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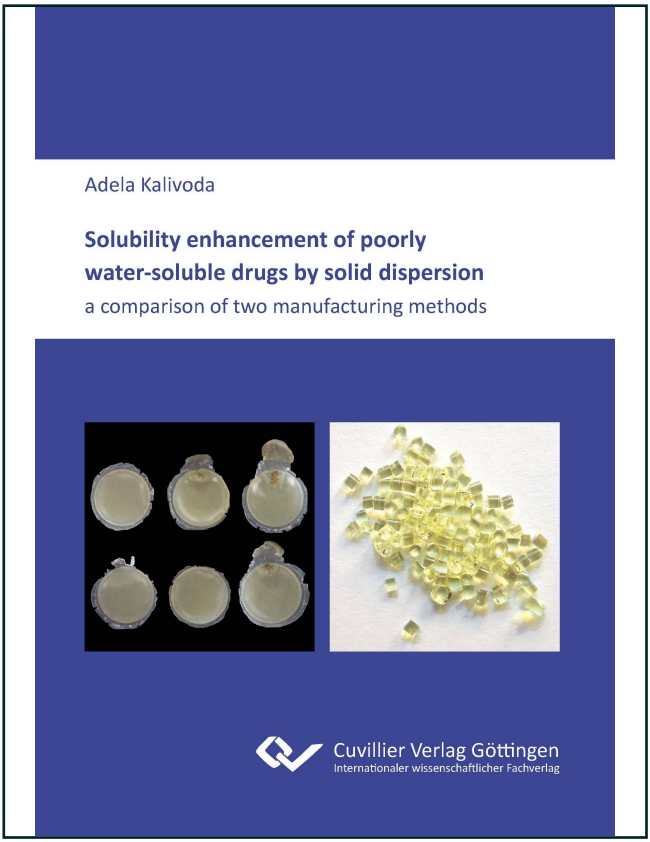
Solubility enhancement of poorly water-soluble drugs by solid dispersion

a comparison of two manufacturing methods



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1 Introduction

1.1 Solubility enhancement of poorly soluble drugs

1.1.1 Methods of solubility enhancement

The oral bioavailability of a drug, which is by definition the degree at which its active form is made available at the site of action after oral administration, is mainly dependent on the solubility of the drug in the gastrointestinal tract, its permeability through the intestinal wall and on effects of the pharmaceutical formulation. According to the biopharmaceutics classification system (BCS) class II drugs are most suitable for bioavailability enhancement through pharmaceutical formulation due to their good permeability which is only limited by their dissolution rate (Amidon et al., 1995). In the field of drug delivery system development for peroral application, the enhancement of in vivo solubility of newly developed drugs is becoming increasingly challenging as the number of innovative but poorly soluble active pharmaceutical ingredients (APIs) is rising. Various methods are available for solubility enhancement that are classified either as chemical or physical approaches.
The formation of salts or prodrugs with an enhanced solubility behavior are examples for chemical approaches. However, these are only suitable in an early stage of development as this approach will lead to fundamental changes in the substance properties.
The theoretical foundation for physical approaches to modify the solubility of a drug is the Noyes-Whitney equation (Noyes and Whitney, 1897), in this case depicted in its modified version according to Nernst and Brunner (Brunner, 1904; Nernst, 1904):

$$\frac{dc}{dt} = \frac{DA(c_s - c_t)}{Vh} \tag{1.1}$$

where dc/dt is the dissolution rate, D is the diffusion coefficient of the compound, A is the surface area, c_s is the solubility of the compound in the dissolution medium, c_t is the concentration of the compound in the dissolution medium at a time t, V is the volume of the dissolution medium and h is the thickness of the diffusion layer adjoining the compound surface.
From Eq. 1.1 it can be concluded that there are various possibilities to influence the dissolution behavior of the drug: an increase of the surface area of the compound available for dissolution, for example through a reduction of the particle size or an improvement of the wetting characteristics, an improvement of the drug's solubility in the medium, an increase of the dissolution medium volume, for example, through the establishment of sink conditions and, finally, the diffusion layer thickness can be reduced. Two strategies shall be emphasized:

The modification of the compound's surface area and the alteration of the apparent solubility c_s of a drug are both classified as physical approaches to dissolution behavior improvement. Examples for the methods mentioned above are listed in Table 1.1.

