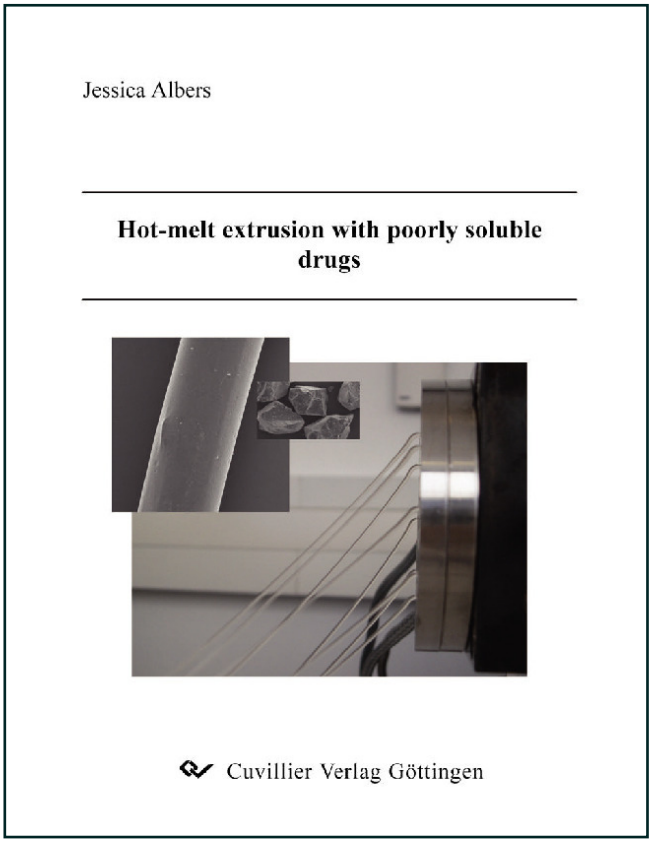

1 Introduction

1.1 Bioavailability of poorly water-soluble drugs

The bioavailability is a measurement of the extent of a therapeutically active drug that reaches the systemic circulation and is available at the site of action. The bioavailability is mainly controlled by the delivery of the drug as determined by its pharmaceutical formulation, the solubility, and the permeability through the gut wall. In addition, the bioavailability can be decreased through decomposition of the drug in the gastrointestinal tract, by formation of non-absorbable complexes, by metabolization, or by premature elimination. These limitations can be influenced by physiological parameters of the gastrointestinal tract or the physicochemical properties of the drug and the formulation.

It is estimated that about 40% of all new chemical entities have poor bioavailability because of low aqueous solubility. This percentage still increases due to combinatorial chemistry and the impact of lipophilic receptors (Kerns 2001).

1.2 Reasons for poor aqueous solubility

The solubility of a substance is influenced by its physical and chemical properties with similar molecules having similar activities. This principle called structure-activity relationship was applied by Meylan and Howard to estimate the octanol-water partition coefficient (P) and the aqueous solubility (S) of drugs. They established a database (Meylan & Howard 1995) and derived from it an equation (Equation 1), which describes the aqueous solubility of a substance (Meylan & Howard 2000). For the estimation of logP values they developed a new fragment constant approach and included correction factors (fi), which were derived from the differences between the logP estimates from atoms alone and the measured logP values. They found out, that the melting point (MP) and the octanol-water partition coefficient as measures for the endeavour to crystallize and for the lipophilicity respectively, influence decisively the solubility of a drug.

$$\log S = -1.03 \log P - 0.011(MP - 25) + 0.34 + \Sigma fi$$
$$(n = 1450; R^2 = 0.97; fi = factor)$$

Equation 1: Calculation of the solubility of a substance; S = solubility, P = partition coefficient; MP = melting point; Σfi = summation of all correction factors

A concentration of 10 µg/mL is often given as a critical value for poor solubility (Shah et al. 1989). With a solubility below this value, problems in pharmacokinetics are likely to occur.

Schamp (2002) developed an equation for the prediction of solubility problems of drugs. According to this approach, the solubility drops below the critical concentration 10 μg/mL, if the sum of logP and MP/100 exceeds the value 4.5. One logP unit and a ΔT of 100 K for the melting point respectively, change the solubility by a factor of 10.

In addition to the solubility, the dose of a drug has to be taken into account also. At a very low dose the poor aqueous solubility of a drug does not always have a negative effect on the bioavailability. In such cases it is important to determine the dose-solubility volume (dose/c_s) (Amidon et al. 1995, Dressman et al. 2001). The calculated value determines the volume necessary to completely dissolve the drug.

