The present chapter is extensively based on the following publication, which has been emanated from this doctoral thesis.

1. **Introduction:**

The development of amorphous drug delivery systems has been widely investigated in academia and by the pharmaceutical industry to overcome the poor aqueous solubility of many drugs. Briefly, the same solid material can be of crystalline or amorphous nature, where amorphous drugs exhibit a significantly higher solubility and dissolution rate compared to their crystalline counterpart [1]. The main drawback of the use of pure amorphous highly soluble drugs is their physical instability with respect to their inherent tendency to recrystallize into the poorly soluble crystalline form due to the fact that they are thermodynamically unstable [2].

As neat amorphous drugs alone often appear not feasible in drug delivery systems, a major focus within amorphous research and development was and is on stabilizing the amorphous form through the use of excipients. Several approaches have been introduced in the literature including polymer based glass solutions, mesoporous silica and co-amorphous formulations. The co-amorphous strategy has recently gained considerable interest in the pharmaceutical field as it provides opportunities to overcome shortcomings connected to polymer and mesoporous silica based approaches. The objective of this review is to provide an overview over the state of the art of co-amorphous drug formulations.

2. **What are co-amorphous formulations?**

Polymer based glass solutions, mesoporous silica and co-amorphous formulations all run under the term glass solutions, which itself is a subcategory of solid dispersions. The use of this expression is very inconsistent in the pharmaceutical field; therefore, this first section will provide a short guidance into the confused classification of solid dispersions.

The term solid dispersion was defined by Chiu and Riegelman [3] in 1971 as “a dispersion of one or more active ingredients in an inert carrier at the solid state prepared by the melting (fusion), solvent, or melting-solvent method.” According to this, solid dispersions can be classified according to their number of solid-state phases and the physical state of these phases. As presented in table 1.1, solid dispersions can be very diverse including eutectic mixtures, solid solutions, glass solutions and glass suspensions [4].
Table 1.1 Classification of solid dispersions (reproduced from [4])

<table>
<thead>
<tr>
<th>Solid dispersion</th>
<th>Number of phases</th>
<th>Physical state of phase(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eutectic mixture</td>
<td>2</td>
<td>C/C</td>
</tr>
<tr>
<td>Solid solution</td>
<td>1</td>
<td>C</td>
</tr>
<tr>
<td>Glass solution</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Glass suspension</td>
<td>2</td>
<td>A/A or A/C</td>
</tr>
</tbody>
</table>

(C: Crystal, A: Amorphous)

Glass solutions, i.e. single amorphous phase systems, are often referred to as amorphous solid dispersions (ASD) and can further be subdivided according to the excipients that stabilize the amorphous drug. Vaka et al. differentiated these into polymeric and non-polymeric excipients, where the polymeric excipients can further be separated into ionic and non-ionic polymers [5]. The group of non-polymeric excipients can further be divided into mesoporous silica based glass solutions and those containing only low molecular weight components, the so called co-amorphous formulations (Fig. 1.1).

By far most investigated ASDs are polymer based, so that nowadays for the most part, the expression solid dispersion is strongly connected to the use of polymers in stabilizing amorphous drugs. This is misleading as solid dispersions are a rather big group of different types of solid mixtures as mentioned in table 1.1. Thus, for clearer differentiation, ASDs with polymeric excipients are called polymer based glass solutions in this review.

![Fig. 1.1 Classification of co-amorphous mixtures within glass solutions based on the choice of the stabilizing agent.](image)

In polymer based glass solutions, polymeric carriers are used in order to stabilize the amorphous drug and improve its solubility and dissolution rate [6]. In these systems, stabilization of the drug in its amorphous form is achieved by several factors. One key aspect is the solubility of the drug in the amorphous polymer [7, 8]. Below its solubility limit, the drug is molecularly dispersed in the amorphous polymer and stabilized by the physical separation
of the molecules between the polymer chains. Most polymeric carriers also have a high glass transition temperature (Tg) and thus, increase the Tg (while reducing the molecular mobility) of the drug in the glass solution compared to the pure amorphous drug [9]. Furthermore, intermolecular interactions between the drug and functional groups of the polymer have been found to play a role in the stabilization mechanism [10]. However, limited drug solubility in the bulky polymeric excipients often makes the dosage size large and does not necessarily make the formulation very stable against recrystallization [11-13]. Another drawback is the hygroscopic nature of many polymeric carriers, which result in absorption of moisture. The absorbed moister acts as a plasticiser, thus, reducing the Tg and increasing mobility, which in turn can result in phase separation and recrystallization [13]. Thus, despite an active research interest, polymer based glass solutions have only led to a few marketed products [5, 14].

In mesoporous silica based glass solutions, the drugs are amorphized by adsorption to the surface of the silica particles, which consist of a matrix of pores with diameters between 2 and 50 nm [15]. Stabilization of the amorphous drug is on the one hand achieved through molecular interactions between the drug and the functional groups of the silica matrix [16, 17]. On the other hand, crystallization is inhibited physically by the pore diameter of the materials, which may be smaller than the size of a crystal nucleus of the drug [18]. The main drawbacks of mesoporous silica based glass solutions are, however, their production, which predominantly involves the use of organic solvents for drug loading [18], and often a limited loading capacity of only 20-30 % [19].

