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The use of molecular descriptors in the development of co-amorphous formulations

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ABSTRACT

Co-amorphous systems consisting of a drug and an amino acid have been investigated extensively for the enhancement of drug solubility and amorphous stability. The purpose of this study is to investigate which molecular descriptors are important for predicting the likelihood of a successful co-amorphisation between amino acid and drug. The predictions are thought to be used in an early screening phase to identify potential drug-amino acid combinations for further studies. A large variety of molecular descriptors was calculated for six drugs (carvedilol, mebendazole, carbamazepine, furosemide, indomethacin and simvastatin) and the twenty naturally occurring amino acids. The descriptor differences for all drug-amino acid combinations were calculated and used as input in the X-matrix of a Partial Least Square Discriminant Analysis (PLS-DA). The Y-matrix of the PLS-DA consisted of the X-ray powder diffraction response ("co-amorphous" or "not co-amorphous") obtained by ball milling all combinations for 60 min. The PLS-DA model showed a clear separation of the not co-amorphous and the co-amorphous samples and was successfully predicting the class membership of 19 out of the 20 completely left out drug-amino acid combinations of mebendazole. The approach seems to be promising for predicting the ability of new drug-amino acids combinations to become co-amorphous.

1. Introduction

Among the strategies to improve solubility and dissolution rate of poorly water-soluble drugs, the most obvious method would be to prepare a salt of the drug molecule (if it is a weak acid or base), and a large number of drug-salts are indeed available on the market. If the formation of a salt is not possible, but a crystalline product is still desired, co-crystal formation is an option that has been shown to be able to lead to an improved solubility and thus potentially to improved bioavailability of the drug (Basavoju et al., 2008; Duggirala et al., 2016; Elder et al., 2013; McNamara et al., 2006; Schultheiss and Newman, 2009). Another frequently investigated method for improving the solubility and dissolution rate of poorly water-soluble compounds, which is not dependent on finding the optimal co-crystal former and thus more generally applicable, is amorphisation. However, in order to tackle the inherent instability of neat amorphous drugs, formulation approaches are usually necessary to obtain a pharmaceutically relevant system. Amorphous solid dispersions, in which the drug is combined with a polymeric excipient, have long been in the focus of attention (Van den Mooter, 2012). More recently, co-amorphous combinations, which are combinations of a drug and another small molecule (either drug or excipient), have been investigated. It has been shown that co-amorphous systems can increase amorphous stability, compared to the neat amorphous drug, and lead to an even higher solubility than for the amorphous drug alone (Allesø et al., 2009; Dengale et al., 2014; Gao et al., 2013; Lobmann et al., 2011; Lobmann et al., 2013; Masuda et al., 2012; Qian et al., 2015; Wairkar and Gaud, 2016). Amino acids have been frequently used as co-formers in co-amorphous drug-amino acid combinations (Huang et al., 2017; Jensen et al., 2015; Kasten et al., 2016; Laitinen et al., 2014; Lobmann et al., 2013). In addition, amino acids seem to be viable salt formers as their water solubility is generally high and due to their ionizable characteristics (Tilborg et al., 2014). It has been shown that intermolecular interactions play a major role in the formation of a co-amorphous system. Of the theoretical possible interactions (e.g. ionic interactions, π-π interactions, hydrogen bonding, and hydrophobic interactions), ionic interactions in the form of (amorphous) salt formation were frequently seen as a major benefit for both amorphous stability and solubility of a co-amorphous system (Jensen

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et al., 2015; Kasten et al., 2016; Lobmann et al., 2011; Lobmann et al., 2013). In the absence of salt formation, weaker interactions such as hydrophobic interactions were also contributing to the stabilization of the co-amorphous system. For co-amorphous drug-amino acid systems hydrogen-bonding has usually not been reported to be of importance in the above references.

Recently, physicochemical descriptors were successfully utilized for selecting co-formers for stable co-amorphous drug-drug systems. It was reported that crystallization tendency, glass transition temperature, melting temperature and molecular flexibility are likely to be of relevance for the formation of a co-amorphous system (Ueda et al., 2016). However, it has so far not been investigated which molecular descriptors for a given amino acid in combination with a drug characterize a good co-former.

Molecular descriptors are numerical values for physicochemical properties that can be calculated computationally from the chemical structure of any compound. The descriptors represent inter alia size, charge, hydrophobicity, and hydrogen bonding abilities, and can be used to predict various properties of chemical compounds. Relevant examples are *in silico* predictions of glass-forming ability, glass transition temperature and phase separation in co-amorphous systems (Alhalaweh et al., 2014; Alzghoul et al., 2014; Mahlin et al., 2011; Pajula et al., 2014). Molecular descriptors have also been used to predict blood-brain barrier penetration (Cruciani et al., 2000), solubility, permeability and absorption of drugs (Bergström, 2005; Rytting et al., 2004; Van de Waterbeemd and Gifford, 2003). Recently, molecular descriptors have been used in the pharmaceutical evaluation of polymer properties (Christensen et al., 2017) and for the assessment of thermal stability of lysozyme in buffer (Meng-Lund et al., 2017).

