in 1 second. It was found by means of DSC that the diazepam in tablets prepared from solid dispersions was fully amorphous (figure 2). They were weighed and subsequently subjected to dissolution experiments.

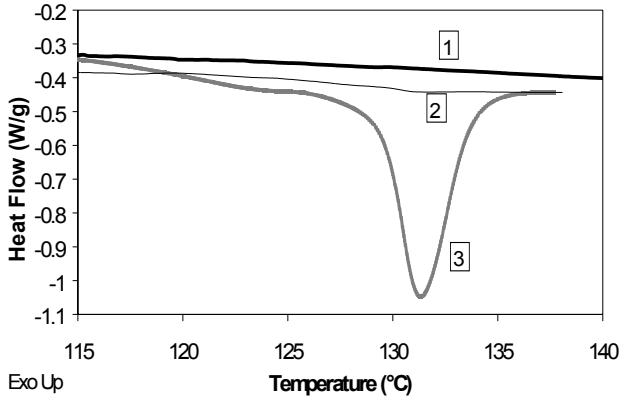

Figure 2: Representative thermograms determined by DSC 1: Solid dispersion inulinDP23 with 20%w/w diazepam. 2: tablet prepared from solid dispersion inulinDP11 with 20%w/wdiazepam before dissolution. 3: tablet prepared from trehalose solid dispersion with 10% diazepam after 5 minutes of dissolution showing a melting endotherm of diazepam (131ºC) which indicates crystallization.

3.4.9. Dissolution experiments

Dissolution was performed on a USP dissolution apparatus II, Rowa Techniek B.V.. All experiments were conducted at 37°C in water with the paddle at 100 rpm. Tablets prepared from physical mixtures, solid dispersions or placebo tablets were analysed in triplicate. To monitor the dissolution of the sugar carrier, 1.00ml samples were taken from the dissolution vessel and subjected to the Anthrone assay

described above. Diazepam concentration in each vessel was measured every 2 minutes spectrophotometrically (Ultrospec III, Pharmacia LKB) at 230nm.

3.4.10. Determination of crystallinity of diazepam during dissolution

To determine the degree of crystallinity of diazepam in the solid dispersion tablets during dissolution, the partially dissolved tablets were removed from the dissolution vessel and immersed in a 20ml vial filled with liquid nitrogen. Subsequently, the tablets were freeze dried according to the procedure described above. The concentration of trehalose as well as the concentration of diazepam was determined in the dissolution medium at the moment the tablet was removed from the dissolution vessel. From the results of these analyses the amount of trehalose and diazepam still present in the removed tablet could be calculated. The tablet of interest was gently ground in a mortar with a pestle in case the remainder of the tablet was not crushed or broken. The obtained powder was weighed in a standard aluminium cup without cover. The crystallinity of diazepam was determined with DSC according to the procedure described above.

3.5. Results

3.5.1. Physical properties of diazepam and sugars in aqueous solutions

Large differences in physical properties of the sugars were found (see Table 1). The aqueous solubilities of both inulins were much lower than those of trehalose and sucrose which were in agreement with literature values [176]. As a consequence the relative viscosities of saturated aqueous inulin solutions were several orders of magnitude smaller than those of the sucrose and trehalose solutions. This implies that the viscosity at inulin-water interfaces is close to that of water, whereas near to trehalose-water or sucrose-water interfaces the viscosity is much higher. Placebo tablets consisting of inulin DP23 dissolved very slowly. This was attributed to formation of a gel layer at the tablet surface during dissolution which could be observed visually. Placebo tablets consisting of inulin DP11, trehalose or sucrose did not disintegrate nor formed a gel layer. Therefore, they showed linear dissolution profiles up to about 80% in water. Inulin DP11 tablets dissolved two times slower than trehalose tablets but sucrose tablets dissolved fastest as can be expected on the basis of their solubilities. From these experiments it is clear that the four sugars used in this study seem to exhibit different dissolution behaviour in water. Furthermore, it was found that at the saturation concentrations of the sugars, diazepam solubility was only slightly increased. This is expected since it is unlikely that the apolar diazepam molecules interact with these sugar molecules. This is in agreement with previous findings that no plasticising effect was observed in the solid state [174].