The co-amorphous drug formulation approach is characterized by the combination of two or more low molecular weight components that form a homogeneous amorphous single-phase system [20, 21]. In order to differentiate glass solution comprising of only small molecules from those with stabilizing polymers or mesoporous silica matrices, Chieng et al. have introduced the expression ‘co-amorphous’ in 2009 [22]. Using this approach, it has been proposed that the amount of stabilizing excipient (if used at all) can be drastically reduced due to the low molecular weight of the co-amorphous co-former. So far two types of co-amorphous principles have been introduced, namely drug-drug combinations and drug-excipient mixtures [21]. In the first type, two pharmacologically relevant drugs intended for multidrug therapies are combined where both drugs stabilize each other in the amorphous form. Thus, both drugs act as active component and stabilizing excipient at the same time. As a result of the stable amorphous system, both of the poorly soluble drugs achieve a higher solubility and dissolution rate. In the second type, low molecular weight excipients such as amino acids are used to prepare stable and fast dissolving co-amorphous drug-excipient blends.
3. **Technologies for the preparation of co-amorphous systems:**

A range of different preparative techniques has been described in the literature to produce the amorphous form of a drug. Depending on their amorphization mechanism, these methods can be divided into thermodynamic and kinetic disordered processes [23, 24]. The thermodynamic pathway has a thermodynamically stable non-crystalline form as a starting point, i.e. the drug as a melt or in solution. In order to obtain the amorphous drug, the melt needs to be subsequently vitrified by rapid cooling, a process called quench cooling, or the drug needs to be precipitated from the solution, followed by solvent removal. The kinetic pathway is carried out by direct solid-state conversion of the crystalline drug into its amorphous form. This can be achieved by continuously introducing crystal defects and disorders through e.g. shear forces, crushing and impact during a milling process [2, 25]. Naturally, both mechanisms have also been described for the preparation of amorphous blends [26].

The co-amorphous drug formulation approach is still in an early stage of development, thus, the vast majority of studies focused on the basic understanding of these systems using lab scale preparative techniques such as quench cooling [11, 27-37], solvent evaporation [38-47] and ball milling [28, 43, 47-57]. All of these techniques are attractive as they represent fast and easy ways of (co-)amorphization, and are ideal for screening purposes as only small sample sizes are required. In addition, quench cooling offers the possibility to quickly assess critical physico-chemical parameters such as the Tg, miscibility and recrystallization, as preparation and analysis of the co-amorphous systems can be directly performed *in situ* within a differential scanning calorimeter (DSC). However, not all of these methods can be applied for any type of drug or co-forming excipient. Quench cooling is only applicable to compounds that are not degrading upon melting. Solvent evaporation can be challenging if the poorly water-soluble components also show poor solubility in organic solvents; or if the two components are not soluble in the same solvent in appropriate concentrations, i.e. one component is only soluble in organic solvents whereas the co-amorphous co-former is only soluble in aqueous solvents. Ball milling on the other hand might not be efficient enough for disruption of the crystal lattice and thus, might not result in a complete (co-)amorphization. Therefore, the physico-chemical properties of drugs and excipients usually determine the preparative technique.

With a view on industrially more feasible production methods, a few studies have reported the use of scalable techniques for the preparation of co-amorphous formulations including spray-drying [58], freeze drying [59] and ultrasound extrusion [60, 61]. Furthermore, inkjet printing
has been applied for the preparation of co-amorphous indomethacin-arginine systems in order to obtain fabricated printed systems that allow flexible and more individualized dosing and thus, the development of fast dissolving personalized medicines [62].

4. **Mechanism of physical stabilization:**

4.1. **Amorphous Solubility:**

As mentioned in section 2, a co-amorphous system is a single-phase amorphous mixture of two or more low molecular weight components. For a system to be able to form a single phase, the components in the blend need to be fully miscible in the amorphous form. For thermo-stable compounds, the miscibility of the components in the molten state can easily be accessed through determination of the phase diagram [11, 28, 33, 36]. By quench cooling these single-phase melts, one can subsequently obtain a single-phase co-amorphous mixture. Similarly, Marsac et al. showed solubility using a melting point depression approach, where miscibility is shown as a depression of the drugs melting point while immiscible or partially miscible systems show little or no melting point depression [63]. For thermo-labile compounds, the use of solubility parameters can be used to estimate whether the components are miscible in the amorphous blend or not [36, 50, 51]. Another strong indicator for the formation of a homogeneous single-phase co-amorphous blend, where both components are dissolved in each other, is the observation of a single T_g [3, 64-66]. In contrast, immiscible or partially miscible components will result in two-phase amorphous mixtures, and thus, result in the observation of two T_g's [67].

Correspondingly, for polymer based glass solutions, the thermodynamic solubility of the drug in the amorphous polymer has been described as one of the primary reason for stability, however, many drugs only possess a limited solubility of the drug in the polymeric carrier (often ≤20 weight %) [68]. When the drug is supersaturated in the polymer, phase separation into drug rich and/or polymer/excipient rich domains may occur, followed by a rapid nucleation and crystal growth. Similarly, partially miscible or immiscible co-amorphous mixtures that form a homogeneous phase initially after preparation might show fast phase separation and crystallization.

