

Thermal analysis of a co-amorphous olanzapine-tryptophan system obtained by a spray drying process

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Introduction

Olanzapine (OLZ), a drug used to treat schizophrenia, exhibits poor water solubility and good permeability through biological membranes. In the dosage forms, OLZ exists in a crystalline state. The salt formation, particle size reduction or amorphization are some of the methods used to increase the dissolution rate and, in consequence, the bioavailability of poorly soluble drugs (Bhalani et al., 2022). Amorphous solids differ from their crystalline counterparts in the order of the molecular network, *i.e.* they have no long-range order, however, some short-range order might exist. Thus, as the amorphous state is a high-energy state, amorphous active pharmaceutical ingredients (APIs) are usually less physically stable due to the tendency to reorganize into a more ordered form by the process of recrystallization or physical aging. Recently, there has been significant interest expressed by both academia and industry regarding improving the dissolution rate and stability of APIs by the formation of co-amorphous systems (Skotnicki et al., 2021). Co-amorphous systems (CAMs) are single-phase amorphous materials (single glass transition temperature) containing an API and a second low-molecular-weight compound as a co-former (an excipient or another API). Therefore, obtaining an olanzapine CAM formulation may improve both bioavailability and physical stability.

In this work, the co-amorphous system of OLZ with an amino acid as a co-former (tryptophan, TRP) was obtained by the spray-drying method and characterized by the thermal analysis supported by the powder X-ray diffractometry (PXRD).

Materials and methods

OLZ and TRP were obtained from Biofarm Sp. z o.o., Poznan, Poland. Amorphous and CAMs were prepared by spray drying using Mini Spray Dryer B-290 (Flawil, Switzerland). A mixture of OLZ:TRP (molar ratio 1:1) was dissolved in dichloromethane and methanol (1.5:10 V/V; 2.19 mg·mL⁻¹). Thermogravimetric analyses (TGA) were carried out on a Netzsch TG 209F3 (Selb, Germany). Ca. 10 mg of the sample was placed in a ceramic crucible and heated from 25 to 400 °C at 10 °C·min⁻¹ rate under a nitrogen flow of 30 mL·min⁻¹. Differential scanning calorimetry (DSC) analyses were performed on a Netzsch DSC 214 Polyma (Selb, Germany). 2 to 5 mg of sample were placed in a pierced aluminium crucible and heated/cooled from 20 to 310 °C (crystalline and spray-dried TRP) or from 20 to 210 °C (crystalline and spray-dried OLZ and OLZ:TRP) at a rate of 10 °C·min⁻¹, under a nitrogen flow of 30 mL·min⁻¹. PXRD analyses were performed on a Bruker D8 Advance (Bruker AXS GmbH, Karlsruhe, Germany). Samples were scanned from 5 to 40° 2θ, with a scanning interval of 0.02 °/step and 2 s/step.

Results and discussion

The amorphous form of TRP and the CAM OLZ:TRP were obtained by spray drying. Based on the TGA results, the thermal degradation occurs at 230 °C, 253 °C, and 181 °C for OLZ, TRP, CAM OLZ:TRP, respectively.

On the DSC curve of the OLZ:TRP physical mixture (PM), a peak at 194.0 °C ± 0.01 °C is observed, indicating the OLZ melting process in the PM. The result suggests no

change in the physical and chemical structure of OLZ until the melting process. However, the enthalpy of fusion of OLZ in the physical mixture ($74.1 \text{ J}\cdot\text{g}^{-1}$) is slightly lower than the theoretical value (ca. $91 \text{ J}\cdot\text{g}^{-1}$), which may indicate an interaction. A second endothermic peak starting at $225.3 \text{ }^\circ\text{C}$ suggests degradation of the material as indicated by TGA analysis of the OLZ:TRP PM.

The DSC analysis of the crystalline OLZ revealed an endothermic melting peak appearing at $194.9 \pm 0.2 \text{ }^\circ\text{C}$ ($\Delta h_f = 151.0 \pm 1.8 \text{ J}\cdot\text{g}^{-1}$). A similar peak occurs for a spray-dried OLZ at $192.8 \text{ }^\circ\text{C}$ ($\Delta h_f = 149.4 \text{ J}\cdot\text{g}^{-1}$), indicating that the spray-dried sample exists in the crystalline state (Fig. 1). For the crystalline TRP, the endothermic melting peak starts at $290.2 \pm 2.1 \text{ }^\circ\text{C}$, while for the spray-dried at $T_m = 287.9 \pm 2.9 \text{ }^\circ\text{C}$. In addition, the DSC analysis of the spray-dried TRP disclosed a cold crystallization peak suggesting that the material exists in an amorphous phase. In the CAM OLZ:TRP, a crystallization process occurs during heating, with $T_c = 132.2 \pm 0.1 \text{ }^\circ\text{C}$, $\Delta h_c = 56.04 \pm 0.31 \text{ J}\cdot\text{g}^{-1}$ and melting, $T_m = 175.4 \pm 0.7 \text{ }^\circ\text{C}$, $\Delta h_m = 49.01 \pm 0.74 \text{ J}\cdot\text{g}^{-1}$. There is a single glass transition observed during the second heating ($T_g = 85.3 \pm 0.1 \text{ }^\circ\text{C}$, $\Delta c_p = 0.28 \pm 0.01 \text{ J}\cdot\text{g}^{-1} \cdot \text{ }^\circ\text{C}^{-1}$), which suggests the molecular interactions between OLZ and TRP.

