Production of co-amorphous systems with olanzapine and indomethacin

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INTRODUCTION

A large number of active pharmaceutical compounds currently under development are poorly water soluble, a characteristic which can limit their bioavailability and results in formulation challenges[1,2]. Strategies to address the problem encompass the conversion of a crystalline drug into an amorphous form to promote its apparent solubility and dissolution, thus resulting in a likely increase in bioavailability[3]. An amorphous solid exhibits high internal energy and enhanced molecular mobility, leading to higher reactivity, resulting in thermodynamic instability as compared to their crystalline counterparts[1,2].

The production of co-amorphous systems has added value to the co-crystallization and amorphization of drugs by enhancing the advantages of both strategies to increase the apparent solubility of a drug. These systems incorporate low molecular mass molecules as co-formers, which are mixed with the drug at the molecular level to form one single co-amorphous phase[1-4].

Co-amorphous systems can be prepared by several methods based on two main different forming mechanisms: either thermodynamic or kinetic disordering processes. The thermodynamic processes consider melt quenching, precipitation from a solution and solvent evaporation methods whereas the kinetic processes consider the mechanical activation processes (e.g. milling)[1,3]. In thermodynamic processes (e.g. melt quenching), the drug moves from a thermodynamically stable form, into a disordered form. During this process, a sufficiently fast cooling rate has to ensure that the amorphous state is maintained by refraining nucleation and crystal growth processes. Alternatively, in kinetic processes, mechanical activation has to induce defects into the crystal lattice of the crystalline drug, *i.e.*, entropy increases, until the amorphous state is obtained[1].

The aim of this study is to produce co-amorphous mixtures of olanzapine, using amino acids as co-formers, by milling, solvent evaporation and quench cooling of molten systems.

MATERIAL AND METHODS

Olanzapine (OLZ; 312.43g/mol) was obtained from Vega Pharma (China), micronized indomethacin (IND; 357.7g/mol) from Capsifar (Portugal), L-tryptophan (TRY; 174.20g/mol) and L-arginine (ARG; 203.23g/mol) from BioChemica AppliChem (Spain); citric acid (CA; 192.12g/mol), tartaric acid (TA, 150.09g/mol), oxalic acid (OA; 90.03g/mol) and solvents (methanol, ethanol, ethyl acetate, dichloromethane and diethyl ether) from Sigma Aldrich (Germany) and nitrogen from Air Liquide (Portugal).

Milling

Drugs were milled with each of the amino-acids or the carboxylic acids (molar ratio 2:1, 1:1 and 1:2), in a ball mill (Retsch, PM 100, Germany) with 8, 3mm balls, at 650rpm, for 12h.

Quench cooling

Mixtures (molar ratios as above) of molten drugs and amino acids or carboxylic acids were quench cooled in aluminum beakers. The melting temperature for each mixture was set at 220˚C. Each sample was kept in the liquid state for 5 min to ensure complete melting with formation of a single liquid phase. Each sample was subsequently quenched with liquid nitrogen.

Solvent evaporation

Drug and the excipients (molar ratios as above) were dissolved in organic solvents (e.g. dichloromethane) prior to slow evaporation.

Characterization of the samples

Samples were characterized by calorimetric analysis (DSC). Thermograms were obtained with a differential scanning calorimeter (TA Instruments, Q200, USA) after calibration with indium (TA Instruments, USA; T_m=156.55, ΔH_m=28.51 J/g) and nitrogen (50mL/min) as the purge gas. Samples (3-5mg) were placed in hermetically sealed crucibles and subjected to heating and cooling cycles at a rate of 10˚C/min, within the range of -40 to 250˚C.

RESULTS AND DISCUSSION

Results have shown that OLZ and IND could be converted into the amorphous state. Quench cooling presented the most promising results whereas milling conditions do not seem to be sufficient to produce amorphous drugs. Equally, blends of drug:co-former were amorphous by quench cooling, but not after milling.

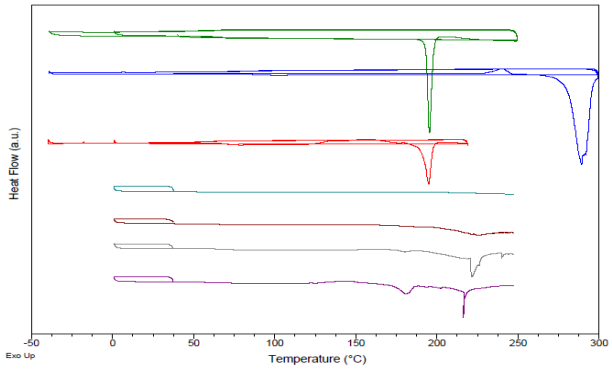

Figure 1. Thermogram of olanzapine and L-tryptophan obtained by quench cooling

–OLZ (raw material) –TRY (raw material) –OLZ (amorphous) –TRY(amorphous) –OLZ:TRY(1:2) –OLZ:TRY(1:1) –OLZ:TRY(2:1)

Figure 1 shows a set of typical thermograms obtained for the different materials: OLZ, TRY (raw material) OLZ, TRY (amorphous) and OLZ:TRY, at different molar ratios, after quench cooling. The best co-amorphous system was obtained at a 1:2 ratio (lower thermogram, with a glass at T_g=44.01ºC).

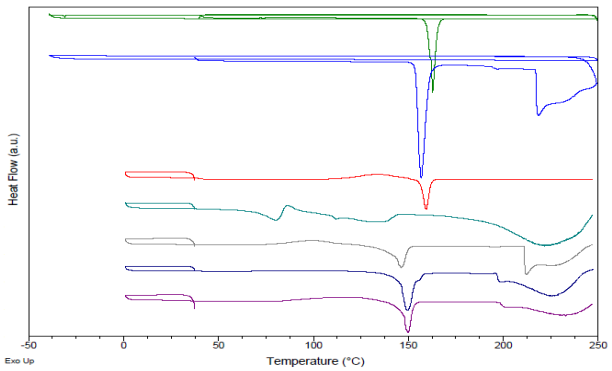

Figure 2. Thermogram of indomethacin and citric acid obtained by quench cooling.

–IND (raw material) –CA (raw material) –IND (amorphous) –CA (amorphous) –IND:CA(1:1) –IND:CA(1:2). –IND:CA(2:1)

Figure 2 represents a set of typical thermograms for IND and CA as raw materials and IND:CA (1:1), produced by quench cooling. In the lower thermogram the formation of a single glass transition (T_g=33.20ºC), a recrystallization (T=76.39ºC / ΔH=54.84J/g) and melting (T=142.43ºC / ΔH=72.72J/g) is observed, suggesting that this co-amorphous system (IND:CA; 2:1) was not stable at higher temperatures.

CONCLUSION

The study has shown the possibility of converting a crystalline drug into a less crystalline or amorphous entity, particularly when in presence of co-formers that help on stabilizing the amorphous structures formed. Certainly the conversion of crystalline drugs into the amorphous state is dependent on their chemical structures and interactions with other chemical entities.

The properties of drug and co-formers (e.g. melting point or crystallization tendency) are critical to select the preparation method. In this work quench cooling was better than solvent evaporation and better than milling.

Since the potential to form co-amorphous systems has been confirmed, both formulations and process methods are currently being optimized, to fulfill the promise of minimizing solubility issues of drugs.

ACKNOWLEDGEMENT

Fundação para a Ciência e a Tecnologia (FCT) is acknowledged for providing financial support to this work (PTDC/CTM-BIO/3946/2014).

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