4.2 **Glass Transition Temperature (T_g)**

The T_g of an amorphous material is defined as the temperature at which the material transforms from its glassy state into the supercooled liquid state upon heating [2, 25]. At the T_g, the material changes from a solid like material into a viscous liquid like material and accordingly
the molecular mobility changes drastically. Due to the higher molecular mobility, materials in the supercooled liquid state crystallize at a much faster rate than in the amorphous glassy state. However, even though the molecules in the glassy state are kinetically frozen, they are still in motion, albeit at a much slower rate. This phenomenon is called relaxation and is the reason for an amorphous material to crystallize over time into a thermodynamically stable form even at temperatures much below its Tg. In order to keep a glassy material in its amorphous form, it has been suggested to store amorphous materials at least 50 degrees below the Tg [2, 9, 64, 66, 69].

In glass solutions, the Tg of the amorphous multi component system is usually found between the Tgs of the individual components. This relationship is described by the Gordon-Taylor equation:

\[ T_{g12} = \frac{w_1 T_{g1} + K w_2 T_{g2}}{w_1 + K w_2} \]

where \( T_{g12} \) is the Tg of the amorphous mixture, \( T_{g1} \) and \( T_{g2} \) the Tgs of the respective individual components, \( w_1 \) and \( w_2 \) the respective weight fractions and \( K \) is a constant. It is thus not surprising that the inclusion of drugs into polymeric carriers with high Tg, such as PVP, has been shown to improve physical stability as a result of the increased Tg of the polymer-drug blend compared to the Tg of the pure amorphous drug [25]. This antiplasticizing effect of polymers is one of the key characteristics in polymer based glass solutions.

Compared to polymeric excipients, low molecular weight components, which the majority of drugs are, usually have a comparatively low Tg. Given that co-amorphous systems contain only low molecular weight molecules, the possibility of anti-plasticization is therefore only limited. Nevertheless, this principle has been shown in several cases of co-amorphous formulations. Especially, the use of amino acids as co-amorphous excipients has been shown to result in relatively high Tgs in co-amorphous blends, e.g. with the drugs carbamazepine and indomethacin [51]. The developed co-amorphous binary and ternary drug-amino acid systems have demonstrated excellent physical stability over at least six months, whereas the pure amorphous drugs recrystallized within seven days. Apart from the increase in Tg, the increased stability of the systems has been assigned to molecular interactions between the drugs and the amino acids [53]. In particular tryptophan showed excellent properties as co-former and antiplasticizer in co-amorphous system because of its high Tg of approx. 140 °C [52, 56]. Furthermore, in the case of strong ionic interactions between the components, the Tg of the co-amorphous systems can be much higher than the Tgs of the individual components [53, 70].
Hence elevated Tg of co-amorphous mixtures over their individual amorphous compounds has been argued as one of the factors for improved physical stability for these systems.

4.3 Intermolecular interactions

Many studies showed that the physical stability of co-amorphous systems is increased compared to the individual amorphous drugs. Since the Tg of co-amorphous systems is usually found in between the Tgs of the individual components, it was argued that the Tg alone cannot explain the increase in physical stability, but that stability is a result of several factors, including molecular interactions between the components in the co-amorphous mixture. The vast majority of reports on the co-amorphous formulation approach have attributed the physical stability of such systems to intermolecular interactions like hydrogen bonding and/or π-π interactions [17, 22, 28, 29, 36, 38, 39, 41-43, 46, 51, 57].

In individual amorphous components, the molecules often are arranged with a certain short-range molecular order, which is reflected in molecular interactions between like molecules, such as the formation of homodimers in amorphous indomethacin or naproxen [37]. The homodimers are often also found similarly in the crystalline state of the drugs and thus, recrystallization in the pure amorphous form occurs usually at a rather high rate. In the co-amorphous blend on the other hand, this molecular short-range order gets disturbed in favour of the formation of intermolecular interactions between non-like molecules, i.e. the two different components in the co-amorphous blend. Such a formation of heterodimers has been shown in several studies of co-amorphous formulations, such as naproxen/indomethacin, ritonavir/quercetin and cimetidine/piroxicam systems [36, 42, 46]. For such a system to recrystallize, it has been argued that the intermolecular bonds within the heterodimer must be broken, followed by a rearrangement to surrounding like molecules to form homodimers and the subsequent establishment of long-range order in the crystal lattice. This cascade is happening on a considerable longer time scale, leading to a reduced likelihood of recrystallization and thus, prolonged physical stability of the co-amorphous systems [20, 21, 56]. Furthermore, the formation of even stronger ionic interactions has been described for co-amorphous systems. Yamamura et al. prepared co-amorphous systems of cimetidine with indomethacin and diflunisal and found salt formation between the imidazole ring of cimetidine and carboxyl groups of indomethacin and diflunisal [38, 39].