Table 1.1: Summary of available strategies to solubility enhancement of poorly water-soluble compounds

Chemical approach	
Salt formation	
Prodrug formation	
Physical approach	
Reduction of the particle size	
	Milling
	Micronization
	Nanoization
Pre-/Solubilization	
	Employment of surfactants
	Employment of cosolvents
	Microemulsions
	Self-microemulsifying drug delivery systems SMEDDS
Complexation	
	complexing agents
	Inclusion complexes (e.g. cyclodextrines)
Solid dispersions	
	Eutectic mixtures
	Solid suspensions
	Solid solutions
Modification of the solid form	
	Use of metastable solid forms
	Use of a better soluble polymorph
	Cocrystals

1.2 Solid dispersions

1.2.1 Definition and historical background

The foundation for the application of solid dispersions as a method for bioavailability enhancement of poorly soluble drugs was laid by Sekiguchi and Obi in 1961 by the introduction of eutectic mixtures as a novel method for solubility enhancement (Sekiguchi and Obi, 1961). An eutectic system is a blend of substances that are fully miscible in their molten state but only to a limited extent in their solid state. Upon cooling, the components of a mixture with

an eutectic composition crystallize out simultaneously. With any other mixture ratio, the components begin to crystallize consecutively. At a specific temperature which is referred to as the eutectic point, the liquid phase and the solid phases of the components of an eutectic mixture are in a chemical equilibrium. When a molten eutectic composition of a drug and a highly water-soluble carrier is rapidly cooled below the eutectic point, very fine and intimately mixed crystals of both substances are obtained. These very fine crystals of the API are rapidly released as the carrier dissolves in, for example, the gastrointestinal fluid. Because of the drastically increased surface area of this suspension, both the dissolution and absorption rate of the drug substance are enhanced.
Goldberg et al. pursued the subject further, suggesting that solid solutions of a drug in a carrier are superior to eutectic mixtures as the particle size is drastically reduced (Goldberg et al., 1965, 1966a,b,c). By definition, the solid solution of two substances is a homogeneous, single-phase system where one component is dissolved in the other at a molecular level and both components are present in their solid state. With a solid solution system, a maximum particle size reduction of the API is achieved. The general term solid dispersion for a dispersion of one or more active ingredients in an inert carrier or matrix at solid state was defined by Chiou and Riegelman in 1971 who also gave a detailed classification of solid solution and solid dispersion systems and a summary of manufacturing methods (Chiou and Riegelman, 1971). A short summary of this classification is given in Table 1.2.
Frequently, a single class cannot be attributed to a manufactured solid dispersion as they often consist of multiple types of solid dispersions. In that case, the dissolution behavior is a result from a combination of the influences of all present solid dispersion types.
In some publications, compound or complex formations are also classified as solid dispersion systems (Breitenbach, 2002; Ford, 1986). However, these cannot truly be regarded as solid dispersions in the classical sense as defined by Chiou and Riegelman; thus, they are not included in Table 1.2.
Traditionally, highly water-soluble carriers have been used for solid dispersion preparation as the aim was to enhance the drug's solubility. Today, water-insoluble carriers are also used for solid dispersion preparation as they offer the possibility to modify a drug's release behavior, for example, through a sustained release formulation.