Based on an experimental study by Kasten et al. (2016), which investigated the likelihood for the formation of a co-amorphous system, the hypothesis for the current study is that detection of crucial molecular descriptors that describe the variation in the properties of drug-amino acid combinations can be performed using multivariate data analysis. This knowledge can then be applied to estimate the likelihood for an interaction between the amino acid and a drug. Such predictions could be used in an early screening phase to select combinations with a high likelihood to form co-amorphous mixtures. Besides the apparent advantage of saving time and money, this approach would also be helpful in the early drug development stages where only small amounts of drug are usually available. A further motivation for this work is that it would be possible to calculate descriptors for drugs that have not yet been tested on their potential to be used in a co-amorphous system or even make predictions for hypothetical structures before they are synthesized.

2. Materials and Methods

2.1. Preparation and Analysis of Samples

This work was based on ball-milled samples prepared by Kasten et al. (2016). Briefly, six drugs (carvedilol, mebendazole, carbamazepine, furosemide, indomethacin, and simvastatin) were ball milled at a 1:1 molar ratio together with the 20 natural amino acids (ALA, ARG, ASN, ASP, CYS, GLN, GLU, GLY, HIS, ILE, LEU, LYS, MET, PHE, PRO, SER, THR, TRP, TYR, VAL). The solid state was analyzed by X-ray powder diffraction using an X'Pert PANanalytical PRO X-ray diffractometer with a PIXcel detector (PANanalytical B.V., Almelo, The Netherlands) using a CuKα radiation source (λ = 1.54187 Å), and an acceleration voltage and current of 45 kV and 40 mA, respectively. Samples were measured in reflection mode from 5 to 35 °2θ with a step size of 0.026 °2θ and a scan speed of 0.067 °2θ/s. For the current study, only the results after 60 min of ball milling were used.

2.2. Calculation of Molecular Descriptors

The dataset of the 20 natural L-amino acids and the six model drugs was constructed utilizing the Maestro small-molecule drug discovery suite (Maestro version 9.9, Schrödinger, LLC, New York, NY, 2014). The OPLS3 force field (Harder et al., 2016) was used to energy minimize all compounds in the absence of solvent (MacroModel version 2017-1, Schrödinger, LLC, New York, NY, 2017). Molecular Operating Environment (MOE) software (2016.08, Chemical Computing Group Inc., Montreal, QC, Canada, 2017) was used to calculate approximately 250 2D and 3D molecular descriptors from the structures of the energy minimized compounds in vacuum. 2D descriptors included physical properties, Hückel theory descriptors, subdivided surface areas, atom counts and bond counts, pharmacophore feature descriptors and partial charge descriptors. The 3D descriptors included surface, area, volume and shape descriptors. For carvedilol, the descriptors were calculated for both the *R*- and *S*-enantiomer. The descriptors were used for calculating the absolute difference between the calculated molecular descriptors of each respective amino acid with each drug. To include ionic interactions in the descriptor set, the pK_a-differences between drug and the amino acids' side chains were calculated for the acidic drugs and basic amino acids (furosemide and indomethacin with ARG, LYS and HIS, respectively) as well as for the basic drugs and acidic amino acids (carvedilol and mebendazole with ASN and GLN, respectively). The difference for the rest of the drugs and amino acids was set to 0, as the remaining amino acids are zwitterionic and thus only subject to intramolecular acid-base reactions.

2.3. Data Analysis

Partial Least Squares Discriminant Analysis (PLS-DA) was performed using the software SIMCA 14 (Umetrics AB, Sweden). In PLS-DA modeling, a Y-data matrix of dummy variables (discrete numerical values) is used in order to encode the class identity of the observations. Membership of new observations to a class is then determined by matching the value of the predicted dummy variable to the workset class, i.e. a value close to one indicates that an observation belongs to a workset class. As all samples were assigned to the nearest class, the practical lower threshold for observations being categorized as members of a workset class was set to 0.5.

The response ("co-amorphous" or "not co-amorphous") determined by X-ray powder diffraction after 60 min of ball-milling (Kasten et al., 2016) was used as Y-matrix in the PLS-DA model. The "co-amorphous" class included only combinations that were fully co-amorphous. The "not co-amorphous" class included all combinations were either the drug, amino acid, or both showed remaining crystallinity. The absolute difference between the calculated molecular descriptors of each respective amino acid with each drug was used as input (X-matrix) for the classification model and is referred to as "the descriptors" in the results and discussion section. The rationale for this mathematical operation is the assumption that "like interacts with like". If the drug and amino acid are similar, the absolute difference in descriptor values would be close to zero and in practical experiments the formulation would become co-amorphous upon ball milling. The PLS-DA model was built including descriptors centered and scaled to unit variance for 120 amino acid:drug combinations (*R*-carvedilol and *S*-carvedilol, carbamazepine, furosemide, indomethacin and simvastatin). The quality of the training model was evaluated by the internal cross validation procedure of the software, applying the leave-one-out principle using seven cross validation groups. Mebendazole-amino acid combinations were left completely out of the model construction and were used to assess the performance of the final model.

After variable selection based on the variable importance for the projection (VIP) plot in the SIMCA software (see Section 3.1) the model included 39 descriptors. These descriptors are shown in Table 1 along with a short description. The calculated descriptor values for each drug-