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Development of a screening method for co-amorphous formulations of drugs and amino acids

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ABSTRACT

Using amino acids (AA) as low molecular weight excipients in the preparation of co-amorphous blends with the aim to stabilize the drug in the amorphous form have been discussed in a range of studies. However, there is currently no theoretical consensus behind which AA would be a suitable co-former for a given drug. In this work, a fast screening process to assess the co-former feasibility in co-amorphous drug-AA blends has been developed on the basis of the amorphization kinetics upon oscillatory ball milling. For this purpose, six model drugs were combined with 20 different AAs and co-milled at an equimolar ratio for different times (1, 5, 15, 30 and 60 min). The degree of amorphization was then studied for the different time points by determination of the area under the curve of the diffraction peaks in X-ray powder diffraction measurements. The results of this study suggest that the choice of AA as co-formers for the formation of the co-amorphous blend could be significantly inferred after 15 min of milling, since a crystallinity decrease higher than 90% after 15 min resulted in successful co-amorphization in approximately 90% of the mixtures after 60 min of milling. The results furthermore suggested that non-polar AAs, such as tryptophan, phenylalanine, leucine, isoleucine, methionine, valine and proline, are a good first choice in the selection of a co-former for a given drug in a co-amorphous formulation. Basic AAs appear suitable for amorphous salt formation in the case of acidic drugs. Acidic AAs however, were shown to be generally poor co-formers for co-amorphous systems.

1. Introduction

It has been estimated that >90% of new active pharmaceutical ingredients (APIs) under development exhibit poor aqueous solubility (Grohganz et al., 2014; Rumondor et al., 2015). Whilst several approaches have been suggested and studied to overcome this issue, so that these new candidates are not ruled out over the early development phase, the use of amorphous solid dispersions (ASD) is one of most promising strategies and has gained significant interest both in academia and industry in the past decades (Bikiaris, 2011; Kawabata et al., 2011; Savjani et al., 2012; Laitinen et al., 2013).

ASDs are defined as glass solutions representing single phase amorphous systems of two or more components. They can be further subdivided by the type of excipient used to stabilize the amorphous drug, i.e. a polymeric or non-polymeric excipient. Polymeric glass solutions are most commonly employing hydrophilic polymers, and the non-polymeric glass solutions can be divided into mesoporous silica based, and co-amorphous formulations (Dengale et al., 2015). Co-amorphous blends may be a combination of two pharmacologically relevant drugs (Allesø et al., 2009; Löbmann et al., 2013b; Dengale et al., 2014) or a combination of a drug with a low molecular weight excipient (Löbmann et al., 2013a; Wickström et al., 2015), which can aid on the stabilization of the drug in the desired amorphous form. The resulting gain in physical stability during the storage period can be associated to lower molecular mobility and a higher glass transition temperature (T_g) (Yoshioka and Aso, 2007).

Several studies have been published indicating the potential of amino acids (AA) as co-formers (Laitinen et al., 2014; Jensen et al., 2015a). For example, the poorly soluble drug indomethacin could form co-amorphous blends with the AAs arginine, tryptophan and phenylalanine at a 1:1 or 1:1:1 M ratio, by ball milling the binary or ternary mixtures for 90 min (Löbmann et al., 2013a). These formulations presented good physical stability (>6 months at room temperature) compared to the pure amorphous drug and also significantly increased the intrinsic dissolution profile. The use of AAs can be advantageous also due to their low molecular weight, as only a small amount of excipient is needed in comparison to the oftentimes large bulk volumes used in polymeric ASDs (Löbmann et al., 2011, 2013a).

Co-amorphous blends can be prepared by different techniques such as ball milling, spray drying, quench cooling, and solvent evaporation (Hancock and Zografi, 1997). Ball milling is often used in the literature as it can be performed on a small scale and does not require the use of

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heat or organic solvents (Zimper et al., 2010). However, in order to obtain amorphous or co-amorphous samples upon ball milling, the standard milling process may be very time consuming, for example taking up to 60, 90 or 180 min when using an oscillatory ball mill (Allesø et al., 2009; Löbmann et al., 2012; Jensen et al., 2015a). Furthermore, there has been no rationale so far for the selection of the co-former for a given drug, and selection is often based on a trial and error. Recently, Ueda et al. (2015) studied the selection of co-formers between naproxen and several other non-steroidal anti-inflammatory drugs by assessing the inhibition of recrystallization on physical mixtures after melting and quench cooling. This approach is particularly feasible for thermally stable components, however, it is not applicable if the components degrade upon heating or melting, such as in the case of AAs. The authors also discussed the importance of physicochemical features of the drugs such as glass forming ability, and parameters related to molecular area, volume and flexibility (molecular weight, rotatable bond number) for the successful formation of co-amorphous blends (Ueda et al., 2015).

In the current study, we aim to establish a fast and simple method of choosing suitable AA candidates for co-amorphous formulations. Ball milling was used as a technique to prepare the formulations as it is a feasible technique for heat labile components such as AAs. The co-milled samples were collected in predetermined time points and their molecular order was evaluated by means of X-ray powder diffraction (XRPD). Six model drugs were chosen for the experiments: carvedilol and mebendazole as basic drugs, carbamazepine and simvastatin as neutral drugs, and indomethacin and furosemide as acidic drugs (Fig. 1a–f, respectively). All drugs except furosemide (class IV) belong to the biopharmaceutics classification system (BCS) class II (Amidon et al., 1995). Therefore, these drugs are considered as poorly water soluble and would benefit from enabling formulation approaches such as co-amorphization to increase their oral bioavalability. Twenty different L-amino acids were tested as co-formers.