Table 1.2: Summary of different solid dispersion types (Chiou and Riegelman, 1971; Ford, 1986)

Type of solid dispersion	Drug	Carrier	Phases
Eutectic mixtures	Crystalline	Crystalline	2
Glassy suspensions	Amorphous or crystalline	Amorphous	2
Amorphous precipitation	Amorphous	Crystalline	2
Solid solutions	Molecularly dispersed	Crystalline	1
Glassy solutions	Molecularly dispersed	Amorphous	1

1.2.2 Methods of manufacture

According to the definition by Chiou and Riegelman, solid dispersions are manufactured via the melting, melting-solvent or solvent method (Chiou and Riegelman, 1971).
With the melting method, a physical mixture of the API and the carrier is heated until it is melted. An accelerated cooling of the molten mixture is essential for the desired outcome. Stirring in an ice-bath (Sekiguchi and Obi, 1961), pouring onto a stainless steel plate (Chiou and Riegelman, 1969) or spraying onto a cooled surface (Kanig, 1964) are all documented approaches for a rapid cooling of the melt. Alternatively, the drug is dispersed in the already molten carrier and solidified by rapidly cooling the mixture. The benefit of the second approach is that the drug is exposed to relative low temperature levels. For heat-sensitive materials however, the melting method might not be suitable.
If the solvent method is used, both drug and carrier are dispersed in a common solvent. Subsequently, the solvent is removed, for example, through evaporation under vacuum. Other possibilities for the removal of the solvent that have been documented in literature are drying at elevated temperatures, lyophilization and spray-drying or the use of supercritical antisolvents (Serajuddin, 1999; Leuner and Dressman, 2000). While the solvent method offers the possibility to produce a solid dispersion of a heat-sensitive drug and a carrier with a high melting point, it might prove difficult to find a common solvent. The reason for this is that often a hydrophobic API is supposed to be incorporated into a hydrophilic carrier through solid dispersion manufacture. In addition, toxicological problems might arise from solvent residues remaining in the manufactured formulation and the use of organic solvents is generally associated with ecological problems.
The melting-solvent method is a combination of the two previously described methods.
Newer methods for the manufacture of solid dispersions include hot-melt extrusion (HME), hot spin mixing (Dittgen et al., 1995) and super critical fluid technology (Van Nijlen et al., 2003; Ghaderi et al., 1999). Furthermore, ultrasound-assisted compaction (USAC) has been proposed as another novel manufacturing method (Fini et al., 2002a,b).
As the main focus of the present work was on HME and USAC, the principles of these methods are described in separate Sections 1.3 and 1.4.

1.2.3 Proposed mechanisms of drug dissolution from solid dispersion systems

Although numerous publications are available on the characteristics and manufacture of solid dispersions, the properties of these systems have not yet been fully understood. This does not only concern their structure or the nature of the prevailing interactions in the system but also the dissolution mechanism leading to the observed improvements in dissolution rate and drug solubility. A summary on possible mechanisms leading to a dissolution enhancement has been given by Chiou and Riegelman (Chiou and Riegelman, 1971):

1. Particle size reduction
2. Solubilization effect resulting from the high concentrations of the carrier in the diffusion layer surrounding the solid dispersion

3. Reduced aggregation of drug particles
4. Improvement of wettability
5. Modifications to the physical form of the drug, e.g. a different polymorphic form

