COMPARISON OF THE CO-AMORPHIZATION ABILITY OF OLANZAPINE WITH AMINO, CARBOXYLIC AND SULFONIC ACIDS

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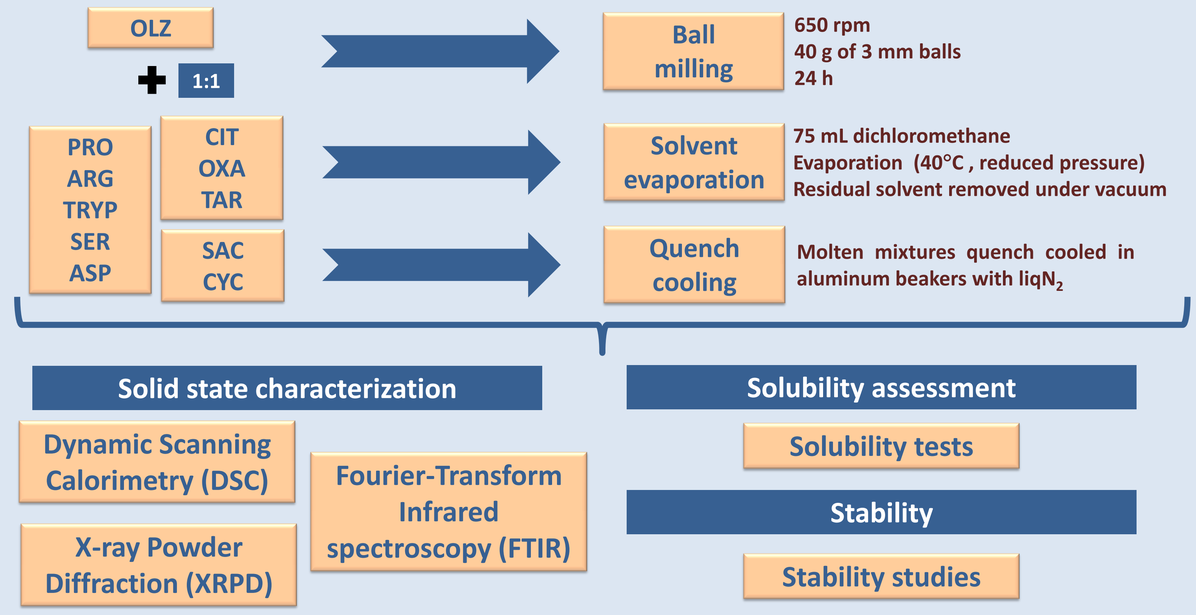
Introduction

A large number of active pharmaceutical compounds, currently under development, are poorly water soluble, a characteristic which can limit their bioavailability, thus representing a challenge for the formulator[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[3]. Co-amorphous systems (CAMs) added value to co-crystallization and amorphization of drugs and they can be prepared by several methods, mainly based on thermodynamic or kinetic disordering processes[3].

The aim of this study is to compare the potential of amino acids (L-proline, PRO; L-arginine, ARG; L-tryptophan, TRYP; L-serine, SER; aspartic acid, ASP), carboxylic acids (citric acid, CIT; oxalic acid, OXA; tartaric acid, TAR) and sulfonic acids (saccharin, SAC; cyclamic acid, CYC) as co-formers, in the production of CAMs with olanzapine (OLZ) by ball milling (BM), solvent evaporation (SE) and quench cooling (QC).

Materials and Methods



Results and Discussion

OLZ produced CAMs with some of the acids considered. BM showed the most promising results, followed by QC. SE did not seem to be able to produce CAMs with the blends containing amino and carboxylic acids (Table 1).

Table 1 – Comparison of the capability of co-amorphization using different techniques and co-formers

Material	QC	SE	BM
OLZ:PRO	Yes[a]	No	No
OLZ:ARG	No	No	No
OLZ:TRYP	No	No	Yes[a]
OLZ:SER	No	No	No
OLZ:ASP	No	No	Yes[a]
OLZ:CIT	Yes[a]	No	Yes[b]
OLZ:TART	Yes[a]	No	Yes[b]
OLZ:OXA	Yes[a]	No	No
OLZ:SAC	Yes[b]	Yes[b]	Yes[b]
OLZ:CYC	No	Yes[b]	Yes[b]

[a] Amorphization incomplete [b] Amorphization complete (CAMs)

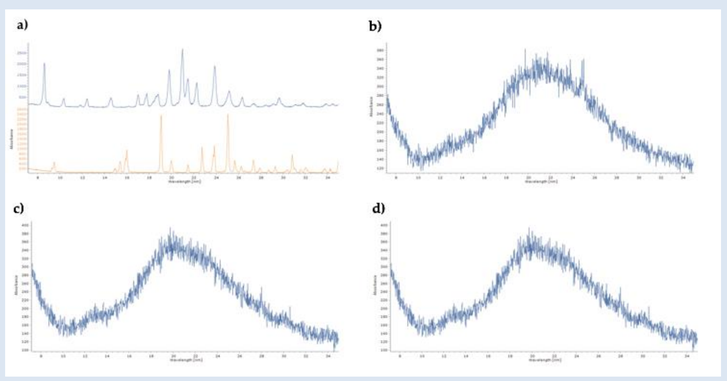


Fig 1 – XRPD pattern of OLZ and SAC (a) and CAMs produced by QC, SE and BM, respectively (b, c and d).

