Chapter 8
Concluding Remarks and Perspectives

8.1. Concluding remarks

The oligo-fructose, inulin has proven to represent a suitable matrix for amorphous solid dispersions. When compared with other commonly used stabilizing sugars, like sucrose or trehalose, the physico-chemical characteristics of inulin are superior in a number of aspects. As a result, lipophilic drugs were stabilised chemically and physically. When samples were exposed to 45%RH, inulin remains in the glassy state whereas the sucrose and trehalose were readily plasticized by the absorbed water, resulting in increased molecular mobility and phase separation, e.g. crystallization of either matrix or drug. The high glass transition temperature and the low tendency to crystallise are crucial advantages of the oligomer inulin over disaccharides such as sucrose or trehalose. Another significant advantage of inulin was found during dissolution. At a drug load of 10wt-% or higher, dissolution of lipophilic drugs was faster from inulin glass dispersions than from trehalose or sucrose glass dispersions. When compared with another commonly used matrix used for the preparation of amorphous solid dispersions, poly(vinylpyrollidone) (PVP), inulin is the preferred because of its low hygroscopicity and the absence of plasticization by incorporated lipophilic drugs.

In this thesis, the development of a new alternative preparation procedure was reported. It is based on the solvent technique. An aqueous matrix solution was mixed with a drug solution using tertiary butyl alcohol as solvent. When these solutions were mixed in the correct volume ratio, a clear solution could be obtained. However, this solution is not thermodynamically stable. Therefore, the solution is rapidly frozen in liquid nitrogen and subsequently lyophilised to obtain amorphous solid dispersions. This preparation method proofed to be highly versatile, because many different drugs and various matrices could be used. Moreover, this preparation procedure can be used for chemically labile compounds, because temperature stress is brought down to an absolute minimum. Thirdly, during lyophilization solvents can be removed without risking phase separation. Moreover, after lyophilization, vials can be easily closed under vacuum, dry and/or nitrogen atmospheres. Finally, it should be noted that with respect to the duration of the lyophilization cycle, the shelf temperature during primary drying can be 10°C higher when using inulin instead of sucrose or trehalose. This creates the possibility to accelerate the costly lyophilization process.

8.2. Perspectives

All recent reviews criticize the arbitrary or trial-and-error approach that is typical in literature on solid dispersions. Therefore, the main goal in solid dispersion research should be to gain insight rather than reporting case studies. The efficiency of research will increase and studies discussing similar solid dispersions are better comparable. A systematic experimental set up should be favoured. Suggestions below might lead to progress in areas of solid dispersion research that are not yet fully explored.

8.2.1. Characterization related

1.) It was shown in chapter 4 of this thesis that the mode of incorporation could be detected with Temperature Modulated Differential Scanning Calorimetry (TMDSC). Nevertheless another technique is required. Not only because TMDSC is incapable of detecting the mode of incorporation in amorphous solid dispersions with low drug loads, but also because the results need to be confirmed. The further development of Fluorescent Resonance Energy Transfer (FRET) as described in chapter 5, would enable assessment of the reported TMDSC measurements.

2.) A more general relation describing the T_g not only as a function of composition but also using cohesive energy densities of drug and matrix, would gain significant insight in the when and to what extent plasticization of the matrix is expected. The assumption of additivity of the free volumes of drug and matrix, used in the Gordon-Taylor equation might need to be reconsidered when the solubility parameters of matrix and drug are different.

8.2.2. Stability related

1.) Question remains about what physical property of the matrix best predicts its stabilizing capacity. What is the validity of the rule of thumb of storage 50°C below the T_g? Is a sudden decrease in crystallization rate observed at the T_g or lower, for example at the Kauzmann temperature? Crystallization rates should be monitored for samples stored at different temperatures. Furthermore, crystallization has never been investigated in relation to drug-matrix interaction and drug-matrix compatibility.

2.) A clear description of the optimal matrix properties for chemical stabilization of a labile drug should be investigated. Is the vitrification or drug-matrix interaction more important? This question is also relevant for solid dispersions with hydrophilic molecules like proteins when stabilized in amorphous sugars. The chemical stabilization efficiency of different matrices with the same Tg incorporating the same drug should be compared or the chain lengths of the matrices should be varied, resulting in different T_g's but similar drug-matrix interaction.

3.) The difference in stability of amorphous drug clusters versus homogeneous dispersed drug is only speculative and has never been measured properly. Such an investigation requires both control of the mode of incorporation during preparation of the solid dispersion and an accurate characterization technique of the produced dispersion.
4.) The geometry of the porous structure in freeze dried and spray freeze dried solid dispersions might affect the stability of labile drugs. Especially a low specific surface area could decrease the amount of drug present at the air-solid interface, thereby increasing the amount of drug that is properly shielded from its environment. The specific surface area can be varied by the concentration of solutes in the solution that is to be freeze dried. Furthermore, freezing rate, water-organic solvent ratio or deliberately and controlled partial collapse of the cake during the drying process can alter the pore structure.

