# PRODUCTION OF CO-AMORPHOUS SYSTEMS WITH OLANZAPINE AND INDOMETHACIN

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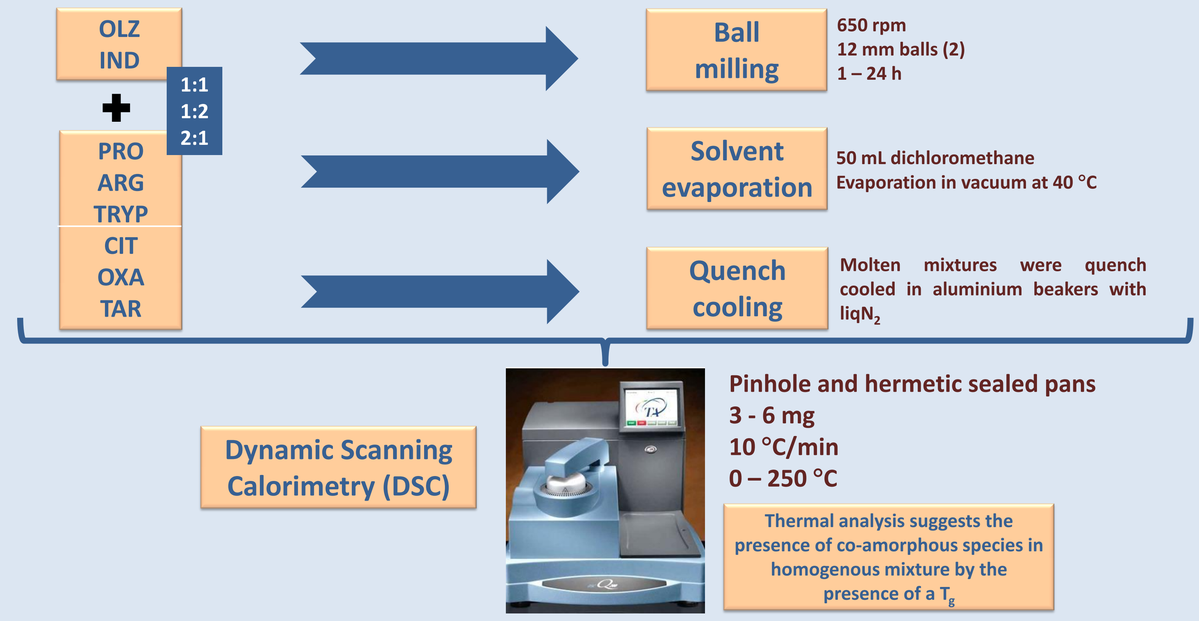
## Introduction

A large number of active pharmaceutical compounds currently under development are poorly water soluble, a characteristic which can limit their bioavailability resulting in 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 can be prepared by several methods, mainly based on thermodynamic or kinetic disordering processes[1-3].

This work aims at producing co-amorphous mixtures of olanzapine (OLZ) and indomethacin (IND), using amino acids, L-proline (PRO), L-arginine (ARG) and L-tryptophan (TRYP) and carboxylic acids, such as citric acid (CIT), tartaric acid (TAR) and oxalic acid (OXA) as co-formers, by milling (M), solvent evaporation (SE) and quench cooling (QC).

## Materials and Methods




## Results and Discussion

Results have shown that OLZ and IND could be converted into the amorphous state, with quench cooling presenting the most promising results. Blends of drugs and co-formers were co-amorphized by quench cooling and solvent evaporation (Tables 1,2 and Figures 1-4).