In 2002, Craig classified the possible dissolution mechanisms from solid dispersion systems as being either *a*) carrier-controlled or *b*) drug-controlled dissolution (Craig, 2002). The theory of the carrier-controlled dissolution mechanism was introduced in 1985 by Corrigan (Corrigan, 1985). The dissolution rate of the polymer alone was shown to be equivalent to the release rate of the drug from a drug-carrier system with a high carrier fraction. This finding was confirmed by Dubois and Ford in 1985 who investigated the release rates of various drugs from polyethylene glycol (PEG) 6000 systems. If a solid dispersion was formed by the drug and the carrier, the rate of dissolution was determined to be equivalent for all investigated drug-carrier systems regardless of the drug properties (Dubois and Ford, 1985). In the case of a drug-controlled dissolution mechanism, the release rate is mainly dependent on the properties of the drug substance (Sjökvist and Nyström, 1988; Sjökvist Saers and Craig, 1992).
It is suggested by Craig that at high drug loadings, the theory of the formation of a drug-rich layer that has been proposed by Higuchi et al. may be applied (Craig, 2002; Higuchi et al., 1965). If a polymer-rich layer is present on the solid dispersion surface which is the case, for example, at low drug loadings, carrier-controlled or drug-controlled dissolution takes place depending on the way the drug passes through the polymer layer. In the case of carrier-controlled dissolution, the drug dissolves in the polymer-rich layer. It is molecularly dispersed in the polymer layer. If a drug-controlled mechanism applies, the drug particles are released almost intact or entirely unaltered as the dissolution in the polymer-rich layer is very slow. Even so, the dissolution rate can be improved through some of the proposed mechanisms, for example, a reduction of the aggregation of the drug particles.

1.3 Ultrasound-assisted compaction technique

1.3.1 Introduction

A comprehensive review on the application of USAC in different sectors, its basic principles and the main effects on the material was published by Levina et al. (2000). In the following section, the main aspects of this technology shall be highlighted to allow a basic understanding of the process.
USAC is a tableting process that combines ultrasound (US) application with the simultaneous compaction of the material. Rodriguez et al. described an USAC machine especially for pharmaceutical usage in 1995 (Rodriguez et al., 1995).
Figure 1.1 gives a short overview of the process. There are two punches which are driven by pneumatic pistons. The material is inserted into the die and is compacted by the bottom punch which moves upwards. Piezoelectric material that is conjoined to a transducer

produces US waves via vibration. The US waves are amplified by an inserted booster and transferred onto the material through the upper punch; therefore, it is also referred to as sonotrode (Fini et al., 2002a,b). The frequency is set at 20 kHz. The starting point of US application can be set manually. In this work, the US energy application begins after a short period of precompaction of the material. Thus, a good transmission of US energy from sonotrode to the material was ensured. After the material has been poured into the Teflon® (PTFE)-lined die, the USAC process is started on the touch of a button. The process flow after start-up can be summarized as follows:

1. Lowering of sonotrode upon material; sealing of the die by applying chosen upper piston pressure
2. Lower punch moves upwards: precompaction of material while air is being pressed out of the die.
3. Further movement of lower punch upwards: compaction of material performed with a previously defined lower piston pressure
4. After a set time period, US application begins while compaction of material continues at constant pressure.
5. When the set US energy level is reached, the process is terminated; both punches stay in position.
6. Cooling time
7. Sonotrode is raised; lower punch moves back into its initial position.
8. The compact is ejected from the die by an upward movement of the lower punch.