Strong molecular interactions have also been shown for drug-excipient mixtures [11, 30, 32, 47]. Especially the use of amino acids as excipients has recently shown strong potential to stabilize drugs in the co-amorphous form [51-53, 56, 58, 70]. The approach was originally based on the assumption that drugs interact at the molecular level with amino acids at their
respective target sites (receptor proteins) in the body and thus, may also be able to interact with amino acids in a co-amorphous mixture [51]. For this purpose, binary and ternary co-amorphous systems comprising indomethacin and carbamazepine with a set of amino acids (receptor and non-receptor) were prepared by ball milling and found to be stable for at least 6 months at 40 °C. The physical stability of the indomethacin/arginine system was attributed to ionic interactions between the carboxylic acid group of indomethacin and the guanidine moiety of arginine. For the tryptophan/carbamazepine system, hydrogen bond and π-π interactions have been found responsible for the increased physical stability. However, there are obvious differences between the anticipated interactions based on \textit{in vivo} binding and actually observed interactions in the co-amorphous mixtures. Unlike \textit{in vivo} where only the side chains of the amino acids are able to interact with the drug, it was found that the whole amino acid molecule i.e. side chain as well as head group interacted with the drug in the co-amorphous states [21, 51].

Such intermolecular interactions in the solid state have been investigated using FTIR spectroscopy [28, 30, 36, 40, 41, 43, 45-47, 49, 52-54, 71] and solid state NMR [32-34, 38, 39, 42, 56]. Furthermore, a deviation of the experimental Tg values from the theoretical Tg values using the Gordon-Taylor equation can be used for identifying molecular interactions. The Gordon-Taylor equation describes the Tg of a homogeneous amorphous blend of two components and is based upon two important assumptions. First, ideal free volume additivity of the two components in the amorphous mixture and second, no specific interactions exist between these components (ideal mixing behaviour). As the Gordon-Taylor equation explains the dependence of Tg on the composition of the amorphous blends under the above mentioned assumptions, deviations of the calculated values from experimentally observed ones have been interpreted as the possibility of intermolecular interactions [64, 72-75].

A modified approach of using the Gordon-Taylor equation has been described for co-amorphous naproxen/indomethacin when the degree of molecular interactions, e.g. the formation of a heterodimer, between the components is known [36]. In such a case, the deviation of the experimentally determined Tg values from the theoretical Tg values calculated from the Gordon-Taylor equation was largest for the co-amorphous system showing the largest degree of molecular interactions, i.e. the heterodimer at the 1:1 molar ratio. Assuming that the heterodimer is one component, whereas any excess drug represents the second component in the co-amorphous blends, the theoretical Tg values of the mixtures can be recalculated. In the above example, an ideal fit of the experimental values with the theoretical Tg values using this modified approach of the Gordon-Taylor equation was obtained. This finding strongly
suggested that ideal mixing behaviour was observed for the heterodimer and any excess drug in those mixtures. Therefore, it has been suggested that one should consider using the interacting adduct between the components in amorphous blends rather than the pure components when using the Gordon-Taylor equation. Vice versa, when looking for the largest deviation from the classical Gordon-Taylor approach by determining the experimental Tgs over a range of different ratios, one might be able to identify the co-amorphous blend with the largest degree of interactions between the components in the mixture.

4.4 Intimate mixing

In some co-amorphous systems, an improved physical stability was observed as a result of intimate mixing, i.e. physical separation of the like molecules in the homogeneous co-amorphous blend. Simvastatin/glipizide systems showed improved physical stability over the individual amorphous drugs without any detectable intermolecular interactions or an increased Tg [50]. Dengale et al. reported similar observations for ritonavir/indomethacin systems after co-precipitation followed by solvent evaporation [45]. The recrystallization of these systems is thought to be a result of slow demixing and phase separation.

