Chapter 9
Summary

Solid dispersions offer a drug delivery platform that may overcome problems related to the absorption of poorly water-soluble drugs in-vivo. This is ascribed to accelerated dissolution of the drug. Nevertheless, up to now a small number of products based on solid dispersions have reached the market. This is due to difficulties in manufacturing, stabilization, dissolution and formulation as resulting in poor control over the physico-chemical characteristics of the product as outlined in the first chapter. Moreover, research is slowed down by a lack of characterization tools that elucidate the molecular structure of solid dispersions. In this thesis, a new platform technology is investigated that has the potential to overcome many of these problems. We set out to develop solid dispersions consisting of a hydrophilic matrix containing the lipophilic drug. In order to stabilise the system, including the incorporated drug substance, materials for the matrix were investigated which were in the glassy state at normal storage conditions.

Firstly, a new method to prepare solid dispersions of a lipophilic drug in a hydrophilic matrix was developed. It was found that lyophilization of a mixture of water and the organic solvent tertiary butyl alcohol (TBA) is a versatile technique to produce such solid dispersions. The problem of dissolving both the hydrophilic matrix and lipophilic drug was tackled by dissolving the matrix in water and the drug in TBA separately, followed by mixing the two solutions. In the mixture, both matrix and drug are supersaturated: eventually the mixture becomes cloudy due to phase separation. However, an optimal TBA-water ratio of 40%v/v was found: this mixture stayed clear and showed no phase separation for several minutes, which is long enough to freeze the mixture. Clear mixtures were frozen and lyophilised. After lyophilization, solid dispersions were obtained in which the lipophilic drug was incorporated in the matrix. This production method could be performed with a series of different lipophilic drugs among which: diazepam, nifedipine, cyclosporine A, and Δ^9-tetrahydrocannanbinol (THC), which proofed the versatility of this manufacturing technique. The lipophilic drugs were completely amorphous at drug loads up to 20%w/w and showed a minor amount of crystallinity at higher drug loads. A new matrix was introduced: the oligo-fructose, inulin. The use of this sugar was compared with commonly used stabilising sugars, such as trehalose and sucrose. Immediately after preparation, all carriers were completely amorphous. It was concluded that a high physical stability is guaranteed as long as the carriers were in the glassy state. Therefore, a carrier with a higher glass transition temperature, like inulin is preferred over trehalose and sucrose.

The amount of residual organic solvent (TBA) in the solid dispersions after lyophilization, was investigated. TBA levels of about 1-2%w/w were found, which could be further reduced to 0.5%w/w by exposing the solid dispersions to humid

air with a relative humidity of 45%. The amount of TBA is such that toxicity is not an issue. With trehalose and sucrose dispersions, TBA removal was accompanied by crystallization of both sugars, while the inulin dispersions, being in the glassy state, remained fully amorphous.

In chapter 3, the (molecular) distribution of the incorporated drug in amorphous solid dispersions was investigated at the nano-scale. It was shown that Temperature Modulated Differential Scanning Calorimetry (TMDSC) could differentiate between homogeneously dispersed drug molecules and solid dispersions containing amorphous drug clusters. Moreover, TMDSC could quantify the fraction of drug present in clusters. Solid dispersions were prepared by lyophilization as described in chapter 2. When poly(vinylpyrollidone) (PVP) was used as carrier, no glass transition of the lipophilic model drug was observed at drug loads up to 35%w/w, indicating that diazepam was homogeneously dispersed. At higher drug loads, diazepam clusters were detected. When inulin was used as carrier, diazepam clusters were observed at a drug load of 20%w/w or higher. Moreover, it was found that PVP was plasticized by molecular incorporated diazepam, whereas inulin was not. Inulin solid dispersions were also prepared by spray freeze drying, a process in which the freezing rate substantially higher due to the large specific surface area of the droplets and direct contact with the liquid nitrogen. It was found that diazepam clustering now only just occurred at a drug load of 50%w/w or higher. This proofed that the mode of incorporation was significantly affected by the freezing rate and that more diazepam could be molecularly dispersed using spray freeze drying instead of freeze drying. Finally, water vapour sorption experiments showed that the hygroscopicity of PVP was decreased by incorporated diazepam. This was used for the estimation of the size of the amorphous drug clusters in PVP (10 to 20 nm). The size of diazepam clusters in inulin solid dispersions could not be calculated, because the hygroscopicity of inulin was not changed by incorporated diazepam.