8.2.3. Process related

1.) In this thesis, the effect of the vitrification rate during freezing of the solutions on the mode of incorporation of diazepam or THC in the resulting solid dispersions was reported. When the vitrification rate can be quantified, the minimum cooling rate required for a given solid dispersion to obtain molecularly dispersed or amorphous drug could be explored. This requires control of the solution temperature before freezing.
2.) Drug-matrix miscibility is related to the mode of incorporation obtained in a certain process. In the ideal situation, the difference in solubility parameters of drug and matrix would enable the calculation of the required cooling rate in a process that results in the desired mode of incorporation.
3.) During the different process steps of the dosage form production, stress-induced crystallization or phase separation can occur. It should be investigated which systems (e.g. fragile or tough glasses) are able to maintain the molecular structure of the solid dispersion intact during the various processing steps like for example tabletting.

8.2.4. Dissolution related

1.) In chapter 3, a model is proposed that might be predictive and could explain why a slow dissolving matrix or a low drug load results in fast release of the lipophilic drug. The schematic representation is given in the left part of figure 1. However, the possibility should be investigated that the drug crystallizes not only in the drug rich layer, but also in the yet undissolved matrix. This is depicted in the right part of figure 1. The amount of dissolved matrix and the amount of crystallized drug during dissolution can be used to derive which situation is applicable. Obviously, this will depend on drug matrix miscibility, drug load and diffusivity of the drug in the wetted but un-dissolved matrix.

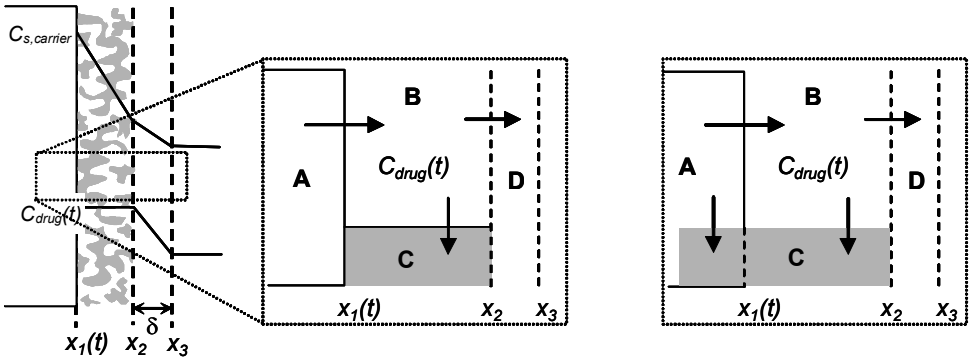

Figure 1: Schematic representation of dissolution of a solid dispersion. C_s is the solubility C_{drug} is the drug concentration. Compartment A is the undissolved solid dispersion, B is the liquid phase in the drug-rich layer, C is crystallised drug, D is the stagnant layer transporting the drug via diffusion to the bulk.

2.) The second step would to be test this model for its predictability, preferably starting with a solid dispersion in which the drug does not crystallize in the undissolved matrix (left picture). In greater detail, the following needs to be done: in a separate experiment the crystallization rate of the drug (from *B* to *C*) should be measured as a function of the supersaturation. Secondly, the dissolution of the matrix as measured during the experiment has to be used to calculate the drug transport from the solid dispersion to the drug rich layer (from *A* to *B*). The transport to the bulk (from *B* to *D*) is proportional to the concentration difference between drug rich layer and bulk. The initial condition to solve the differential equation describes the process at the start of the dissolution. Only transport from *A* to *B* is present and the rate of that would be proportional to intrinsic dissolution rate of the matrix and to drug load.

3.) Investigating the effect of molecularly dispersed drug or amorphous drug clusters. Although most reports consider an amorphous solid dispersion with molecularly dispersed drug as optimal for fast drug release, this has never been proven: it could lead to higher supersaturation and more drug crystallization. The comparison with amorphous drug clusters is of great interest. Moreover, a comparison of drug release between solid dispersions containing amorphous drug clusters and crystalline drug particles could reveal interesting phenomena. If the description in figure 1 is correct, molecularly dispersed drug will cause the highest supersaturation and the most rapid formation of the drug-rich layer resulting in the slowest dissolution! This hypothesis has to be checked for several drug-matrix combinations. However, it requires both control of the mode of incorporation during preparation as well as proper characterization.
4.) The effect of the crystallization rate of the drug needs to be investigated. It can be hypothesized that slow crystallizing drug molecules will be released faster from a solid dispersion with the same matrix, but experimental confirmation is needed.