Overall, for most co-amorphous systems, a clear separation of the above mentioned stabilization mechanisms is not possible but the increased stability is rather the result of a combination of these mechanisms. Along with molecular interactions, Löbmann et al. for example attributed the physical stability of co-amorphous systems of indomethacin and carbamazepine with various amino acids to the molecular level mixing of drug with amino acids, molecular interactions between those and the increased Tg after ball milling [51, 53]. It is important to mention that solid-state solubility of the components is the first requirement for a co-amorphous blend, whereas increased Tg, molecular interactions and intimate mixing result out of the miscibility of the components in the amorphous blend. Table 1.2 summarizes the factors that have been attributed to be mainly responsible for the increased stability of different co-amorphous formulations.
<table>
<thead>
<tr>
<th>System</th>
<th>Main type of stabilization</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine /Indomethacin</td>
<td>Salt formation</td>
<td>[39]</td>
</tr>
<tr>
<td>Cimetidine/Diflunisal</td>
<td>Salt formation</td>
<td>[38]</td>
</tr>
<tr>
<td>γ-Indomethacin/Ranitidine</td>
<td>Hydrogen bonding</td>
<td>[22]</td>
</tr>
<tr>
<td>hydrochloride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen/ Cimetidine</td>
<td>π – π interactions</td>
<td>[57]</td>
</tr>
<tr>
<td>Cimetidine/Piroxicam</td>
<td>Hydrogen bonding</td>
<td>[42]</td>
</tr>
<tr>
<td>γ-Indomethacin/Naproxen</td>
<td>Hydrogen bonding</td>
<td>[36]</td>
</tr>
<tr>
<td>Simvastatin/Glipizide</td>
<td>Intimate mixing</td>
<td>[50]</td>
</tr>
<tr>
<td>Ritonavir/Indomethacin</td>
<td>Intimate mixing</td>
<td>[45]</td>
</tr>
<tr>
<td>Acyclovir/Indomethacin</td>
<td>Hydrogen bonding</td>
<td>[41]</td>
</tr>
<tr>
<td>Indomethacin/Arginine</td>
<td>Salt formation, Tg increase</td>
<td>[51, 53]</td>
</tr>
<tr>
<td>Indomethacin/Tryptophan</td>
<td>Hydrogen bonding and π-π interaction, Tg increase</td>
<td>[51, 53]</td>
</tr>
<tr>
<td>Indomethacin/Phenylalanine</td>
<td>Hydrogen bonding and π-π interaction</td>
<td>[51, 53]</td>
</tr>
<tr>
<td>Indomethacin/Phenylalanine/Tryptophan</td>
<td>Hydrogen bonding and π-π interaction</td>
<td>[51, 53]</td>
</tr>
<tr>
<td>Carbamazepine/Arginine/Tryptophan</td>
<td>Hydrogen bonding and π-π interaction</td>
<td>[51, 53]</td>
</tr>
<tr>
<td>Carbamazepine/Phenylalanine/Tryptophan</td>
<td>Hydrogen bonding and π-π interaction</td>
<td>[51, 53]</td>
</tr>
<tr>
<td>Carbamazepine/Tryptophan</td>
<td>Hydrogen bonding and π-π interaction</td>
<td>[51, 53]</td>
</tr>
<tr>
<td>Indomethacin/Arginine/Phenylalanine</td>
<td>Salt formation and hydrogen bonding</td>
<td>[51, 53]</td>
</tr>
<tr>
<td>Naproxen/Indomethacin</td>
<td>Hydrogen bonding</td>
<td>[52]</td>
</tr>
<tr>
<td>Naproxen/Arginine/Proline</td>
<td>Salt formation and hydrogen bonding</td>
<td>[52]</td>
</tr>
<tr>
<td>Naproxen/Tryptophan</td>
<td>Hydrogen Bonding</td>
<td>[52]</td>
</tr>
<tr>
<td>Naproxen/Tryptophan/Proline</td>
<td>Hydrogen bonding</td>
<td>[52]</td>
</tr>
<tr>
<td>Naproxen /Arginine</td>
<td>Salt formation</td>
<td>[52]</td>
</tr>
<tr>
<td>Paracetamol/Citric Acid</td>
<td>Hydrogen Bonding</td>
<td>[32]</td>
</tr>
<tr>
<td>Indomethacin/Tryptophan</td>
<td>π – π interaction</td>
<td>[56]</td>
</tr>
<tr>
<td>Furosemide/Tryptophan</td>
<td>Hydrogen bonding</td>
<td>[56]</td>
</tr>
</tbody>
</table>
5. **Dissolution properties:**

As a result of the higher internal energy of amorphous phases, they possess a higher solubility and dissolution rate compared to their crystalline counterparts [2, 20, 65, 76]. Accordingly, co-amorphous systems have been found to show improved dissolution behaviour over their crystalline counterparts and their individual amorphous forms (Table 1.3) [36, 45, 47, 50-52, 55, 57]. For example, Allesø et al. observed a higher dissolution rate of co-amorphous naproxen/cimetidine compared to both crystalline drugs, but also compared to amorphous cimetidine (a comparison to amorphous naproxen was not made because of its high instability and fast recrystallization immediately after preparation). The dissolution rate of pure amorphous cimetidine was found to be identical to that of crystalline cimetidine indicating its recrystallization upon contact with the dissolution medium. However, when co-milled together with naproxen, cimetidine showed a two-fold increase in dissolution rate without any evidence of recrystallization. The authors suggested that co-amorphization prevented cimetidine from recrystallization upon dissolution [57]. Similarly, fast solvent mediated recrystallization was observed for pure amorphous lurasidone HCl during dissolution and resulted in a fast offset of the dissolution rate comparable to the dissolution rate of crystalline lurasidone HCl (Figure 1.2). Recrystallization was confirmed as birefringence on the surface of the intrinsic dissolution compact. On the other hand, co-amorphous lurasidone HCl/saccharin showed a continuous fast dissolution (5.6 fold faster than crystalline lurasidone HCl) over the duration of the dissolution experiment [47]. Unlike pure amorphous lurasidone HCl, birefringence was not observed on the surface of the co-amorphous tablet indicating the absence of recrystallization during dissolution. Thus, co-amorphization does not only increase the dissolution rate of the drug but can also help preventing solvent induced recrystallization upon dissolution. Again molecular interactions played a crucial role in this stabilization mechanism [36, 57, 70]. On the other hand, Dengale et al. found that ritonavir/indomethacin systems showed an improvement in the dissolution rate of ritonavir as a result of intimate mixing without the presence of intermolecular interactions [45].
Apart from enhanced dissolution rates, some co-amorphous mixtures have shown a pair-wise or synchronized dissolution of the individual components as a result of their short-range molecular order, i.e. the formation of hetero-dimers through hydrogen bonds [36, 57]. For co-amorphous naproxen/cimetidine, it has been suggested that pair-wise solvation and their interdependency upon dissolution were responsible for the synchronized release. Both are a result of the intermolecular interactions at a 1:1 molar ratio. Similar findings were also reported for co-amorphous naproxen/indomethacin, and again related to the intermolecular interactions between the two drugs in the mixture [36]. Since synchronized release of two components from the co-amorphous blends appears to be a result of strong intermolecular interactions between them, it has been suggested that the dissolution rate of a poorly soluble drug can be tailored by the solubility/dissolution rate of the co-amorphous co-former [52, 70]. In the case that strong intermolecular interactions exist between the two components, the co-former might facilitate the dissolution of a given poorly water-soluble drug. In other words, the dissolution rate of the poorly soluble component is
dependent upon the solubility of the co-former. In this regard, it was found that dissolution rates for several non-salt forming co-amorphous indomethacin/amino acid systems were dependant on the solubility of the co-forming amino acid [51]. A similar approach was reported for ternary co-amorphous naproxen/tryptophan/proline and naproxen/arginine/proline mixtures. In this particular study, Jensen et al. applied two formulation principles. First, the amorphous form of naproxen was stabilized by co-amorphization with the high Tg amino acid tryptophan (see section 4.2) or the strongly interacting amino acid arginine (salt formation). Second, dissolution improvement was achieved by inclusion of the highly soluble amino acid proline, which itself was a poor amorphous stabilizer [52]. As a result, both ternary mixtures had an increased dissolution rate compared to the binary mixtures naproxen/tryptophan and naproxen/arginine. However, in a subsequent study, it could be shown that the use of highly soluble co-formers to facilitate the dissolution of a given drug only works to a certain degree [70]. When the solubility of the co-former is too high and/or interactions between the components are not strong enough, then the highly soluble co-former dissolves too fast from the co-amorphous system, leaving the pure amorphous form behind. As a consequence, the drug loses its amorphous stabilizer and is thus, prone to recrystallize.