2. Materials and methods

2.1. Materials

Carvedilol (CAR) was obtained from Cipla Ltd. (Mumbai, India). Mebendazole (MEB) was purchased from Sigma Aldrich (St. Louis, USA). Carbamazepine (CBZ), furosemide (FUR) and indomethacin (IND) were purchased from Hawkins Pharmaceutical Group (Minnesota, USA). Simvastatin was obtained from Hangzhou Dayangchem Co. Ltd. (Hangzhou, China). L-arginine (ARG), L-aspartic acid (ASP), L-cysteine (CYS), L-glutamic acid (GLU), L-glycine (GLY), L-histidine (HIS), L-lysine (LYS), L-proline (PRO), L-phenylalanine (PHE) and L-tryptophan (TRP) were purchased from Sigma Aldrich (St. Louis, USA). L-alanine (ALA), L-asparagine (ASN), L-glutamine (GLN), L-isoleucine (ILE), L-leucine (LEU), L-methionine (MET), L-serine (SER), L-threonine (THR), L-tyrosine (TYR), L-valine (VAL) were purchased from Th Geyer Danmark Aps (Roskilde, Denmark). All substances were of reagent grade and used as received.

2.2. Methods

2.2.1. Preparation of co-amorphous mixtures

The formation of co-amorphous mixtures was assessed by mechanical activation. Briefly, 1000 mg of powder containing the drug and AA at a 1:1 M ratio were milled in an oscillatory ball mill (Mixer mill MM400, Retsch GmbH & Co., Haan, Germany) at a frequency of 30 Hz in 25 mL jar containing two stainless steel balls with a diameter of 12 mm. At predetermined time points (1, 5, 15, 30 and 60 min), aliquots of approximately 10 mg of powder were collected for further analyses. In the beginning of the experiment the powder was homogenized by milling the mixtures for 5 min without the stainless steel balls. These samples are designated as '0 min' milling samples. Additionally, the single components were ball milled for the same time intervals as above to compare their amorphization behavior with that of the binary mixtures.

2.2.2. X-ray powder diffraction (XRPD)

XRPD measurements were performed using an X'Pert PANalytical PRO X-ray diffractometer (PANalytical, Almelo, The Netherlands) with CuKα radiation (1.54187 Å), acceleration voltage and current of 45 kV and 40 mA, respectively. The samples were scanned in reflectance mode between 2° and 35° 2θ with a scan rate of 0.067335° 2θ/s and a step size of 0.0262606°. The data was collected and analyzed using the software X'Pert Data Collector (PANalytical, Almelo, The Netherlands).

2.2.3. Statistical analysis of the XRPD data

To compare the obtained experimental data, all diffractograms were baseline corrected on X'Pert HighScore Plus software (PANalytical, Almelo, The Netherlands) based on the algorithm of Sonneveld and Visser (1975). Then, 1142 data points representing the XRPD diffractograms for all samples from 5° to 35° 2θ were used to calculate the area under the curve (AUC) by the linear trapezoidal method. The '0 min' milling samples were designated as 100% crystalline and the

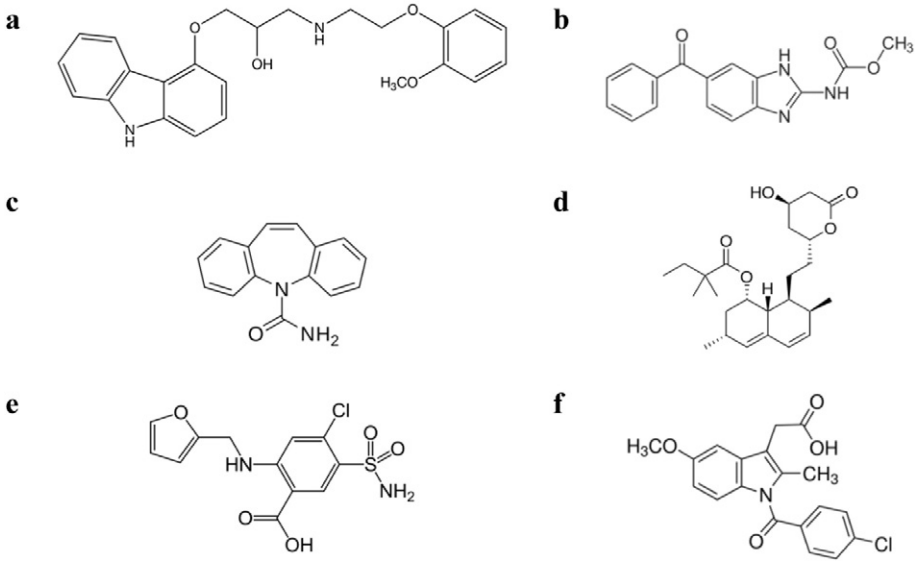

Fig. 1. Chemical structures of carvedilol (a), mebendazole (b), carbamazepine (c), simvastatin (d), furosemide (e) and indomethacin (f).