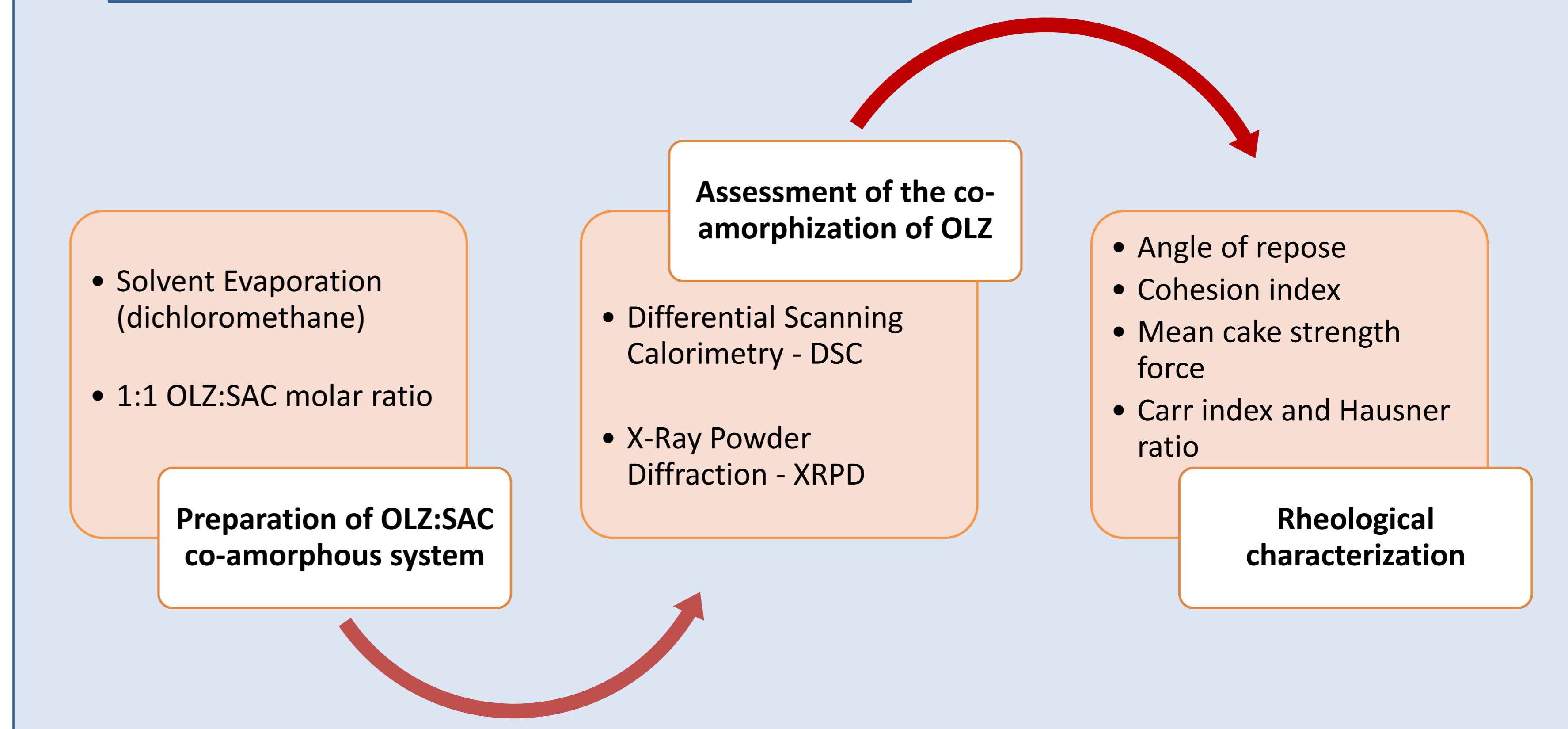


Introduction

Co-amorphization of poorly water-soluble drugs has been shown to promote significant increase in solubility, dissolution rate and bioavailability. While the preparation of co-amorphous entities is well described in literature, the evaluation of the processability of these entities in the manufacture of final dosage forms is still in an early stage [1]. Measurements of flowability and compressibility related attributes are critical to ensure the manufacturability of formulations [2], particularly during tableting since they influence the quality attributes of tablets, such as uniformity of weight and content [3].

The work developed aimed at the evaluation of the feasibility of using co-amorphous olanzapine:saccharin (OLZ:SAC) in the fabrication of tablets. For that, the flowability (e.g. angle of repose) and compressibility properties (e.g. Carr index), of this material were measured and compared to those of its crystalline counterpart.

Materials and Methods



Results and Discussion

OLZ:SAC co-amorphous systems were produced by solvent evaporation using dichloromethane.

Co-amorphization of OLZ and SAC was ascertained by XRPD and DSC. Diffractograms (Fig. 1A, orange) present a characteristic halo pattern and the absence of peaks related to the crystalline materials (Fig. 1A, blue and green), suggesting the full amorphization of OLZ and SAC. Concomitantly a unique T_g at 57°C and the absence of events due to melting of crystalline arrangement (Figure 1B), further support the co-amorphization of both substances and the probable mutual miscibility.

The higher angle of repose of co-amorphous OLZ, as compared to its crystalline counterpart (Table 1), anticipates problems of flow of the amorphous materials. Herewith, it is important to remark that particle size of all samples was kept constant to minimize the effect of this parameter on powder flowability. These results can possibly be explained in view of the higher cohesiveness and caking tendency of co-amorphous OLZ, compared to the physical mixture of crystalline materials (Table 1).