In order to investigate drug supersaturation from co-amorphous formulations, Heikinnen et al. studied the dissolution of different co-amorphous drug amino acid formulations under non-sink conditions in phosphate buffer and biorelevant media i.e. fasted (FaSSIF) and fed state simulated intestinal fluid (FeSSIF) [55]. All of the investigated systems (simvastatin/lysine, glibenclamide/serine, glibenclamide/threonine and glibenclamide/serine/threonine) showed an increased dissolution rate and a long lasting supersaturation compared to the individual amorphous and crystalline drugs (Fig. 1.3). In the case of glibenclamide, the pure amorphous form provided a similar supersaturation as the co-amorphous systems, however, the dissolution rate of the pure amorphous form was slightly slower (Fig. 1.3, b). Given that the pure amorphous form performed similar to the co-amorphous blends in this example, it is worth mentioning that the formation of a co-amorphous form was still beneficial due to the prolonged physical stability of amorphous glibenclamide [54]. Similarly, Shayanfar et al. showed a long lasting supersaturation of the two drugs atorvastatin and glibenclamide from their respective co-amorphous mixtures [40].

Overall, the dissolution of co-amorphous formulations has been shown to be improved compared to the pure crystalline and amorphous drugs. Molecular interactions again proofed to be important for preventing solvent induced recrystallization, but also contributed to a possible synchronized release of the components from the co-amorphous mixtures. The
dissolution rate of the poorly soluble drug from the co-amorphous blend is dependent on the solubility of the co-former and the strength of the molecular interactions between drug and co-former. Furthermore, co-amorphous formulations can provide long lasting supersaturation.

Fig. 1.3 Powder dissolution profiles of crystalline, amorphous and co-amorphous (a) simvastatin (SVS) and (b) glibenclamide (GBC) formulations indicating long lasting supersaturation achieved using the co-amorphous drug-amino acid formulation approach. For clarifying the differences of the dissolution profiles of glibenclamide, a magnification of the first 90 minutes was inserted. (Abbreviations: LYS = lysine, THR = threonine, SER = serine, CM = cryomilled, PM = physical mixture) (adapted from [55])
Table 1.3. Comparative account of dissolution properties of co-amorphous systems.