Table 1: Physical properties of sugars and diazepam at 37°C

	aqueous solubility	density saturated aqueous solution	aqueous solubility	relative viscosity saturated solution	initial dissolution rate 9mm tablet	diazepam solubility in saturated solutions
	(mg/ml)	(kg/m3)	(%w/w)	(-)	(mg/min)	(mg/l)
inulin DP23	50	1005	5.0	1.07	2.6	74
inulin DP11	67	1007	6.6	1.10	20	74
trehalose	600	1212	55	14.5	36	80
sucrose	977	1300	75	246	47	not determined
water	-	-	-	1	-	65
diazepam					1.6	

3.5.2. Effect of carrier dissolution rate at a drug load of 10%w/w diazepam

In-vitro dissolution profiles of solid dispersions were compared with those of physical mixtures. In figure 3 the results are presented. All tablets in figure 3 weighed 100mg and contained 10mg diazepam. The application of inulin DP23 or inulin DP11 as carrier in sugar glass dispersions resulted in largely accelerated dissolution of diazepam.

Dissolution profiles of inulin DP23 and diazepam coincided for solid dispersion tablets (figure 3a). Inulin DP23 from physical mixture tablets dissolved very slowly: a gel layer could be observed during dissolution, just like the placebo tablet with inulin DP23. However, no gel layer was formed during dissolution of the solid dispersion tablets. Apparently, incorporation of amorphous diazepam in the inulin DP23 carrier prevents the formation of a gel layer, thereby accelerating inulin DP23 dissolution. It was found before that carbamazepine release from a solid dispersion also prevented gel layer formation of the carrier poly(vinylpyrrolidone-co-vinylacetate) (PVP/VA). However, only when drug loads were higher than 20% [75].

Inulin DP11 dissolves faster that inulin DP23. This can be seen from table 1 but also from the fast dissolution of inulin DP11 from physical mixture tablets (figure 3b). In contrast to what may be expected, diazepam from solid dispersion tablets with the faster dissolving inulin DP11 was released a little slower than from inulin DP23 solid dispersion tablets. Initially diazepam is released slowly but release gradually accelerates during the first 8 minutes. This phase is followed by a fast and constant release rate of diazepam from inulin DP11 solid dispersion tablets until all inulin DP11 was dissolved. During the third phase the last 20% of diazepam dissolves slowly.

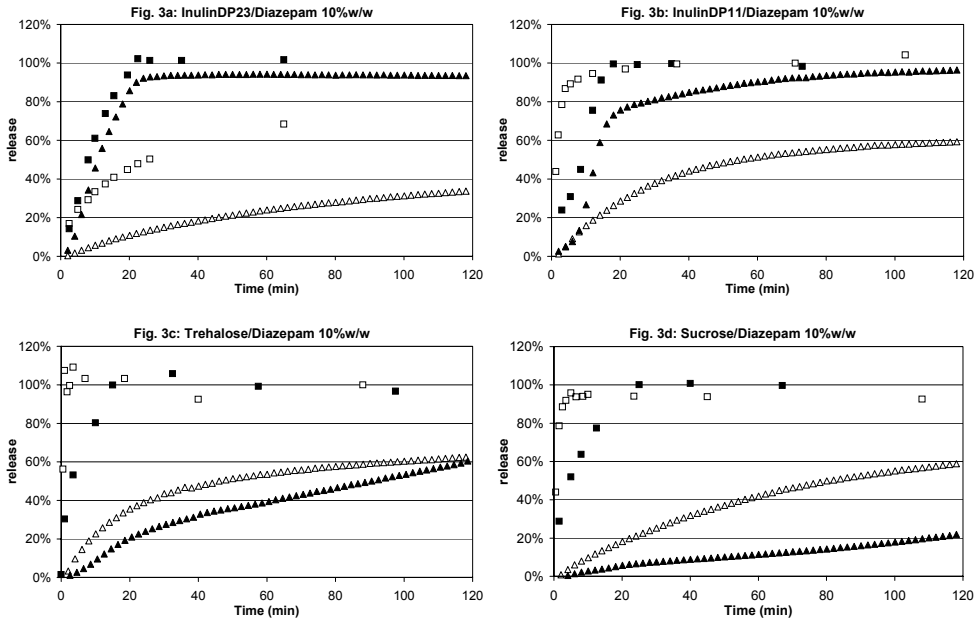

Figure 3: Dissolution of tablets prepared from solid dispersions and physical mixtures containing 10%w/w diazepam prepared with different sugars. 3a: inulinDP23, 3b: inulinDP11, 3c: trehalose, 3d: sucrose. (Key: ■: sugar from solid dispersion, ▲: diazepam from solid dispersion □: sugar from physical mixture, △: diazepam from physical mixture) (n=3 tablets, all s.d.< 10%)

