In-situ co-amorphization of olanzapine in pellets

Raquel Azevedo[1]; Nuno F. da Costa[1,*]; Ana I. Fernandes[2]; João F. Pinto[1,*]

[1] iMed.Ulisboa, Faculdade de Farmácia, Universidade de Lisboa, Avenida Professor Gama Pinto, P-1649-003 Lisboa, Portugal
[2] CiiEM, Instituto Universitário Egas Moniz, Campus Universitário, Quinta da Granja, Monte de Caparica, P-2829-511 Caparica, Portugal

jfpinto@ff.ul.pt

INTRODUCTION

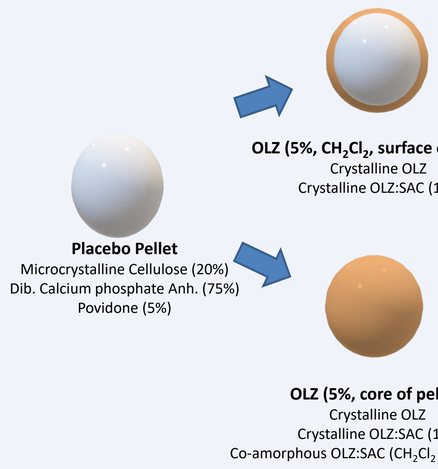
Approximately 70% of novel drug candidates present poor aqueous solubility, which is likely to have a negative impact on their bioavailability [1].

Co-amorphization of drugs has been described as a promising strategy to enhance the solubility and dissolution rate of drugs [2]. However, co-amorphous systems, when submitted to stress conditions (e.g. heat or moisture required to manufacture solid dosage forms), are likely to have the drug recrystallized, affecting negatively its solubility and thus, a decrease of the dissolution rate in aqueous systems [3]. Strategies to manufacture dosage forms containing amorphous drugs from their crystalline counterparts have been suggested [2,3]. However, little information is available on the manufacture of such dosage forms from co-amorphous systems or from crystalline co-formers (co-amorphized during manufacture), particularly in the presence of water.

This work aimed at the in situ co-amorphization of olanzapine (OLZ) while coating nonpareil beads (placebo) to simultaneously enhance the dissolution rate and reduce the recrystallization of the amorphous drug.

MATERIALS AND METHODS

PREPARATION



CHARACTERIZATION

RESULTS AND DISCUSSION

SOLID-STATE CHARACTERIZATION

Solid-state studies were conducted on powdered samples and pellets using both XRPD and FTIR characterization techniques. Diffractograms of samples containing OLZ, without SAC, suggested the maintenance of crystalline OLZ when present either in the core or on the surface of pellets **(Fig. 1)**. Likewise, the FTIR spectra confirmed the results gathered from XRPD **(Fig. 1)**. PCA analysis of spectral data indicated a cluster comprising the samples containing crystalline OLZ **(Fig. 2)**.

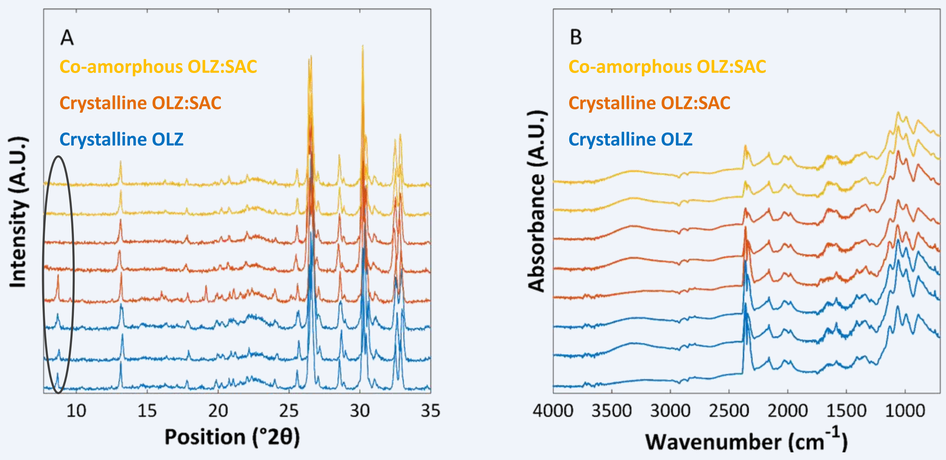


Figure 1. Diffractograms (A) and FTIR spectra (B) of samples containing crystalline OLZ or OLZ:SAC.
(upwards: physical mixture, uncoated pellets and coated pellets) (the ellipse shows the signals related to crystalline OLZ).

On the contrary, the addition of SAC to the mixture resulted in the production of pellets whose diffractograms presented a halo pattern with the disappearance of crystalline peaks, regardless of the presence of OLZ in the core, or on the surface of pellets. These results suggest the *in-situ* co-amorphization of OLZ and SAC, when water or dichloromethane were used to prepare drug-containing pellets, either in the core or on the surface. These results were confirmed by FTIR spectra, with the formation of a cluster including samples with the co-amorphous system prepared previously by solvent evaporation, which have not shown signs of recrystallization (**Fig. 2**).

