Amino acids as amorphous stabilizers and dissolution enhancers for poorly water soluble drugs

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ABSTRACT SUMMARY
A novel approach to stabilize the amorphous form and to improve the dissolution rate of the two poorly water soluble drugs carbamazepine (CBZ) and indomethacin (IND) by using low molecular weight excipients, i.e. amino acids, is presented. The reason for the improved physico-chemical properties of the resulting co-amorphous drug – amino acid mixtures could be explained by an increased glass transition temperature of the mixture and molecular level mixing of drug and amino acids.

INTRODUCTION
Converting a crystalline to an amorphous form of a compound is a well known strategy to improve the dissolution rate and solubility of poorly water soluble drugs. However, amorphous materials are characterized by their high internal energy making them prone to recrystallization, resulting in low physical stability and the loss of dissolution rate advantages compared to the crystalline state. In order to gain from the dissolution rate and solubility advantages associated with the amorphous form of poorly water soluble drug, there is a need to stabilize its amorphous form.

One of the strategies to overcome limitations with poor physical stability is the preparation of co-amorphous formulations. These systems are characterized by mixing two low molecular weight components into a homogeneous single phase co-amorphous blend. This concept was introduced by Chienget al. when ball milling the two drugs IND and ranitidine hydrochloride intended for combination therapy, into a co-amorphous formulation. The increased physical stability and dissolution rate improvement of these systems was explained by the formation of strong and specific intermolecular interactions between the components in the mixture. However, studies on the co-amorphous formulation approach so far concentrated on the combination of two drug molecules of similar molecular weight, which had to be a pharmacologically relevant pair. Thus there is a need to expand this concept to the use of low molecular weight excipients to further explore the potential of this promising new formulation approach. In this study, amino acids are introduced as low molecular weight excipients in co-amorphous drug formulations to stabilize the amorphous form and to improve the dissolution rate of the two poorly water soluble drugs CBZ and IND.

EXPERIMENTAL METHODS
The two drugs carbamazepine (CBZ) and indomethacin (IND) together with the four amino acids arginine (ARG), phenylalanine (PHE), tryptophan (TRP) and tyrosine (TYR) as excipients were investigated towards their ability to form co-amorphous blends of drug and excipients. Various mixtures at the molar ratios 1:1 (drug:excipient), and 1:1:1 (drug:excipient 1:excipient 2) were prepared as co-amorphous formulations by vibrational ball milling.

Their solid state properties were analyzed with X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC), and tested towards their chemical and physical stability using HPLC and XRPD, respectively. Intrinsic dissolution studies were performed to identify dissolution rate advantages of the co-amorphous blends over the crystalline and amorphous forms of the individual drugs.
RESULTS AND DISCUSSION

CBZ could only be obtained in its amorphous form when combined with its biological receptor binding amino acid TRP, whereas this was not possible with CBZ alone. On the other hand, IND could be successfully milled individually and in combination with several amino acids to generate amorphous forms. The presence of amino acids, however, facilitated the amorphous transformation as the amorphous material was achieved after shorter milling times when compared to the pure drugs. In the case of CBZ, the presence of TRP was necessary to even achieve amorphization of the drug.

Differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) analysis revealed that co-milling of drug and amino acids resulted in homogeneous single phase mixtures, indicated by the appearance of a single glass transition temperature (T_g) and an amorphous halo in the X-ray diffractograms, respectively. In addition, the T_g's of the co-amorphous mixtures were significantly increased over those of the individual drugs (ball milled IND and quench cooled CBZ). This can be seen as an advantage over the single amorphous forms, since generally a higher T_g is connected to a higher physical stability of the material.

Furthermore, the intrinsic dissolution rates (IDR) of all co-amorphous drug-amino acid mixtures was found to be significantly increased over the IDR of the respective crystalline and amorphous pure drugs.

The drugs remained chemically stable during the milling process and the co-amorphous formulations showed excellent physically stability over at least 6 months at 40 °C under dry conditions (Fig. 1). In an earlier study on co-amorphous simvastatin and glipizide, it was found that molecular level mixing can increase the physical stability of co-amorphous mixtures. Thus, the improved stability of these mixtures was related to an elevated T_g of the mixtures as mentioned above and a molecular level mixing effect between drug and amino acid.

CONCLUSION

It could be shown that amino acids are promising future excipients for the use in co-amorphous drug formulations to increase the dissolution rate of poorly soluble drug and to improve the amorphous stability of these drugs.

REFERENCES

1. Aaltonen, J. et al.; Dissolution Technol. 2009, 16, 47-54

Fig. 1: X-ray powder diffractograms of physically stable co-amorphous materials after 6 months: (a) CBZ-TRP, (b) CBZ-PHE-TRP, (c) CBZ-ARG-TRP, (d) IND-ARG-PHE, (e) IND-PHE-TRP, (f) IND-TRP, (g) IND-ARG.