1.3 Ways of solubility enhancement

In general, there are both chemical and physical ways to improve the solubility of a drug. The formations of soluble salts, like ibuprofen-lysinate instead of ibuprofen, or prodrugs, for instance sulfamoyl sulfonate prodrugs, are chemical tools, which are often found in pharmaceutical formulations. Physical methods to improve the dissolution rate can be derived from the equation by Noyes and Whitney (Noyes & Whitney 1897):

$$\frac{dc}{dt} = \frac{A \cdot D \cdot (c_s - c_t)}{V \cdot h}$$

Equation 2: Equation according to Noyes and Whitney

In this equation dc/dt is the dissolution rate, A is the surface area, D is the diffusion coefficient of the compound, c_s is the solubility of the compound in the dissolution medium, c_t is the concentration of drug in the medium at time t, V is the volume of the medium, and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound. According to this equation there are two main possibilities of improving the dissolution rate of a drug by physical influence. First, A can be increased by micronizing the compounds or changing the surface properties, thus, increasing the wettability of the particles. The second method is to increase the apparent c_s by changing to modifications with higher energetic states or by addition of solubility enhancing excipients.

In an early stage of development the solubility of a poorly water-soluble drug can be changed by chemical methods, like salt selection, prodrug formation, or change of the modification (Figure 1.1). If the chemical design of the drug is brought to a close, formulation approaches

have to be undertaken. The simplest way to enhance the solubility is to micronize the poorly soluble drug through pin, ball or jet milling. A property, which is accompanied by the increase of the surface area, is the increase of wettability which can be realized by the use of surfactant in the formulation. If these standard formulation approaches fail, advanced approaches need to be used. Depending on the pharmaceutical dosage form, several methods are available (Figure 1.1).

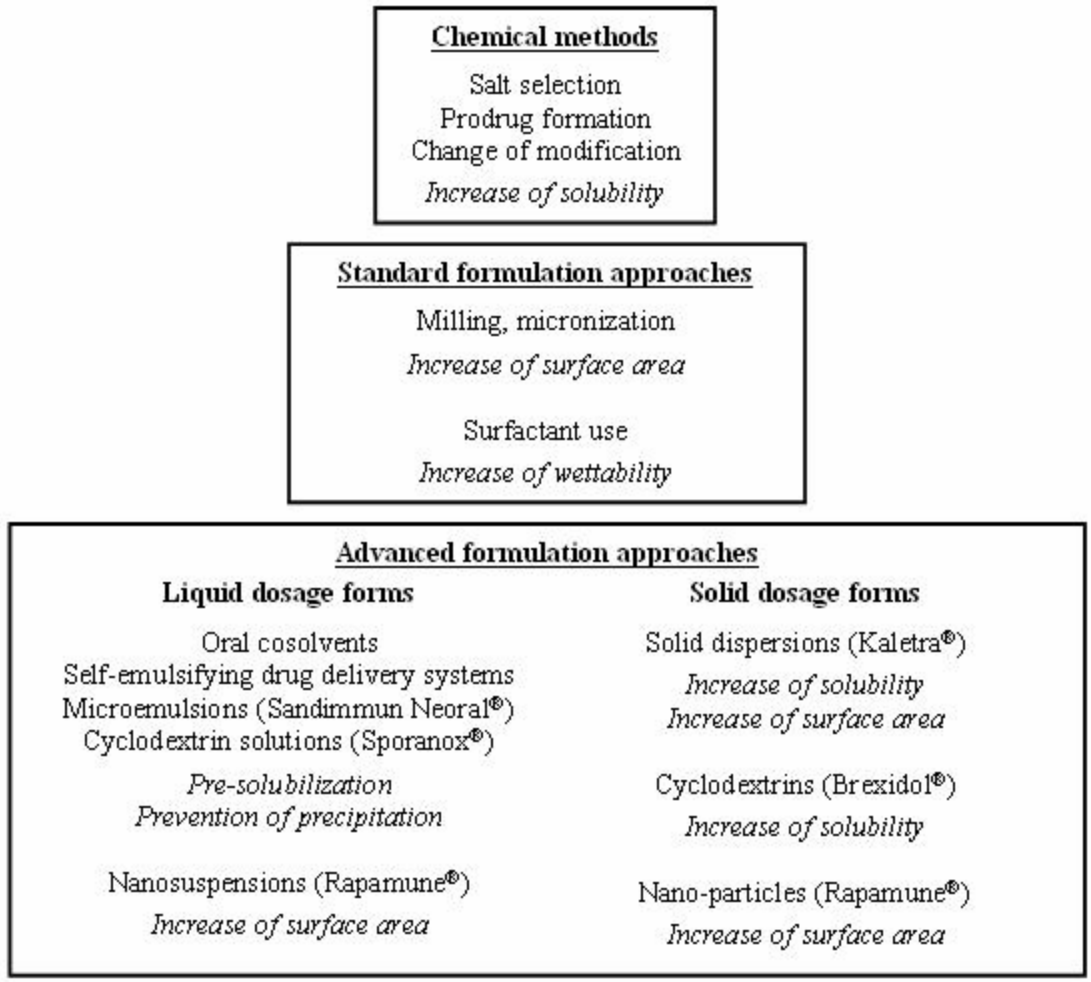

Figure 1.1: Strategies for solubility enhancement of poorly water-soluble drugs

Two main strategies can be observed in enhancing the solubility of poorly water-soluble drugs. On the one hand, the drug is pre-solubilized in a liquid dosage form, like in self-emulsifying drug delivery systems or microemulsions. When such formulations are released into the lumen of the gut, they disperse to form a fine emulsion, so that the drug remains in solution. Thus, the dissolution step, which often limits the rate of absorption of the drug, can be avoided (Pouton 1997, Constantinides 1995). On the other hand, the drug is transferred into its amorphous state, or dispersed on a molecular basis in solid dosage forms, maximizing