In chapter 4, a method is proposed that discriminates between clustered and molecularly dispersed drug molecules. This method is not limited by microscopic resolution, but detects clustering of drug molecules by proving that they are in close proximity at the nanometer scale. Fluorescence Resonance Energy Transfer (FRET) between two model molecules is dependent on the distance between the molecules and is only possible within the Förster distance (3-10 nm). In this study, a lipophilic donor (Bodipy R6G) and a lipophilic acceptor (Bodipy650/665) are introduced to mimic a lipophilic drug that is incorporated into a carrier to form a solid dispersion. The amount of energy transferred from donor to acceptor can be measured by confocal microscopy. First, several control experiments are discussed. Secondly, theoretical considerations show that solid dispersions in which the fraction of lipophilic molecules in amorphous clusters is one (f = 1), the FRET efficiency will be independent of the drug load. Therefore, when an increase in FRET efficiency is observed, this implies that more molecules are clustered. It is concluded that the method proposed in this chapter, can be used to detect the molecular distribution of lipophilic molecules in amorphous solid dispersions with

low drug loads. The full potential of this method can only be revealed when experiments are performed.

In chapter 5, the dissolution behaviour of sugar glass dispersions was investigated. Diazepam was used as model drug. Four different sugar matrices were used sucrose, trehalose, and two types of inulin, having a number average degree of polymerization (DP) of 11 and 23. The solid dispersions were compressed to form tablets without any excipients, like lubricants, fillers, binders or disintegrants. The dissolution mechanism was accurately monitored by measuring both drug and carrier dissolution profiles. Unexpected slow dissolution of diazepam was found when fast dissolving sugar carriers like sucrose or trehalose were used or when high drug loads were applied. This was caused by crystallization of drug during dissolution, which was observed both visually and with differential scanning calorimetry. When diazepam crystallised at the liquid-solid interface to form a drug-rich layer, non-overlapping dissolution profiles of sugar and drug were found. When crystallization occurred, three phases in the dissolution process could be discerned. In the first phase, drug release was initially slow but increased until a constant release phase started. The first phase turned out to be a non-steady state situation, which governed the rest of the dissolution. To predict this non-steady state behaviour, a model was proposed in which crystallization could be included. In the second phase, a constant dissolution rate was reached: the transport of dissolved drug to the drug-rich layer was balanced by crystallization and transportation to the bulk. The release rate in this phase was determined by the dissolution rate of the carrier, which depended not only on carrier type but also on the thickness of the drug-rich layer. The third phase, starting when the carrier was completely dissolved involved dissolution of crystallised drug. However, when applying a slow dissolving matrix, like inulin, supersaturation in the boundary layer of the tablet was reduced, crystallization during dissolution was not observed resulting in a rapid release of the lipophilic drug. Moreover, low drug loads could reduce the supersaturation and hence accelerate the release of lipophilic drug from the solid dispersion tablets. A model was proposed that could describe, at least qualitatively, all phenomena observed in this study. It was concluded that for the fastest release of a lipophilic drug, slow dissolving carriers like inulin or low drug loads are preferred.

In the last part of this thesis, various applications of sugar glass technology are described. Chapter 6 shows the application of inulin glass dispersions for chemical stabilization and formulation of a tablet. The chemically labile and lipophilic THC oxidises completely within 40 days when it is unprotected. However, when THC was incorporated in inulin glasses, not more than 20% degradation was observed after 300 days. Pure THC is a sticky resin and difficult to handle, but the solid dispersion obtained by freeze drying enabled the preparation of formulations. Rapidly disintegrating tablets could be formulated from which 80% of the THC was released within 3 minutes in an aqueous dissolution medium. Therefore, it is expected that the oral bioavailability of this tablet is improved when compared to the oil filled soft gelatine capsule that is currently used and from which hardly any drug dissolves in aqueous dissolution media.

Chapter 7 shows the application of inulin glass dispersions as inhalation powder. Moreover, the use of spray freeze drying is investigated. Spray freeze drying using the water-TBA mixture (40%v/v TBA) as solvent was found to be a suitable process to produce a solid dispersion powder that contains THC incorporated in a glassy matrix of inulin. The spray freeze dried products thus obtained appeared as a fluffy powder that consisted of particles with porosities ranging from 89 to 97%. The THC in solid dispersions prepared by spray freeze drying is effectively stabilised for all drug loads tested. When drug loads of 20%w/w or higher are considered, the stability of THC in spray freeze dried solid dispersions is significantly higher than in freeze dried solid dispersions. The improved stability of the spray freeze dried products was ascribed to the higher cooling rate resulting in more effective incorporation of THC. Moreover, dispersed with an air classifier type inhaler, the different powders generated aerosols with aerodynamic particle size distributions that are suitable for pulmonary administration. Fine particle fractions up to 50% were found in in-vitro inhalation experiments.