The Carr index and the Hausner ratio suggest a higher compressibility than its crystalline counterpart (Table 1) with higher consolidation forces between particles, which can be advantageous in tablet manufacturing due to the expected increased capacity of volume reduction. These calculations are in agreement with the angle of repose results and the high cohesiveness presented by blends.

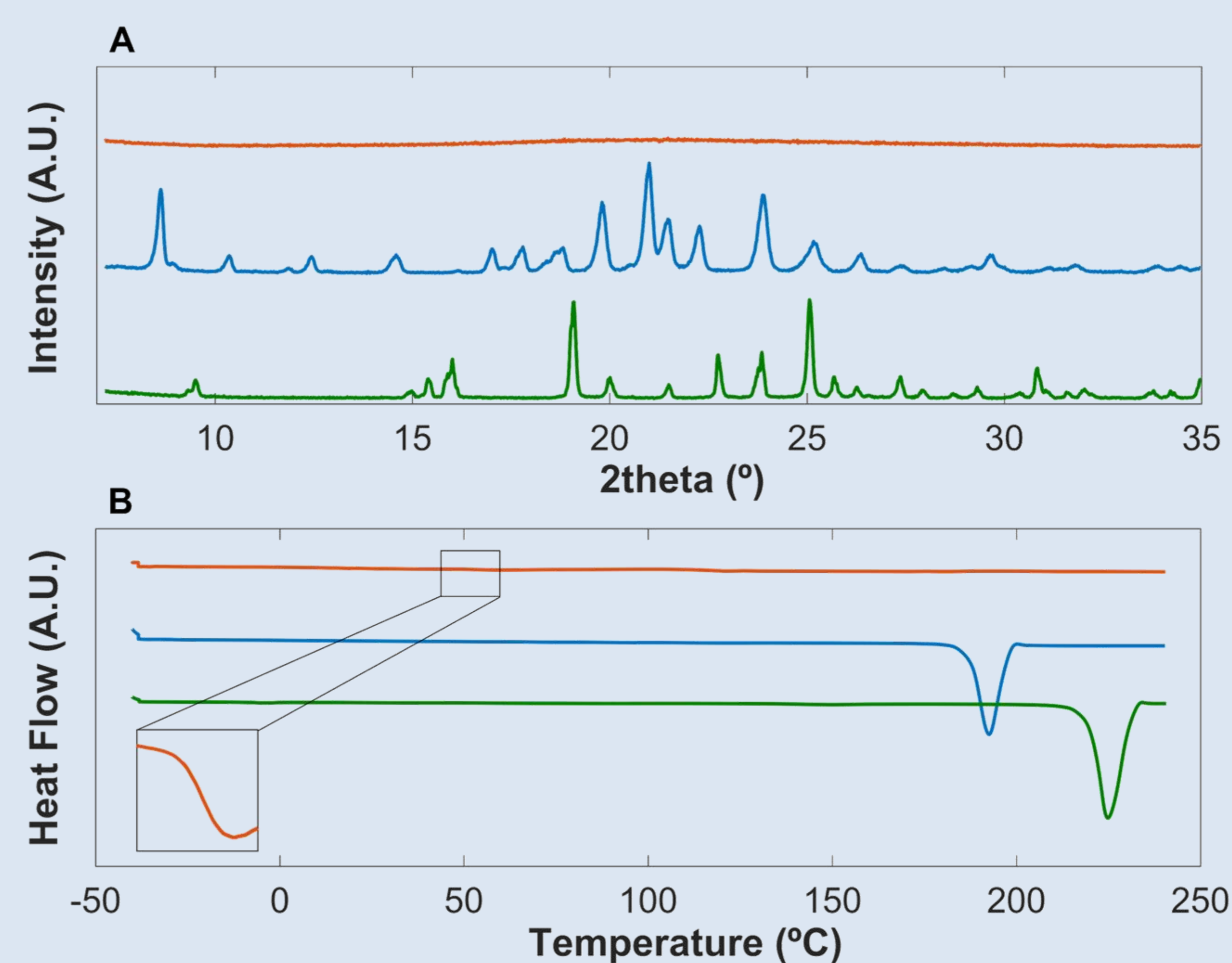


Fig. 1 - XRPD diffractograms (A) and DSC thermograms (B) of co-amorphous OLZ (orange), pure crystalline OLZ (blue) and pure crystalline SAC (green)

Table 1 – Rheological characterization of crystalline and co-amorphous OLZ:SAC

Drug	Angle of repose (°)	Cohesion index	Cake strength (g)	Carr index	Hausner ratio
Crystalline	50.97 ± 0.89	1.30 ± 0.06	159.62 ± 6.88	35.516 ± 0.172	1.551 ± 0.004
Co-Amorphous	54.60 ± 1.72	2.48 ± 0.15	171.82 ± 5.93	36.663 ± 0.630	1.579 ± 0.016

The poor flow properties presented by the amorphous materials may be improved by the criterious selection of excipients and the reported ability of direct tableting of crystalline materials to produce co-amorphous systems (see poster "Solid state conversion of olanzapine during tableting") can also be used advantageously to solve this problem.

Conclusions

- Co-amorphization of OLZ and SAC has resulted in the production of a highly cohesive powder, which demonstrated poor flow properties.
- The use of co-amorphous OLZ in the manufacture of oral dosage forms (e.g. tablets) is thus expected to raise difficulties (e.g. non-uniform dye filling).

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