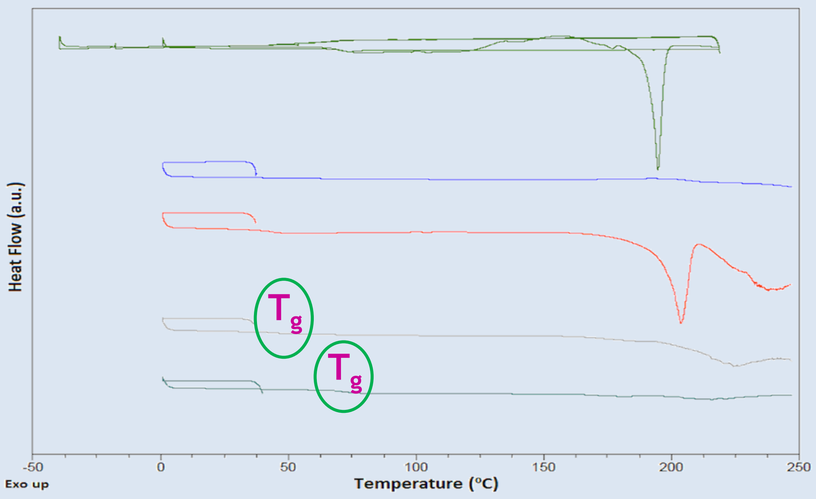



Fig 1 – Thermograms of mixtures of OLZ and TRYP (1:2) and PRO (1:1) obtained by QC.
OLZ QC — TRYP QC — PRO QC — OLZ:TRYP (1:2) QC — OLZ:PRO (1.1) QC —

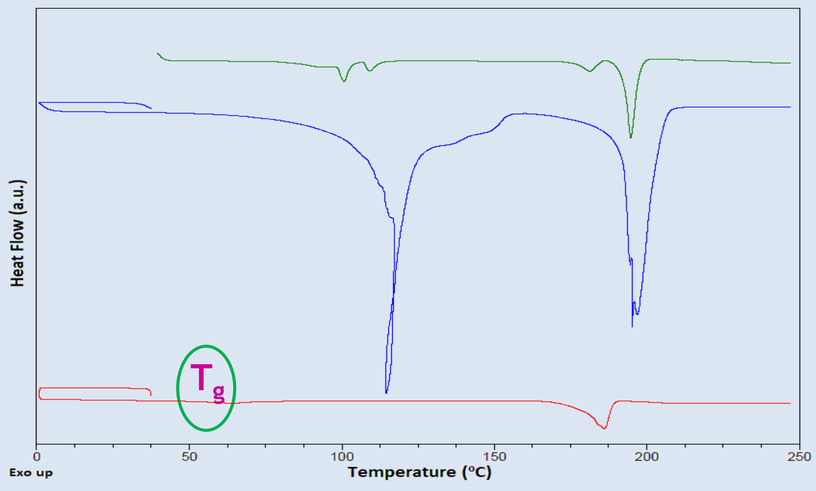



Fig 2 – Thermograms of mixtures of OLZ and OXA (1:1) obtained by SE.
OLZ SE — OXA SE — OLZ:OXA (1:1) SE —

Table 1 - $T_g$ and $T_m$ of mixtures of OLZ and co-formers

| Material | $T_g$ (°C) | $T_m$ (°C) |
|---|---|---|
| OLZ | 69.13[a] | 193.4 |
| TRYP | 92.07[a] | 280.88 |
| PRO | nd | 150.22<br>236.79 |
| OXA | nd | 99.05 |
| OLZ QC | 72.67 | 176.88<br>194.25 |
| OLZ SE | nd | 176.67<br>192.56 |
| TRYP QC | 45.11 | nd |
| PRO QC | 44.15 | nd |
| OXA SE | nd | 195.03 |
| OLZ:TRYP 1:2 QC | 44.01 | nd |
| OLZ:PRO 1:1 QC | 72.70 | nd |
| OLZ:OXA 1:1 SE | 55.70 | 179.54 |

[a] Calorimetric analysis (DSC / second heating cycle)
nd - not detected

In the co-amorphous powders, the molecular short-range order, characteristic of the amorphous state, gets disturbed in favour of the formation of intermolecular interactions between drugs and co-formers. In particular, the use of amino acids and carboxylic acids has been described to show a high potential to stabilize drugs in the co-amorphous form[2], with a glass transition ($T_g$) and neither recrystallization, nor a melting point (Figures 1-4).