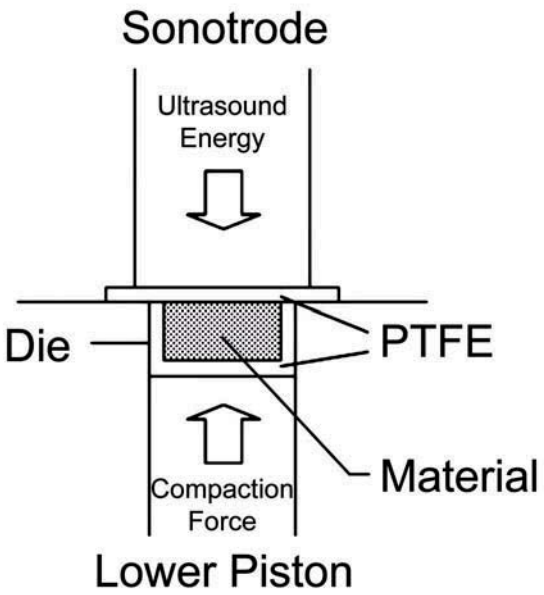

Figure 1.1: Schematic description of the USAC working principle

1.3.2 Effects of ultrasound-assisted compaction technique on the material

This section shall focus on the physical processes that are induced by USAC application and summarize the findings of the various publications that are available on this subject.
An overview of the effects generated by the application of US energy on solid material was given by Suslick et al. in 1987 and 1990: A particle size reduction is induced through an increase of interparticle collisions, the intercalation rate is increased, an aggregation of small-sized particles is induced, changes in the particles' surface morphology occur and local heating effects are observed (Suslick et al., 1987; Suslick and Doktycz, 1990).
The combination of pressure, heat and US as it occurs during USAC application leads to a formation of interparticulate bonds and the incorporation of the API into the thermoplastic polymer. Specific effects of US application in USAC are particle rearrangement and the supplying of energy for interparticulate bonding via partial melting and subsequent fusion of particles (Levina and Rubinstein, 2002), particle size reduction and transformation of the crystalline API into its amorphous state (Fini et al., 2009). An increase of mechanical strength of the compacts can be attributed to interparticulate bonding and leads to a decrease of the dissolution rate (Levina and Rubinstein, 2002).
USAC application was shown not to promote interactions between API and polymer on a molecular level (Sancin et al., 1999). Nevertheless, it was demonstrated that the drug is amorphized during the process and stabilized by the polymeric carrier, possibly due to an adsorption of the drug to the surface of the polymeric particles (Sancin et al., 1999).
Differences in viscosity of the material at elevated temperatures lead to an asymmetric drug distribution in the compacts (Fini et al., 2009).
Both the mechanical effects as well as the thermal effects of US application are essential for the outcome and the thermal effects were shown to predominate at higher US energies (Rodriguez et al., 1998). Hence, the properties of a USAC compact in comparison to a conventionally compacted tablet are dependent on the amount of US energy that has been delivered to the material.
Not only the amount of US energy delivered to the material, but also the moment of US energy input are crucial for the outcome (Levina and Rubinstein, 2000). As a result, the US energy is applied simultaneously with the compression force during this work.

1.3.3 Application of ultrasound-assisted compaction technique in the pharmaceutical sector

The literature available on the application of ultrasound for formulation development in the pharmaceutical sector is very limited. In 1993, a patent was filed by Gueret on the manufacture of so-called "pharmaceutical or cosmetic compacted powders" (Gueret, 1993). A mixture of thermoplastic (e.g. polyethylene and polyvinyl chloride) and non-thermoplastic ingredients (minerals and organic substances, for example zinc oxide and silk powder) was compacted under simultaneous US application with the aim to produce a compact with optimized solidity properties. It was demonstrated that if 5-80 % of thermoplastic material are

present in the mixture, a framework is formed which holds the non-thermoplastic material. The solid state properties were successfully optimized, resulting in a sufficiently friable but still firm compact.

Various research groups employed USAC for the manufacture of sustained- and immediate-release solid dosage forms which are shortly described in the following paragraphs.

Saettone et al. (1996) and Rodriguez et al. (1995) applied USAC for the preparation of a sustained release formulation of theophylline (30 %, 50 % or 75 % drug load), Eudragit® RL and Eudragit® RS with added talc (1 %) and magnesium stearate (1 %). The material was either conventionally compacted or US-compacted, whereby the former was only possible at drug loads of 30 %. It was shown that the preparation of sustained release formulations with high drug loads is possible via USAC, presumably due to the melting of the excipients and their subsequent coating of the API particles. Further details on the theophylline-Eudragit® RL formulation were published by Rodriguez et al. (1998).

Caraballo et al. (2000) and Millán and Caraballo (2006) investigated the effects of particle size on US-compacted tablets and their percolation threshold using potassium chloride as drug model and Eudragit® RS as polymeric carrier. It was observed that the results gained with USAC are less dependent on the particle size of the drug than the conventional compaction method. Also, it was shown that the excipient surrounds the drug resulting in a higher percolation threshold thus offering the possibility for the application of this technology for the manufacture of sustained-release formulations.