When the faster dissolving disaccharides, trehalose and sucrose were used as carrier they showed similar dissolution behaviour. However, this behaviour is completely different from that of solid dispersions of the inulins. The release of diazepam from solid dispersion tablets of disaccharides was extremely slow, even slower than from physical mixture tablets. Again three phases could be distinguished in the diazepam release from the solid dispersion tablets, but the first phase in which diazepam release is gradually accelerated was very short: about 6 and 4 minutes for trehalose and sucrose, respectively. During the second phase a somewhat faster diazepam release was observed, whereas in the third phase, starting as soon as all carrier was dissolved, the release was even slower but linear in time. In the dissolution beaker a skeleton of a tablet was still visible although all carrier had been dissolved. Such a skeleton consisted of pure crystalline diazepam as was established with DSC. The skeleton structure remained intact resulting in a constant diazepam dissolution rate. Furthermore, it can be seen in figure 3c, 3d and to lesser extend in 3b that the release of sugar carrier from solid dispersion tablets was decelerated compared to physical mixture tablets. This implicates the formation of a drug rich layer consisting of crystalline diazepam, which forms a barrier for dissolved sugar diffusing from the tablet.

The dissolution experiments plotted in figure 3 clearly show large differences in dissolution behaviour. Solid dispersions of inulin accelerate the dissolution of diazepam to a large extent. From a solid dispersion with inulinDP23, release of

carrier and diazepam coincide, which is an ideal release profile. The dissolution rate is constant until carrier and drug are both completely dissolved. A completely different dissolution behaviour is observed in figures 3c and 3d. They show far from coinciding release profiles. In figure 3b an intermediate situation is encountered. In the profiles obtained with sucrose, trehalose and inulinDP11 dispersions, three different phases are distinguished for the diazepam release. During the first phase diazepam release is slow but is gradually accelerated. This is observed during the first 8 minutes for inulinDP11 solid dispersion tablets, during the first 6 minutes for trehalose and during the first 4 minutes for sucrose solid dispersions. Furthermore, it can be observed that during the first minute of this first phase, the carrier quickly dissolves and subsequently slows down, due to the formation of the drug rich layer. The second phase a linear release at higher rate than during the first phase is observed. This linear phase stops as soon as all carrier is dissolved. At that point all that is left is crystalline diazepam. During the third phase this crystalline diazepam dissolves slowly. The geometry of the undissolved crystalline diazepam skeleton, determines the release profile. In figure 3b 20% of the diazepam is left when all inulinDP11 is dissolved. Apparently, this is not enough to form a robust skeleton tablet: diazepam particles will be dispersed in the dissolution medium and dissolve according to a first-order release profile. On the other hand, when all trehalose or sucrose is dissolved, over 80% or 90% of the diazepam is still undissolved: a skeleton of crystalline diazepam is formed, yielding a zero-order release of diazepam. Similar behaviour was reported before by Allen and co-workers for tablets prepared from dispersions of small saccharides like sucrose, mannitol and sorbitol [177]. They attributed the faster release phase to a molecular incorporated fraction and the slow release to a crystalline fraction of the lipophilic drug, which was present due to incomplete dissolution of the drug in the molten sugar during preparation [120]. Since in our study the drug in the sugar glass dispersions was fully amorphous before dissolution, the results imply that crystallization occurred during dissolution of disaccharide solid dispersions.

3.5.3. Crystallization during dissolution

To investigate in further detail the slow release of diazepam from solid dispersion tablets with a disaccharide as carrier, the crystallinity of diazepam was determined by DSC during dissolution. In figure 4 the percentage of diazepam that is crystalline is shown. It can be seen that diazepam present in trehalose solid dispersion tablets crystallised immediately after the tablets came into contact with the dissolution medium. Already after about 3 minutes about 85% of the diazepam was crystallised and after 13 minutes when all trehalose was dissolved, all non dissolved diazepam was completely crystallised. This means that crystallization of amorphous diazepam is the main reason for the slow release of diazepam from solid dispersion tablets. Obviously, crystallization starts immediately after the trehalose tablets are brought into contact with the dissolution medium.