Table 2 - $T_g$ and $T_m$ of mixtures of IND and co-formers

| Material | $T_g$ (°C) | $T_m$ (°C) |
|---|---|---|
| IND | 32.47[a] | 161.91 |
| TRYP | 92.07[a] | 280.88 |
| PRO | nd | 150.22<br>236.79 |
| CIT | nd | 153.84 |
| IND QC | 40.73 | 156.34 |
| IND SE | nd | 161.91 |
| TRYP QC | 45.11 | nd |
| PRO QC | 44.15 | nd |
| CIT SE | nd | 155.01 |
| IND:TRYP 1:1 QC | 49.73 | nd |
| IND:TRYP 2:1 QC | 51.00 | nd |
| IND:PRO 1:1 QC | 47.92 | 179.54 |
| IND:PRO 1:1 SE | 44.77 | nd |

[a] Calorimetric analysis (DSC / second heating cycle)
nd - not detected

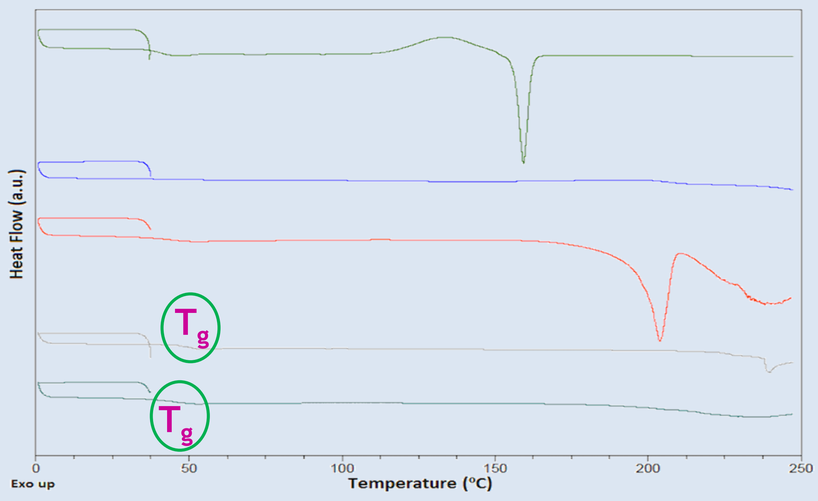



Fig 3 – Thermograms of mixtures of IND and TRYP (2:1) and PRO (1:1) obtained by QC.
IND QC — TRYP QC — PRO QC — IND:TRYP (2:1) QC — IND:PRO (1.1) QC —

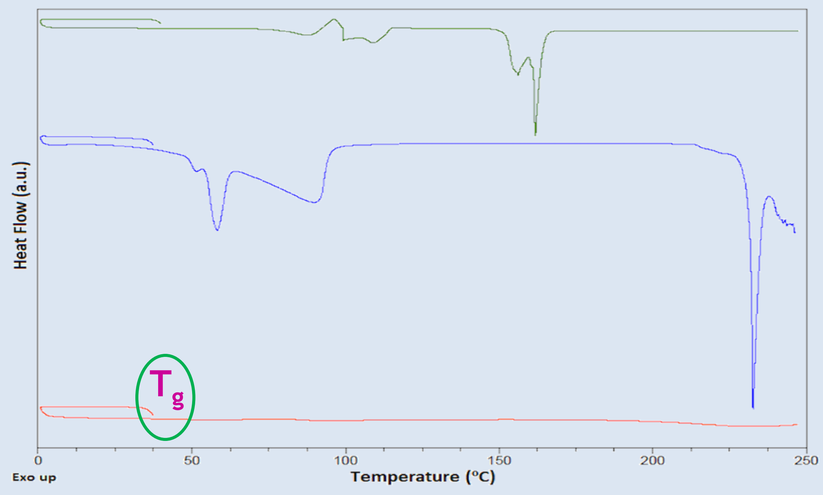



Fig 4 – Thermograms of mixtures of IND and PRO (1:1) obtained by SE.
IND SE — PRO SE — IND:PRO (1:1) SE —

## 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 help stabilization of the amorphous structures formed.
- In this work, the quench cooling technique was better than its counterparts, solvent evaporation and milling.
- Proven the ability of these techniques to form co-amorphous systems, formulations and process conditions are under optimization to fulfill their potential to improve the solubility of indomethacin and olanzapine.

## References

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## Acknowledgements

Fundação para a Ciência e a Tecnologia (PTDC/DTP-FTO/1057/2012) is acknowledged for funding.

*Member of:
Pharmaceutical Solid State Research Cluster (www.pssrc.org)