Levina and Rubinstein investigated the ultrasound-assisted compaction of ibuprofen and paracetamol with dibasic calcium phosphate dihydrate and microcrystalline cellulose (Levina and Rubinstein, 2000, 2002). It was demonstrated that the application of USAC increases tablet hardness and dissolution times of these formulations.

Ketoprofen and Eudragit® S-100 were subjected to USAC technology by Sancin et al. (1999) using drug loads of 25 %, 50 % and 75 % (w/w). A conversion of the API into its amorphous state was observed. Eudragit® S-100 reduced recrystallization of the drug. Furthermore, it was pointed out that neither changes of the hydrogen bonding of the drug nor the formation of drug-polymer associates are induced via US application. Although the authors made a suggestion on the application of USAC for solubility enhancement, it seems that this specific drug-polymer combination was not pursued further as no additional literature is available on this topic.

A high-energy US compaction was shown to improve the dissolution behavior of indomethacin as the ultrasound-compacted mixture of indomethacin and betadex (β-cyclodextrin) showed higher initial release rates than pure API, the physical mixture of the components and conventionally compacted mixture. Also, the total amount of dissolved API was improved. The reason for this dissolution enhancement is a transformation of indomethacin into its amorphous state. Furthermore, the molten API was found to form a coating on the β-cyclodextrin particles. However, similar results were obtained if the mixture was ground in a mortar (Fini et al., 1997).

If polyvinylpyrrolidone (PVP) or different kinds of PEG were employed as carriers, the dissolution rate of indomethacin was even further enhanced (Fini et al., 2002a,b). In comparison to co-evaporation as another method to manufacture solid dispersions, USAC was shown

to result in comparable dissolution profiles (Fini et al., 2002a). USAC was also employed for the formulation of ibuprofen-isomalt compacts (Fini et al., 2009). It was demonstrated that the distribution of the API in the compact is not homogeneous. Unfortunately, no dissolution studies were reported.

1.4 Hot-melt extrusion

1.4.1 Introduction

Hot-melt extrusion (HME) is the process of melting and mixing a blend of drug and carrier inside a heated barrel. The molten material is transferred through the barrel using one or two rotating screws and pressed through a die into a product of uniform shape and high density.
An extruder can be divided intro three main zones: the feeding zone, the compression zone and the metering zone (see Figure 1.2).

