Co-amorphous Formulations Seen From a Molecular Descriptor Perspective
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Purpose
The purpose of this work is to use multivariate data analysis to identify molecular descriptors that are crucial for describing the variation in the properties of amino acids used for successfully forming co-amorphous mixtures with drugs.

Methods
Maestro software (Schrödinger, LLC, New York, NY) was used for sketching and energy minimizing 5 model drugs (indomethacin, furosemide, mebendazole, carbamazepine, carvedilol) and 20 L-amino acids, resulting in overall 100 different combinations. Molecular Operating Environment software (Chemical Computing Group Inc., Montreal, QC, Canada) was used to calculate surface area, volume and shape (VolSurf-like) descriptors from the 3D structures. The multivariate data analysis software SIMCA 14.1 (Umetrics AB, Umeå, Sweden) was used for Partial Least Squares Discriminant Analysis (PLS-DA). X-ray powder diffraction (XRPD) was used to investigate whether 1:1 molar ratio drug-amino acids samples formed a co-amorphous system upon 60 minutes of ball milling.

Results
The hypothesis of this study is that intermolecular interactions play a major role in the formation of a co-amorphous system. The likelihood for an interaction can be estimated based on the molecular structure which is described by molecular descriptors in this study. The main interaction mechanisms assumed are ionic interaction, hydrogen bonding as well as hydrophobic interactions. Due to the more frequent occurrence of hydrophilic and hydrophobic interaction over ionic interactions in the systems studied, it was expected that descriptors capturing this information were likely to dominate the findings. Furthermore, the current data treatment of the descriptors favours the interaction of similar molecules and would thus not capture salt formation as the latter is based on two molecules with opposite charges.

In the PLS-DA score plot, the majority of drug:amino acid combinations were separated into two clusters (Figure 1). These clusters correspond well with the obtained experimental results with regard to solid state of the sample, i.e. whether an XRPD amorphous or a crystalline product was obtained. Amino acids with hydrophobic side chains (ALA, ILE, LEU, MET, PHE, TRP, TYR, and VAL) were generally more likely to form co-amorphous mixtures with the model drugs used in this study. Two exceptions to the otherwise systematic clustering of samples were indomethacin-arginine and indomethacin-lysine which were located in the “not amorphous” cluster, while the XRPD measurements confirmed that they did in fact become fully amorphous. These systems are well known to form co-amorphous salts and it can thus be concluded that the current model does not take salt formation into account, but rather describes hydrogen bonding and hydrophobic interactions.

Following the overall model, single models for each drug were developed in a similar manner and observed versus predicted plots (Figure 2) showed a clear separation between amorphous and not amorphous systems for each individual drug. Generally, a variety of descriptors were suitable to indicate that a system will not form an amorphous mixture, however, only a limited number were actually indicators of the formation of an amorphous system. Depending on the model drug, the importance and influence of the different descriptors varied, as could be expected due to the different structures of the various drugs and amino acids, respectively. Generally, descriptors relating to hydrophobic properties of the molecule dominate the loadings for amorphized mixtures. Here the hydrophobic interaction energy was found to be the most prominent molecular descriptor describing the likelihood of obtaining a co-amorphous mixture. Finally, the variable selection process can have a strong impact on the quality of the model; however, the general tendency observed was not influenced by this.

Conclusion
The use of molecular descriptors in the development of co-amorphous formulations is a promising approach to limiting the experimental workload for finding new co-amorphous drug-amino acid combinations.