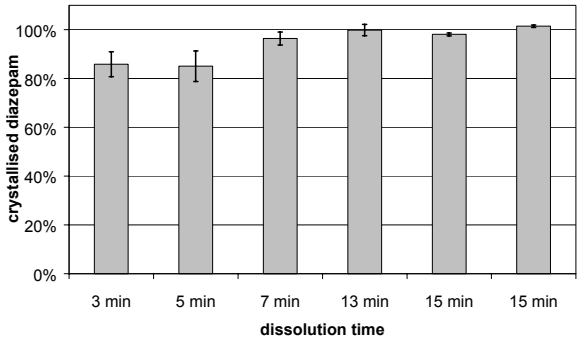

Figure 4: Amount of crystalline diazepam present during dissolution of solid dispersion tablets containing trehalose and 10%w/w diazepam (n=3 DSC, ± s.d)

3.5.4. Decreasing drug loads in trehalose and sucrose solid dispersion tablets

It was investigated whether diazepam crystallization could be inhibited or prevented by decreasing the drug load. If the drug load in sucrose solid dispersions was decreased from 10% to 7%, diazepam was released faster in the first stage of dissolution (figure 5a), but a second slower phase still appeared as soon as all sucrose carrier was dissolved. The same results were found for trehalose (data not shown). However, if only 3.3% diazepam was incorporated in sucrose solid dispersions, dissolution of diazepam and carrier coincided completely and diazepam was released rapidly from these tablets (figure 5b). Furthermore it was noticed that upon decreasing the drug load, sucrose dissolution was accelerated and became comparable to the dissolution rate of pure sucrose. The same behaviour was found for trehalose (data not shown). This implies that at 3.3% drug load no drug rich layer consisting of crystallised diazepam was formed during dissolution.

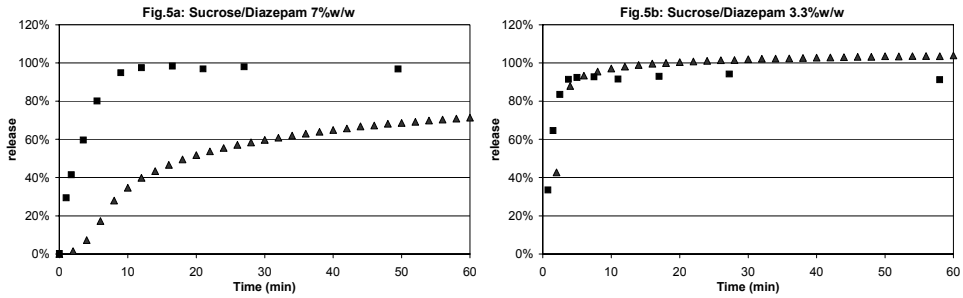

Figure 5: Dissolution of sucrose solid dispersion tablets with 5a: 7% diazepam, 5b: 3.3% diazepam (Key: ■: sucrose release, ◢: diazepam release) (n=3 tablets, all s.d.< 8%)

3.5.5. Increasing the drug load in inulin solid dispersion tablets

Finally, it was tested whether diazepam crystallization could be induced in inulin solid dispersions by increasing the drug load. When the drug load in inulinDP23 solid dispersion tablets was increased from 10 to 20%, diazepam and inulinDP23 dissolution profiles still almost coincided (figure 6a) and diazepam was released fast. However, the three phases described above could now be discerned. The first phase was observed up to 10 minutes, and the second up to 25 minutes. When inulinDP11 was used as carrier at a drug load of 20% the three phases were much more pronounced. A large difference was seen between carrier and diazepam release (figure 6b), implying the formation of a drug rich layer of significant thickness and a long period of non-steady state dissolution. Again, it was found that during the first phase, the dissolution rate of diazepam was not constant but gradually increased followed by a second phase of constant dissolution rate. The third phase started when all carrier was dissolved and involved the dissolution of particles of crystalline diazepam: no skeleton was seen at the start of the third phase, and therefore a first-order release instead of zero-order as found for trehalose and sucrose was observed.