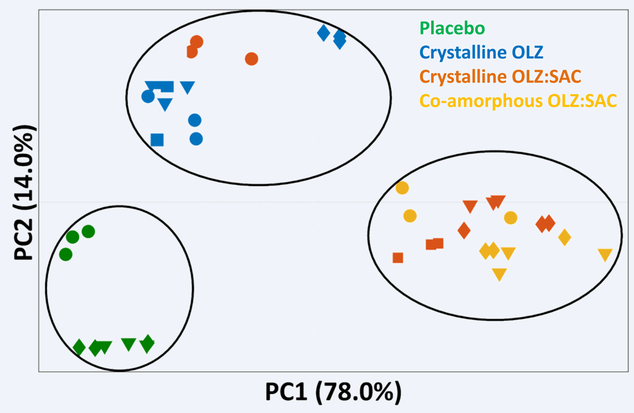


Figure 2. PCA applied to FTIR data of formulations containing OLZ, crystalline OLZ:SAC, co-amorphous OLZ:SAC and the placebo as a physical mixture (circle), an extrudate (diamond), non-coated pellet (triangle) or coated pellet (square).

DISSOLUTION STUDIES

Dissolution tests performed on pellets containing OLZ in the core, without SAC, presented a t_{50} ≈ 75 min, which was significantly higher when compared to pellets coated with the model drug (t_{50}= 44 min) **(Fig. 3).** This was expected since OLZ present on the surface of the pellet was available for immediate release by contrast to OLZ present in the core, whose release was hampered by the matrix-like structure of the pellets.

The presence of SAC in the core of pellets was found to increase the dissolution rate of the drug (t_{50}= 31 min) **(Fig. 3).** Interestingly, pellets containing both crystalline OLZ and SAC as starting materials, which failed to present crystallinity as determined by XRPD and FTIR, presented a higher dissolution rate compared to those pellets containing the co-amorphous system prepared previously by solvent evaporation (t_{50}= 48 min). The variation observed was likely to have resulted from structural differences of pellets, with the latter presenting less brittle and less elastic properties than the former (crushing strength of 33.6 *vs* 36.4 N, for pellets containing crystalline and co-amorphous OLZ:SAC as starting materials, respectively).

The co-amorphous powder was stickier than the physical mixture made of OLZ and SAC. The OLZ and SAC on the surface of pellets (by application of coating solution), present as amorphous entities, enhanced the dissolution rate of OLZ, as reflected by the lowest median dissolution time (t_{50}= 7 min) observed. Consequently, it was expected that the bioavailability of OLZ would be the highest when amorphous OLZ is present on the surface of pellets.

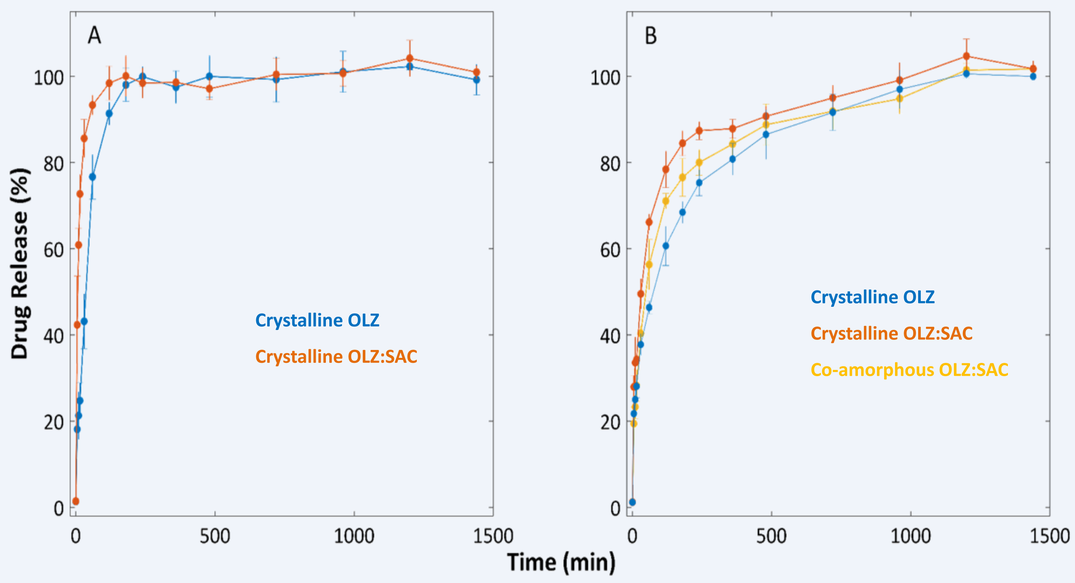


Figure 3. Dissolution profiles of coated (A) and non-coated (B) pellets with crystalline OLZ, crystalline OLZ:SAC and the co-amorphous OLZ:SAC.

CONCLUSIONS

- The *in-situ* co-amorphization of OLZ was accomplished either in the core or on the surface of pellets, when SAC was present in formulations;
- Coating of placebo beads has proved to be a feasible technique to prepare *in-situ* co-amorphous systems, leading to a higher dissolution rate compared to non-coated pellets;
- The *in-situ* co-amorphization of OLZ discards the need to prepare co-amorphous systems prior to the manufacture of oral drug products and minimizes the exposition of these entities to stress conditions;
- Coating of granules and tablets can become alternatives to current manufacture procedures supporting the feasibility of the *in-situ* co-amorphization procedure proposed in this work.

REFERENCES

1. Thayer, A; Finding solutions. Chemical & Engineering News (2010). 88, p. 13-18.
2. Liu, J; Grohganz, H; Löbmann, K; Rades, T; Hempel, N; Co-Amorphous Drug Formulations in Numbers: Recent Advances in Co-Amorphous Drug Formulations with Focus on Co-Formability, Molar Ratio, Preparation Methods, Physical Stability, In Vitro and In Vivo Performance, and New Formulation Strategies. Pharmaceutics (2021). 13, p. 389.
3. da Costa, N F; Fernandes, A I; Pinto, J F; Measurement of the amorphous fraction of olanzapine incorporated in a co-amorphous formulation. International Journal of Pharmaceutics (2020), 588, p.119716.

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