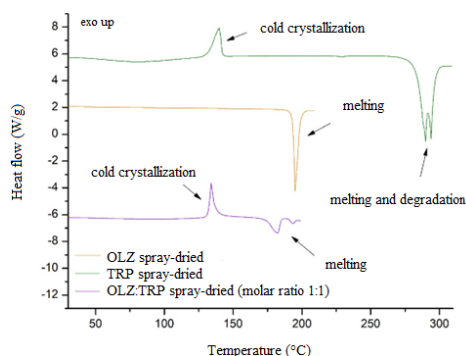


Fig. 1. DSC curve (1st heating) for spray-dried: OLZ, TRP and OLZ:TRP (co-amorphous) samples.

The T_g of the CAM OLZ:TRP determined during the second heating, is ca. $15 \text{ }^\circ\text{C}$ higher than that of the amorphous OLZ ($T_g = 70.7 \pm 0.1 \text{ }^\circ\text{C}$).

The CAM OLZ:TRP system was stored at $30 \text{ }^\circ\text{C}$ for 28 days to determine the physical stability. The DSC curves (Fig. 2) show a similar pattern for all tested samples after storage for different periods. The process of crystallization and melting can be seen, the observation confirms the physical stability (no recrystallization at the storage temperature) of the CAM system (confirmed by PXRD). However, there is a clear increase in the enthalpy relaxation with the increase of the storage time, which indicates the local ordering of the amorphous structure (physical ageing).

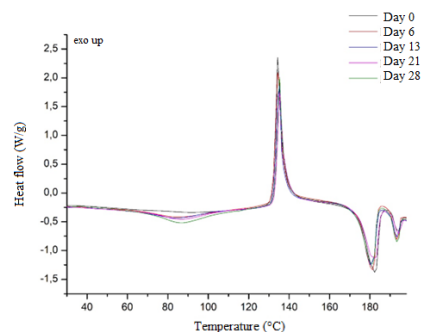


Fig. 2. DSC curve of the spray-dried OLZ:TRP aged up to 28 days at $30 \text{ }^\circ\text{C}$.

Conclusion

Using the spray drying technique, a CAM API-excipient system, with a single glass transition ($T_g = 85.3 \text{ }^\circ\text{C}$) was obtained, which suggests the intermolecular interactions between OLZ and TRP. It was proven that the use of a co-former allows OLZ to be amorphized in the spray drying process, which was not possible for OLZ by itself.

The CAM system was stable for up to 4 weeks at $30 \text{ }^\circ\text{C}$ (no crystallization occurred). This was probably achieved by increasing the OLZ T_g in the CAM system. However, physical aging occurs during storage.

It has been confirmed that DSC is a suitable tool for the analysis of amorphous pharmaceuticals. It allows observing the local ordering of the amorphous material during storage, changes that are impossible to observe by a standard PXRD.

Acknowledgements: LM work was financially supported by “Carol Davila” University of Medicine and Pharmacy Bucharest, Romania through Contract no. 33PFE/2021 funded by the Ministry of Research and Innovation within PNCDI III, Program 1—Development of the National RD system, Subprogram 1.2—Institutional Performance—RDI excellence funding projects.

References

- Bhalani, D.V., Nutan, B., Kumar, A., Singh Chandel, A.K., 2022. Bioavailability Enhancement Techniques for Poorly Aqueous Soluble Drugs and Therapeutics. *Biomedicines*, 10(9), 2055. <https://doi.org/10.3390/biomedicines10092055>
- Skotnicki M, Jadach B, Skotnicka A, Milanowski B, Tajber L, Skotnicki, M., Jadach, B., Skotnicka, A., Milanowski, B., Tajber, L., Pyda, M., Kujawski, J., 2021. Physicochemical characterization of a co-amorphous atorvastatin-irbesartan system with a potential application in fixed-dose combination therapy. *Pharmaceutics*, 13(1), 118. <https://doi.org/10.3390/pharmaceutics13010118>