<table>
<thead>
<tr>
<th>Co-amorphous system</th>
<th>Individual component</th>
<th>Measured dissolution property</th>
<th>Dissolution improvement</th>
<th>Synchronized release</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen (NAP)/Cimetidine (CIM)</td>
<td>Crystalline NAP</td>
<td>0.359 ± 0.016*</td>
<td>NA</td>
<td>NA</td>
<td>[57]</td>
</tr>
<tr>
<td></td>
<td>Crystalline CIM</td>
<td>0.659 ± 0.038*</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>NAP co-milled</td>
<td>1.49 ± 0.108*</td>
<td>4-fold</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>CIM co-milled</td>
<td>1.32 ± 0.104*</td>
<td>2-fold</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalline IND</td>
<td>0.055 ± 0.002*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalline NAP</td>
<td>0.300 ± 0.001*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indomethacin (IND)/NAP</td>
<td>IND (NAP:IND 1:1)</td>
<td>0.491 ± 0.012*</td>
<td>9-fold</td>
<td>Yes</td>
<td>[36]</td>
</tr>
<tr>
<td></td>
<td>NAP (NAP:IND 1:1)</td>
<td>0.411 ± 0.003*</td>
<td>1.37-fold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalline SVS</td>
<td>6.7 ± 1.4*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalline GPZ</td>
<td>7.6 ± 2.9*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin (SVS)/Clipizide (GPZ)</td>
<td>GPZ (SVS:GPZ 1:1 BM)</td>
<td>28 ± 11†</td>
<td>3.7-fold</td>
<td>Nil</td>
<td>[50]</td>
</tr>
<tr>
<td></td>
<td>GPZ (SVS:GPZ 1:1 CM)</td>
<td>24 ± 15†</td>
<td>3.1-fold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalline CBZ</td>
<td>0.034 ± 0.001*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine (CBZ)/Amino acids</td>
<td>CBZ (CBZ: Arginine:Tryptophan)</td>
<td>0.047 ± 0.005*</td>
<td>Marginal (&lt;0)</td>
<td>Nil</td>
<td>[51]</td>
</tr>
<tr>
<td></td>
<td>CBZ (CBZ: Pheryllamine:Tryptophan)</td>
<td>0.041 ± 0.003*</td>
<td>Marginal (&lt;0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CBZ (CBZ: Tryptophan)</td>
<td>0.037 ± 0.001*</td>
<td>Marginal (&lt;0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IND/Amino acids</td>
<td>IND (IND: Arginine: Phenylalanine)</td>
<td>11.19*</td>
<td>200-fold</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IND (IND: Arginine)</td>
<td>12.25*</td>
<td>200-fold</td>
<td>Nil</td>
<td>[51]</td>
</tr>
<tr>
<td></td>
<td>IND (IND: Tryptophan)</td>
<td>0.096*</td>
<td>1.5-fold</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IND (IND: Phenylalanine)</td>
<td>0.175*</td>
<td>3-fold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalline RTV</td>
<td>0.13†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalline IND</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir (RTV)/IND</td>
<td>RTV (RTV:IND 1:1)</td>
<td>0.56†</td>
<td>43-fold</td>
<td>Nil</td>
<td>[45]</td>
</tr>
<tr>
<td></td>
<td>IND (RTV:IND 1:1)</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lurasidone HCl (LH)/Saccharine (SAC)</td>
<td>Crystalline LH</td>
<td>0.0066*</td>
<td>NA</td>
<td>Nil</td>
<td>[47]</td>
</tr>
<tr>
<td></td>
<td>LH (LH:SAC)</td>
<td>0.0371*</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NI Not investigated.
NR Not reported.
NA Not applicable.
† Dissolution rates expressed in μg/mL.
* Intrinsic dissolution rates expressed in mg cm⁻² min⁻¹.
6. *In vivo* performance:

In order to demonstrate the potential of the co-amorphous formulation approach, the positive *in vitro* dissolution results also need to be reflected in an increased *in vivo* bioavailability. Since the co-amorphous technology is a rather new approach in the improvement of amorphous stability of drugs and their dissolution, only a limited number of studies have been published on *in vivo* performance of these systems [44, 46, 71]. For example, poorly water-soluble curcumin has been co-amorphized with artemisin and administered to Sprague Dawley male rats for bioavailability analysis [44]. Because of the poor solubility of pure crystalline curcumin, the drug was not detected in the plasma when administered alone. On the other hand, a considerable high amount of curcumin was found when administering it as co-amorphous formulation together with artemisin. However, no control groups where analysed, i.e. pure amorphous curcumin or a physical mixture of curcumin and artemisin. Therefore, one has to be careful in the interpretation of these results, since it is unclear whether the increase in bioavailability was solely due to amorphization of curcumin or a result of its co-amorphous formulation.

In addition to poor solubility, poor intestinal permeability can add to the low bioavailability of a given drug. Poorly soluble and poorly permeable drugs are classified as class 4 drugs in the biopharmaceutics classification system (BCS) and are particularly problematic, since an increase in dissolution and solubility alone might not result in an increased bioavailability. In this context, poor permeability can be due to the physico-chemical properties of the drug molecule, such as size and polarity, but often is due to being substrate of so-called intestinal efflux pumps [77, 78]. These efflux pumps are situated in the absorption cell layer of the intestine and their main purpose is to avoid that toxins enter the systemic blood circulation. Their mechanism of protection is to remove toxins that enter the first cell line within the intestine by immediately pumping them back into the intestine. The process of protecting the body from toxins also extends to many drugs, as they are also substrates of these efflux pumps. In order to overcome the challenges associated with poorly soluble drugs that are at the same time efflux pump substrates, Teja et al. applied the co-amorphous formulation approach to address both problems at the same time. In particular, the authors’ co-amorphized the poorly soluble and permeable drug talinolol, an efflux pump substrate, with the efflux pump inhibitor narginin [71]. Using this approach the authors were able to improve the dissolution rate of talinolol while at the same time increasing absorption of the drug through efflux pump inhibiton of the co-administered narginin. The bioavailability of talinolol in wistar rats could thus, be
significantly improved. The mean AUC\textsubscript{\text{0-\text{t}}} from co-amorphous talinolol/narginin was found to be 5.4-fold higher compared to the administration of pure crystalline talinolol (Figure 1.4). In order to study the influence of narginin on talinolol’s permeability, the author further studied the permeability using the \textit{in situ} intestinal closed loop method. Talinolol permeability was found slightly increased from \(2.48 \times 10^{-5}\) cm/s (control value in absence of naringin) to \(3.16 \times 10^{-5}\) cm/s when formulated as co-amorphous talinolol/naringin system. The bioavailability increase of talinolol was thus attributed to a combination of increased solubility from the co-amorphous formulation together with the efflux pump inhibition of narginin. Again, these findings have to be considered carefully as no control groups using pure amorphous talinolol or a co-administration of physically mixed narginin were investigated. Thus, a direct connection to the co-amorphous formulation approach cannot be drawn.