the surface area that comes into contact with the medium during dissolution. Thus, the solubility of the drug is improved, but the drug is not prevented of precipitation.

Solid dispersion formulations show a great variety relating to the state of the solid dispersions and the technique to produce them (Chiou & Riegelman 1971, Sethia & Squillante 2003). This is demonstrated by the number of products present on the market: Certican® tablets (everolimus / HPMC), Cesamet® tablets (nabilone / PVP), Gris-PEG® tablets (griseofulvin / PEG), Isoptin® SR-E (verapamil / HPC / HPMC), Nivadil® tablets (nivaldipine / HPMC), ProGraf® capsules (tacrolimus / HPMC), Rezulin® tablets (troglitazone / PVP), Sporanox® capsules (itraconazole / HPMC).

Nano-particles can be produced by high pressure homogenization, wet ball milling or precipitation and can be incorporated into tablets for oral delivery (Mueller 2001). Cyclodextrin formulations are quite common complexation aids to enhance solubility. Cyclodextrins are molecules with a great variety resulting in about 100 different CD-derivatives commercially available (Szente 1999).

However, the most frequent strategy for increasing the dissolution rate is the improvement of solubility through advanced formulation approaches. The method of solid dispersion formulation has been used in this work on solubility enhancement and will, therefore, be addressed in greater detail in the following chapters.

2 Outline and goal of this work

The main objective of this thesis was to establish the hot-melt extrusion technique for solubility enhancement. In this context attention was focussed on the elucidation of the mechanism of drug release from melt embeddings, the understanding of physico-chemical processes taking place during hot-melt extrusion, the prediction of drug carrier miscibility, and the thermodynamical stability of those systems. Specific aims were:

-To develop a formulation for improving solubility of a poorly water-soluble drug

In a first step various excipients were examined for suitability as solubility enhancers in melt embedding processes. To find suitable carriers, different tools like solubility parameter calculation, theory of Gordon-Taylor, differential scanning calorimetry, hot stage microscopy, and intrinsic dissolution were employed. The behaviour of the molten samples was compared to the behaviour of the respective physical mixtures to examine the effect of the melting process. Furthermore, it was evaluated whether the coevaporation technique results in similar products as the hot-melt extrusion technique.

-To optimize the hot-melt extrusion technique for solubility enhancement of a poorly soluble drug and to prove the applicability of the technique for different carriers and drugs

The hot-melt extrusion process, which was chosen as technique for melt embedding, had to be optimized regarding process parameters like screw configuration, die plate design, temperature setup and formulation parameters like drug carrier fitting, and drug load. The influence of process parameters and formulation on the resulting products was investigated. Physical and chemical processes taking place in the melt embeddings were analyzed with differential scanning calorimetry, Fourier-transform infrared spectroscopy, and X-ray powder diffraction.

-To elucidate the mechanism of solubility enhancement in hot-melt extruded products

The solid state of the extrudates was evaluated with differential scanning calorimetry, X-ray powder diffraction, and scanning electron microscopy and was correlated with the in-vitro dissolution behaviour. The mechanism of drug release from melt embeddings was elucidated with the help of solid state characteristics and the interpretation of the dissolution process.

-To find rules to predict the miscibility of drugs and carriers and to correlate these predictions with the hot-melt extrusion process

As the miscibility of drug and carrier plays a decisive role in melt embedding, tools for the prediction of miscibility were developed. These approaches were based on the chemical understanding of interactions occurring in melt embedding and the chemical and physical characteristics of basic materials, physical mixtures and molten products. Tools to investigate these characteristics and interactions involved solubility parameter calculation, molecular dynamics simulations, and thermoanalytical characterization.

-To solve stability problems and avoid recrystallization during dissolution

A main objective in melt embeddings is the thermodynamic stability of the products. Therefore, a great part of this study deals with the stability of melt embeddings and the inhibition of recrystallization on mechanical input, storage, and dissolution.

-To produce solid dosage forms

The formation of solid dosage forms from melt embeddings is a great challenge, since the characteristics of the material are different from those usually applied to the production of solid dosage forms. As the dissolution rate in those systems is mainly controlled by the solid state characteristics of the drug, mechanical influences during processing have to be taken into account.