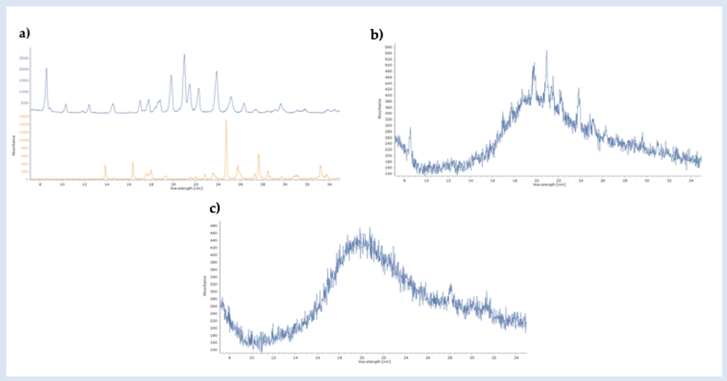


Fig 2 – XRPD pattern of OLZ and CIT (a) and CAMs produced by QC and BM, respectively (b and c).

XRPD patterns of the binary mixtures (1:1) produced with SAC by QC, SE and BM and with CIT by QC and BM are shown in Fig 1 (b-d) and Fig 2 (b, c) respectively, showing the typical halo and the absence of crystalline peaks when the co-amorphization was complete. Incomplete amorphization resulted in halos with crystalline peaks (Fig 2b).

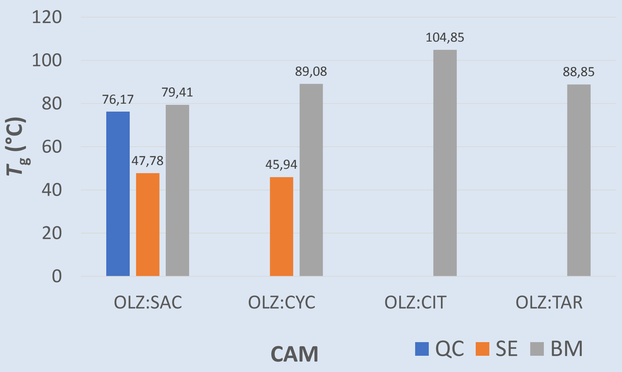


Fig 4 – Comparison of T_g values of CAMs produced by QC, SE and BM, respectively.

The T_g value of the CAMs (Fig 4) was higher for the systems produced by BM, followed by QC and SE. A higher T_g value suggests that the amount and strength of bonding between OLZ and the co-formers may be stronger in when the BM and QC techniques are used.

The FTIR spectra for the CAMs produced were the superposition of those of two single components and in all of them the intermolecular interactions, suggest hydrogen-bonding between the molecules (Fig 3).

Fig 3 – FTIR spectra of crystalline OLZ and SAC and QC OLZ:SAC

Table 2 – Comparison of the solubility enhancement of CAMs using different techniques and co-formers

Material	QC	SE	BM
OLZ	4.6	-	-
OLZ:CIT	-	-	213
OLZ:TART	-	-	269
OLZ:SAC	129	199	188
OLZ:CYC	-	184	132

Crystalline OLZ presented low solubility (40.1 mg/L) in distilled water but by conversion into an amorphous form (only possible by QC), its solubility was enhanced 4.6 times. A general increase in the solubility of the CAMs formulations in comparison to the pure crystalline and amorphous drug is shown in Table 2. This significant increase (up to 269 times; BM with TART) unveils the possibility of improved dissolution profiles and bioavailability.

Table 3 – Onset of recrystallization in weeks of the pure amorphous OLZ and CAMs produced

Material	11% RH / 25 °C	53% RH / 25 °C	75% RH / 25 °C	75% RH / 40 °C	93% RH / 25 °C
OLZ QC	3	3	1	< 1	< 1
OLZ:CIT BM	> 8	> 8	1	< 1	< 1
OLZ:TART BM	> 8	> 8	1	< 1	< 1
OLZ:SAC*	> 8	> 8	1	< 1	< 1
OLZ:CYC*	> 8	> 8	1	1	< 1

* Produced by different techniques

Stability testing results highlight the ability of some co-formers, especially carboxylic and sulfonic acids, to stabilize the OLZ amorphous systems (Table 3). They are also in agreement with the FTIR results, which revealed the presence of strong interactions between the two molecules, as intermolecular bonding. Stability studies are still ongoing.

Conclusions

- 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 which stabilize the amorphous structures formed.
- Ball milling achieved better results than solvent evaporation and quench cooling, and sulfonic acids were more successful in the stabilization of the CAMs obtained.
- Due to the dramatic increase in solubility CAMs could be a successful way to process active compounds with poor water solubility.

References

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