The same group also investigated the bioavailability of co-amorphous ritonavir/quercetin, where ritonavir is an efflux pump substrate and quercetin a efflux pump inhibitor [46]. However, unlike talinolol/naringin, there was no statistically significant improvement in the bioavailability (AUC) of ritonavir from its co-amorphous formulation as compared to the crystalline control. Even though a 5-fold improvement of the \textit{in vitro} saturation solubility was achieved for ritonavir from its co-amorphous system, the advantage could not be translated into a significant \textit{in vivo} outcome. On the other hand, the \(T_{\text{max}}\) value was significantly reduced from 6 h to 4 h for the co-amorphous formulation compared to pure crystalline ritonavir, indicating improved absorption. This improvement was again attributed to enhanced solubility and permeability due to co-amorphization and efflux pump inhibition. However, similar to the above-mentioned studies, this study did not investigate any other controls.

Overall, the few \textit{in vivo} studies that have been performed using co-amorphous formulations indicated the potential of the co-amorphous approach. Nevertheless, there are still some open questions whether the improved bioavailability was due to pure amorphization of the drug or a result of the co-amorphous formulation itself. Furthermore, a direct comparison to other amorphous stabilization techniques such as polymer or silica based glass solutions would be interesting.
Figure 1.4: Mean plasma concentration–time profile for pure talinolol (triangles) and co-amorphous talinolo/narginin (squares) (adapted from [71])

7. Concluding remarks and future outlook:

The co-amorphous technology has established itself as a promising approach to increase dissolution/solubility of poorly water-soluble drugs and potential to achieve bioavailability improvement. Whilst it has potential to become a platform technology to deal with these drugs, it is still a very young technology and the concept needs to be further established.

Most of the referred studies concentrated on the fundamental understanding of co-amorphous formulations, their stabilization mechanism and their behaviour during dissolution. However, there are still many unknowns and it is important to get a deeper understanding on how these systems work. For example, like polymer-based glass solutions, the tendency of moisture uptake may also prove problematic for co-amorphous systems. Most of the stability studies of co-amorphous mixtures have been conducted in dry conditions. Thus, it would be interesting to study the effect of water on the performance of co-amorphous systems.

Especially, in co-amorphous drug-excipient mixtures, there is no clear rationale when an excipient is suitable as a co-former or not. In the studies using amino acids as excipients, it could be shown that certain amino acids can be successfully co-amorphised with one drug but not necessarily with another. Therefore, finding a good co-former might become a labour
intensive search given the plethora of different amino acids and other co-formers. A suitable screening method to quickly assess which amino acid (or any other excipient) is suitable as co-amorphous excipient for a given drug would thus be very valuable.

With respect to co-amorphous drug/drug formulations, it might be difficult to find a suitable partner molecule with a suitable pharmacological profile. Another important issue here are regulatory constraints and the compliance of administering more than one drug at the same time at a fixed ratio between the two drugs.

The in vivo studies performed on co-amorphous drug formulations so far showed a potential in increasing the bioavailability of poorly water soluble drugs. However, more studies and better understanding is required to draw conclusions on their behaviour in vivo. For example, the co-amorphous formulations need to be tested against the individual amorphous drugs as well as other competing technologies like polymer based or mesoporous silica based glass solutions.

Down-streaming of the formulations into final dosage forms, i.e. capsules or tablets, is another important factor that needs to be considered in future. For this purpose, more understanding on scalable production techniques, such as spray drying and melt extrusion, is necessary to make this approach feasible in an industrial setup. Furthermore, there is only little knowledge on the process ability of co-amorphous formulations. Amorphous materials have shown problems with powder flow, pulverization and sticking to punches in tablet presses [12]. Another issue could be to find a suitable granulation process. A wet granulation may not be feasible as the introduced water acts as a plasticiser and can induce crystallization. On the other hand, using melt granulation, the introduced heat could be above the Tg of the co-amorphous formulation, which as well may carry a risk for recrystallization. It has also been reported that amorphous materials can have significant problems with disintegration when formulated into tablets [79, 80]. In this context, Lenz et al. were the first to report a successful tablet formulation using the co-amorphous approach [58].

Despite the challenges, co-amorphous formulations have shown to be a very promising and upcoming technique to stabilize the amorphous form of drugs, increase the dissolution and bioavailability of poorly soluble drugs, and to overcome drawbacks related to other amorphous formulation strategies. Many studies have been published that point out the possibilities this approach might lead in the future.
References:


