Abstract

Today, approximately 40% of the approved drugs and 90% of the drug candidates under development are poorly water-soluble, usually resulting in poor and variable oral absorption and therefore, a low and variable bioavailability after administration. Thus, improving dissolution rate and solubility of poorly water-soluble drugs has become an important topic in pharmaceutical drug development. In this context, one promising formulation approach is the preparation of co-amorphous systems, i.e., homogeneous amorphous systems consisting of a drug and a low molecular weight co-former.

This thesis focuses on the role of the co-formers used in co-amorphous systems, in particular their co-formability (the ability to form a co-amorphous system with a given drug), their dissolution enhancement and physical stabilization propensity. Specifically, a set of different co-formers has been investigated with respect to (i) the role of structural similarity of two co-formers, where one allows for salt formation and the other does not, (ii) the combination of two amino acids with good co-formability and dissolution enhancement into one molecule, i.e. a dipeptide, (iii) organic acids as potential co-formers and the influence of the molar ratio between drug and organic acid, and (iv) the use of co-formers where a formation of both co-amorphous and co-crystal systems is possible.

In the first study of this thesis, the role of salt formation versus structural similarity between the drug and the co-former was investigated by using the structurally similar amino acids arginine (ARG) and citrulline (CTL) as co-formers for two basic and two acidic drugs. The results showed that salt formation of ARG with the acidic drugs, rather than the structural similarity of the co-former CTL, determined the formation of a co-amorphous system with an improved dissolution rate and high physical stability. Furthermore, compared to ARG, CTL showed poor co-formability with the basic drugs.

In the second study, the dipeptide analogue aspartame and five dipeptides were investigated as co-formers, based on the assumption that a combination of good co-formability of one amino acid and potential dissolution enhancement of the other amino acid may result in a better performance than the single amino acids or a physical mixture of the two amino acids. Mebendazole (MEB) was used as the model drug. Aspartame and most dipeptides indeed showed better co-formabilities than the corresponding single amino acids or physical mixtures of two amino acids, assumed due to the higher molecular weights of aspartame and the dipeptides. Furthermore, different dipeptides
enhanced the dissolution rate of MEB to varying degrees, offering various options for tailoring specific desired release profiles. However, the role of the type of amino acid included in the dipeptides on co-formability and dissolution rate enhancement remains to be further investigated.

In the third study, three organic acids (OAs) (benzoic acid, malic acid and citric acid, containing one, two, three -COOH groups, respectively), together with the basic model drug carvedilol (CAR), were used to investigate the suitability of organic acids as co-formers. It was assumed that the use of a co-former with more than one -COOH group can result in very beneficial drug loadings since potentially more than one (basic) drug molecule can form a salt with a single co-former molecule. Amorphous salt formation was indeed observed between CAR and the OAs, and the degrees of salt formation varied according to the molar ratios of CAR and OAs. Complete salt formation usually resulted in high physical stability of the obtained co-amorphous systems. OAs with more than one -COOH group offer a higher “drug-loading” compared to amino acid based co-amorphous systems, where the co-former and the drug previously usually form co-amorphous systems at a 1:1 molar ratio.

In the last study, four organic acids, saccharin and nicotinamide were used as potential co-formers to investigate whether a stable co-amorphous system can be prepared when at the same time a corresponding co-crystal between the drug and co-former exists. Carbamazepine (CBZ)-co-former co-crystals and CBZ-co-former physical mixtures were subjected to a milling process. Upon milling, it was found that CBZ and the co-formers tended to maintain or form co-crystals, rather than forming co-amorphous systems. If, on the other hand, quench cooling was used as a preparation method, co-amorphous systems could be prepared. However, the obtained co-amorphous systems were rather unstable and recrystallized within a short time. Thus, it is suggested to avoid the use of co-formers that can form co-crystals with a given drug for the preparation of co-amorphous systems.

In conclusion, various co-formers for co-amorphous systems were investigated in the work performed for this thesis. In addition to “traditional” single amino acids, aspartame, dipeptides, and organic acids have been shown to be potential co-former options with different properties useful for co-amorphous systems. Overall, this thesis has shed more light on the applicability of different co-formers, potentially helping to guide the decision-making on co-former selection to development of co-amorphous formulations with desired properties in the future.