PRODUCTION OF CO-AMORPHOUS MATERIALS WITH THERAPEUTIC ACTIVITY

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INTRODUCTION

Orally administered drugs must have sufficient water solubility to ensure that they are absorbed in the gut, as required for bioavailability and therapeutic activity. As the number of poorly water soluble drug molecules entering the clinic rises, the strategies to enhance solubility also become increasingly important. Conversion of a crystalline drug into the amorphous form is one way to improve its apparent solubility and dissolution rate (a measure of bioavailability). Unfortunately, the large internal energy and molecular movement of the molecules in the amorphous state may also cause the material to convert spontaneously back to its stable crystalline form during processing, storage or dissolution (1,2). Co-amorphous structures containing one, or more, small molecular weight compounds, which are homogenously mixed to form a new entity with a single amorphous phase (2,3), have been shown to stabilize the amorphous form of a drug in the solid state (2). Finding low molecular weight excipients compatible with the model drug may, however, be challenging (3). In this respect, amino acids have proved their potential to form co-amorphous systems with some drugs and are the object of the present work (1,2). Different techniques are available to obtain co-amorphous systems, namely ball milling or quench cooling, since these techniques inflict limited chemical degradation to the drug (1,2).

MATERIALS AND METHODS

Mixtures of olanzapine and L-arginine and L-tryptophan (1:1) and paroxetin and L-arginine, L-tryptophan, L-proline, L-lysine, L-tyrosine and L-phenylalanine (1:1) were processed by ball milling and quench cooling. The new products were characterized by ***Differential Scanning Calorimetry*** (DSC) in order to identify the formation of co-amorphous between each drug and the amino acid.

DSC is a calorimetric analytical technique that looks at how a material's heat capacity (C_p) is affected by temperature. A sample of known mass is heated or/and cooled and the changes in its heat capacity are tracked as changes in the heat flow. This allows the detection of transitions such as **melts** (T_m) and **glass transitions** (T_g).

RESULTS AND DISCUSSION

Results have shown that olanzapine seems to be converted into the amorphous state in combination with arginine or tryptophan, either by quench cooling, or ball milling (Fig 1 and 2, respectively). Olanzapine alone became amorphous by quench cooling and by milling too, like paroxetine. Paroxetine was converted into the amorphous form when in combination with the amino acid L-proline (Fig 3).

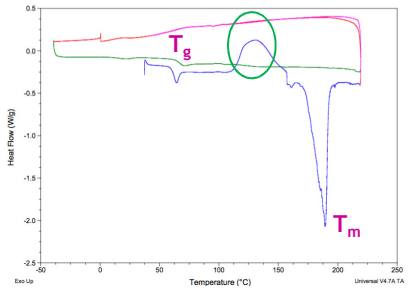

Fig 1 – Thermogram of the co-amorphous olanzapine and L-arginine produced by quench cooling

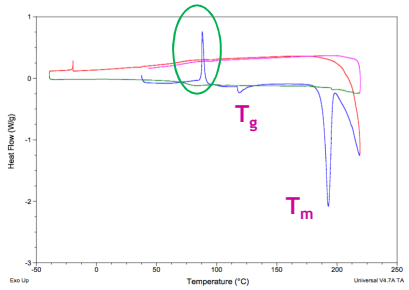

Fig 2 – Thermogram of the co-amorphous olanzapine and L-tryptophan produced by ball milling (6h at 650rpm)

LEGEND TO FIGURES

1st run - heating and cooling
2nd run - heating and cooling

Recrystallization events are circled in green

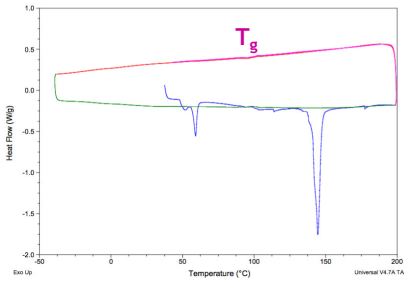

Fig 3 – Thermogram of the co-amorphous paroxetine and L-proline produced directly on the DSC

Thermal analysis suggested the presence of co-amorphous species in homogenous mixtures, by the presence of T_g and absence of T_m

CONCLUSION

The study has shown that the conversion of crystalline drugs into the amorphous state is dependent on their chemical structures and interactions with other chemical entities. For the model drugs studied the use of specific amino acids, in combination with the appropriate processing technique, has confirmed the potential to form co-amorphous systems. The use of amino acids seems to be a promising approach, worth to be explored further, provided the right combination (drug:amino acid) and processing technique have been identified.

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