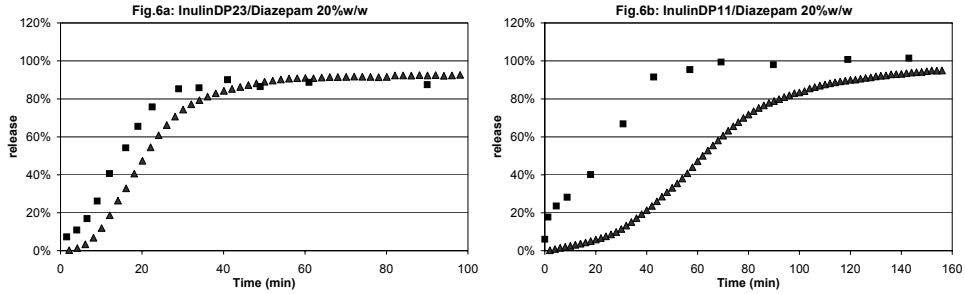

Figure 6: Dissolution of solid dispersion tablets containing 20% diazepam based on 6a: inulinDP23, 6b inulinDP11 (Key: ■:inulin release, ◢:diazepam release)(n=3 tablets, all s.d.<7%)

3.6. Discussion

Overlapping release profiles of drug and sugar are observed when diazepam does not crystallise during dissolution of solid dispersions. Diazepam is transported to the bulk in dissolved state along with the carrier. This is the ideal situation for solid dispersions: it results in fast dissolution of the lipophilic drug (i.e. 80% dissolved within 20 minutes) and therefore it may result in an increased bioavailability [2-6]. Non-overlapping release profiles are observed when diazepam does crystallise during dissolution. Only a part of the diazepam is transported to the bulk, but a significant part forms a crystalline layer. This results in decelerated release of diazepam and undesired dissolution behaviour. Crystallization is favoured by large supersaturation at the tablet surface. Crystallization starts immediately when the tablet is immersed in the dissolution vessel. Carrier and drug dissolve rapidly but hardly any diazepam is transported to the bulk. This is the beginning of the first

phase. Both carrier and drug dissolve according to a non-linear profile: the first phase shows non-steady state dissolution and involves the formation of a drug rich layer. Drug dissolution is gradually accelerated during the first phase until the release rate is constant in time. The second phase begins when the release rate of drug is constant in time and ends when all carrier is dissolved. Obviously, during the second phase dissolution of the solid dispersion results in diazepam transport to the bulk. The third phase involves dissolution of crystallised drug. A zero-order but very slow release is observed when the amount of drug at the end of phase two is high enough to keep the skeleton intact. In other cases, it will fall apart and crystalline drug particles will be dispersed throughout the dissolution vessel resulting in first-order release.

It is especially useful to understand the first phase, the non-steady state part, because it seems to govern the rest of the dissolution process. In spite of the high viscosity in the boundary layer of tablets with trehalose or sucrose (see table 1), extensive crystallization was observed with these tablets. The differences between the sugars in the extent of crystallization are not caused by differences in the solubility of diazepam since they are very small (table 1). Therefore the observed crystallization differences must be the result of variations in the local drug concentration. The local drug concentration during dissolution of solid dispersions can be much higher than the solubility because amorphous drug is dragged along with the carrier into solution. If the supersaturation is very large, the rate of crystallization will be considerable. Furthermore, the local drug concentration will determine the flux to the bulk according to equation 1. Since it is observed that drug release is not constant during the first phase of dissolution, it can be concluded that the local drug concentration varies in time. In order to understand and predict the dissolution rate, one should know $C_{drug}(t)$ (see figure 7). This is the drug concentration in the liquid compartment of the drug rich layer.