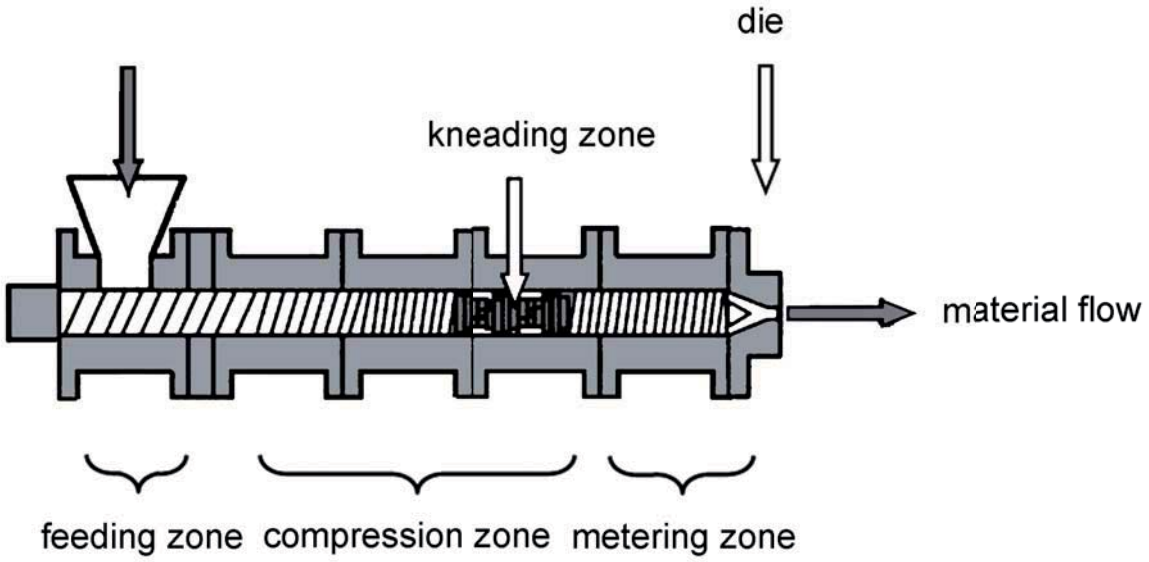

Figure 1.2: Schematic description of the HME working principle (reproduced with modifications from Nakamichi et al., 2002)

Solid material is inserted into the extruder through a feeding system. The material is gently mixed and transported to the compression zone by the conveying system which consists of one or two rotating screws. In the compression zone, the material is homogenized and compressed. Also, the main melting process takes place in this region. Kneading screw

elements may be applied to intensify the effects by an increase of shear energy introduced to the material. In the metering zone, the material is transported to the die. A build-up of pressure takes place in this section of the extruder. The main function of the metering zone is to reduce pulsating flow. Finally, the material is pressed out through the die. Downstream equipment may be connected to the system, for example, calendering, pelletizing or film-forming equipment may be used.
Coming from the plastics industry, HME was first used for pharmaceutical formulation in 1971 by El-Egakey et al. and refined in later years by various research groups (Breitenbach, 2002; El-Egakey et al., 1971; Repka et al., 2008). The advantages of HME in comparison to other solid dispersion manufacturing methods are the continuity of the process, its flexibility both in the instrument set-up and the settings of the process parameters and the wide variability of downstream equipment available. In addition, it overcomes the disadvantages of both the melting and the solvent method. Unlike the solvent method, it is a solvent-free process thus being environmentally friendly and economically efficient without the need for additional drying steps to facilitate solvent removal. In the early stages of pharmaceutical application of HME, especially the process temperatures and residence times were discussed as possible drawbacks of the technology. However, it was shown by various research groups that HME processing is even possible at lower temperatures through a modification of the extrusion equipment or through the addition of plasticizers to lower the glass transition temperature (T_g) thus reducing the required process temperatures (Repka and McGinity, 2000; Repka et al., 1999; Zhu et al., 2002).

1.4.2 Application of polymeric blends as carriers in hot-melt extrusion

The choice of the carrier plays an important role in solid dispersion formulation as the physicochemical characteristics of the carrier have a strong influence on the properties of the manufactured formulation. Various polymers have been applied in literature for hot-melt extruded formulations: PEG, PVP or sugar alcohols for immediate release and methacrylic acid copolymer (Eudragit® L 100; Evonik Roehm GmbH, Darmstadt, Germany) or ethylcellulose for sustained release solid dosage forms (Repka et al., 2008).
Crowley et al. used polyethylene oxide (PEO) for a sustained release formulation of chlorpheniramine maleate in 2002 (Crowley et al., 2002). Because of difficulties with the thermal stability of PEO, low molecular weight PEO was incorporated. Thus, the stability of the formulation was improved without significant changes to the release profile.
The application of polymeric blends as carriers offers the possibility to modulate the dissolution profile of a hot-melt extruded formulation (Coppens et al., 2006). Acetaminophen and nifedipine were used as APIs and hydroxypropyl methylcellulose (HPMC), PEO, ethylcellulose and blends of these as carriers.
Janssens et al. (2008) applied blends of PEG 6000 and HPMC as carriers for poorly water-soluble drug itraconazole. The dissolution behavior was successfully enhanced with all hot-melt extruded formulations containing the amorphous form of the drug, regardless of the carrier system. If a ternary blend of the API and excipients was used, a super-additive effect

on the dissolution profile was observed. The authors contributed this effect to the properties of PEG 6000 which is assumed to improve the wetting, inhibit recrystallization and act as a cosolvent for itraconazole.
Nollenberger et al. (2009a,b) added ethyl acrylate and methyl methacrylate copolymer dispersion (Eudragit® NE 30 D, Evonik Röhm GmbH, Darmstadt, Germany) to a mixture of aPMMA and felodipine (FD) thus stabilizing the supersaturation level of the extrudate reached in dissolution studies.
Blends of polymers were also applied as carrier for poorly water-soluble drug clotrimazole in HME (Prodduturi et al., 2007). It was pointed out that the characteristics of a hot-melt extruded film could be improved by adding another polymer with more favorable properties. In this particular case, the poor mechanical properties of a hydroxypropyl cellulose film were successfully modified through the addition of polyethylene oxide while maintaining the film's enhanced release properties.

1.5 Manufacture of solid dispersions using the applied drugs

1.5.1 Solid dispersions with fenofibrate

In the past, different methods were applied to improve the dissolution behavior and the bioavailability of fenofibrate (FF) preparations. Special emphasis was laid on developing a FF solid dosage form which may be applied independently from food uptake. Micronization (Munoz et al., 1994), stabilization of micronized FF through a coating process (Guichard et al., 2000), SMEDDS (Patel and Vavia, 2007) were all methods which were applied for optimization of FF formulations. More recently, solid dispersions were examined as another possibility to improve FF dissolution behavior. It was shown by various research groups that the solubility of FF may be enhanced via the manufacture of a solid dispersion (Sheu et al., 1994; Vogt et al., 2008). Various polymeric carriers were employed, for example copovidone (COP) and aPMMA (He et al., 2010), PVP and COP (Kanaujia et al., 2011) or polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (PVCL-PVAc-PEG) (Djuric and Kolter, 2010).

1.5.2 Solid dispersions with felodipine

Although solid dispersions of FD were successfully manufactured using various methods, for example the solvent method (Rumondor et al., 2009a,b), spin-coating method (Marsac et al., 2008) or spray-drying (Nollenberger et al., 2009b), only limited information is available on hot-melt extruded formulations with FD. The reason for this might be the documented thermal instability of FD when exposed to elevated temperatures (Marciniec and Ogrodowczyk, 2006). Nevertheless, mixtures of FD and aPMMA were successfully extruded at process temperatures of 160 °C (Nollenberger et al., 2009a; Qi et al., 2010). The dissolution rate was significantly improved with this formulation. Supersaturation stability was achieved with

the addition of 2.5-10 % of Eudragit® NE (Evonik Röhm Pharma Polymers, Darmstadt, Germany) (Nollenberger et al., 2009a).

1.5.3 Solid dispersions with oxeglitazar

Spray-freezing (Badens et al., 2009), co-evaporation and supercritical antisolvent (SAS) methods (Majerik et al., 2006, 2007; Majerik, 2006) were successfully employed for the manufacture of oxeglitazar (OX) solid dispersions. Drug loads of approximately 50 % (w/w) were applied. Depending on the manufacturing method and the polymeric carrier, different polymorphic forms of OX and different crystallinity indices of the samples were obtained. While the crystallinity index of solid dispersions manufactured using crystalline excipients was shown to be at approximately 60-100 %, formulations with amorphous excipients showed low degrees of crystallinity. If poloxamers 188 and 407, PEG 8000 and PVP K17 were used as polymeric excipients, the dissolution rate was improved with all of the mentioned manufacturing methods. Although the dissolution rate was reduced in dissolution medium pH 7.4 if Eudragit® E or RL were applied as polymeric carriers, it was improved in dissolution medium pH 1.2 which can be attributed to the solubility of the applied substances in these media (Majerik, 2006). Additionally, solution enhanced dispersions (SEDS) were manufactured using supercritical fluids (Majerik, 2006). No dissolution results are reported with SEDS.