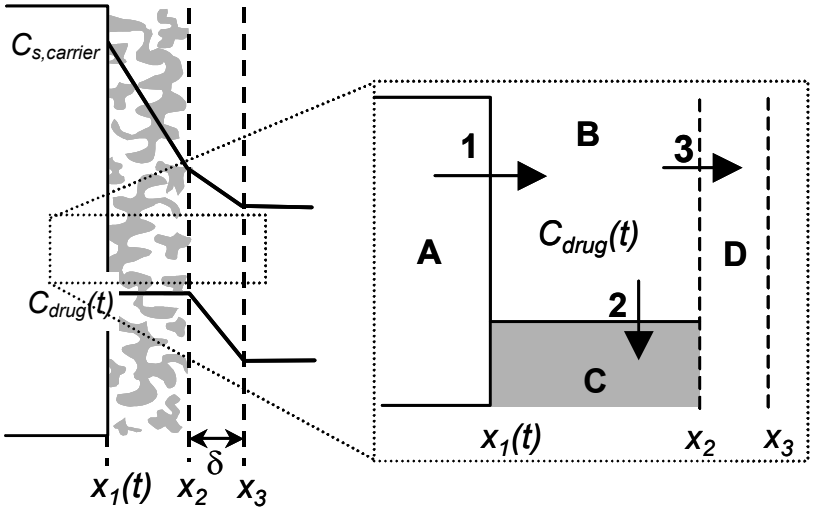

Figure 7: Schematic representation of dissolution behaviour of drug from solid dispersion tablets during phase1 and phase2.

To predict drug release during the non-steady state dissolution phase, it is proposed to set up a mass balance over the drug-rich layer. A model for this is given in figure 7. Four different compartments are distinguished:

A: The undissolved solid dispersion tablet
B: The liquid in the drug-rich layer
C: The crystallised drug in the layer
D: The stagnant diffusion layer

named accordingly in figure 6. During the first phase of dissolution three processes are involved in drug transport:

1.) Dissolution of the solid dispersion, thereby releasing drug from compartment *A* to *B*.
2.) Crystallization of drug (from *B* to *C*)
3.) Release of drug to the boundary layer and bulk (from *C* to *D*)

In the mass balance, it is necessary to allow for volume change of the drug rich layer because in general the dissolving front at x_1 moves with different speed than x_2. It may be expected that a model based on these processes, more accurately describes the dissolution of amorphous solid dispersion tablets compared to Higuchi's model, since the phase transition during dissolution from amorphous to crystalline diazepam is also considered. Furthermore, such a model is capable of dealing with altered dissolution behaviour due to crystallization before dissolution as was described in many studies [30, 74, 121, 178].

The model also explains the second phase observed in the anomalous dissolution profiles. This phase starts when the increasing amount of crystallised drug has decelerated the dissolution of the solid dispersion to such an extent that the rate of drug dissolution from the dispersion (from *A* to *B*) is of the same size s that of the transport from the drug-rich layer to the stagnant diffusion layer (from *B* to *D*). Furthermore it explains why drug and sugar dissolve at the same rate. Obviously, this second phase ends when all solid dispersion is dissolved as indicated by the fact that sugar is completely dissolved at this point in time. This hypothesis is completely in line with the findings for the dispersion of trehalose with 10% diazepam. The second phase covers a release of about 15%. This corresponds with the finding in figure 4 that after 5 minutes (the start of phase two) about 15% of the drug in the tablet is still amorphous. Furthermore, it is learned that crystallization of drug in phase one as observed for the disaccharides starts throughout the entire tablet immediately after contact with water.

From this description it can be learned that the undesired crystallization can be prevented by choosing either a low drug load or a slow dissolving carrier, since in that way initially less drug is transported of drug from *A* to *B*, which results in drug concentrations in compartment *B* that are too low to induce crystallization. The threshold of drug load above which crystallization occurs during dissolution is higher for carriers that dissolve slower. Therefore, inulins are preferred over trehalose and sucrose for carriers in solid dispersion tablets. Obviously, the threshold will also depend on the crystallization kinetics of the drug (process 2), which is affected by the type and solubility of the drug.

3.7. Conclusion

Anomalous dissolution behaviour of tablets prepared from amorphous sugar glass dispersions is found when a fast dissolving sugar carrier is used or when high drug loads are applied in relation to the dissolution rate of the carrier. When diazepam crystallised at the liquid-solid interface to form a drug-rich layer, non-overlapping dissolution profiles of sugar carrier and diazepam were found. When crystallization occurred, dissolution in three phases was observed. The first phase governed the rest of the dissolution process: diazepam release was initially slow but accelerated until all carrier was dissolved. Diazepam release was not constant due to an increasing concentration of dissolved diazepam in the drug rich layer. To predict this non-steady state behaviour, a model was proposed in which crystallization was included.