

Discovery And Continuous Production Of α -Lipoic Acid Co-crystals In A Oscillatory Baffled Crystalliser

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1. Introduction

Advantages of co-crystals:

- Modify physical-chemical properties of molecular solids such as stability and solubility; Generate new IP

Challenges:

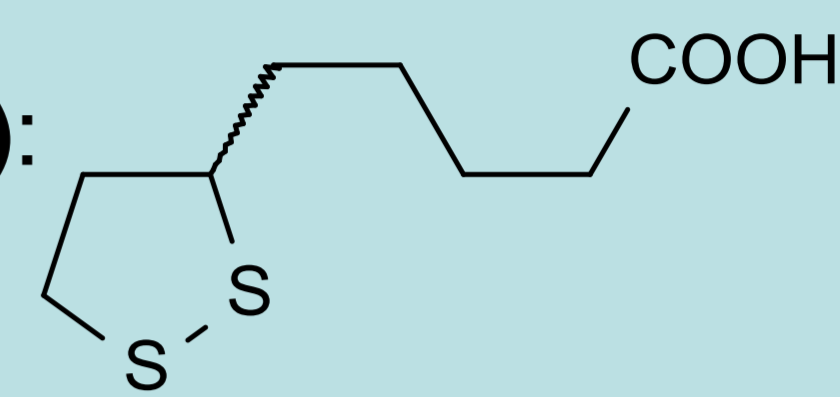
- Difficult to scale-up due to multi-component system

2. Objectives and scope

- Find suitable co-formers for α -Lipoic Acid (ALA) to produce novel co-crystals to improve chemical stability
- Characterise co-crystal(s)
- Scale-up the co-crystallisation process (5mL [0.3g] \rightarrow 500mL [30g])
- Develop a continuous crystallisation using a continuous oscillatory baffled reactor (COBC) for production of co-crystals (details below [>1 kg])

3. Model compound

α -Lipoic acid (ALA):



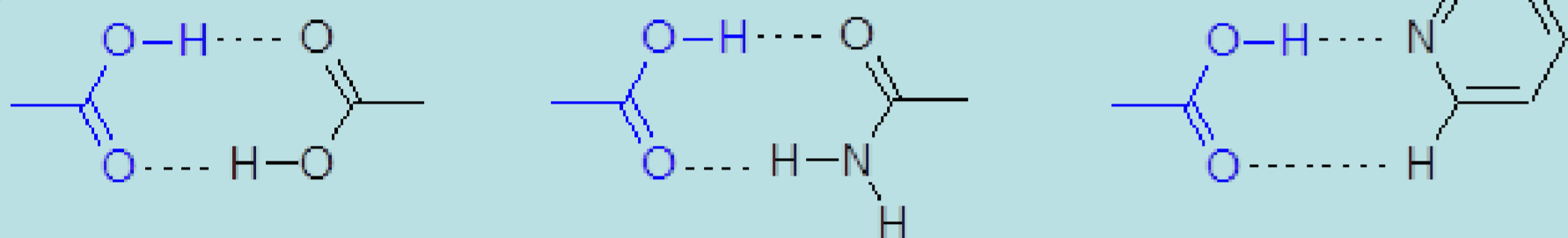
- Nutraceutical compound
- Chemically unstable on exposure to heat and light, prone to polymerisation



Viscous polymer solution from commercial ALA sample

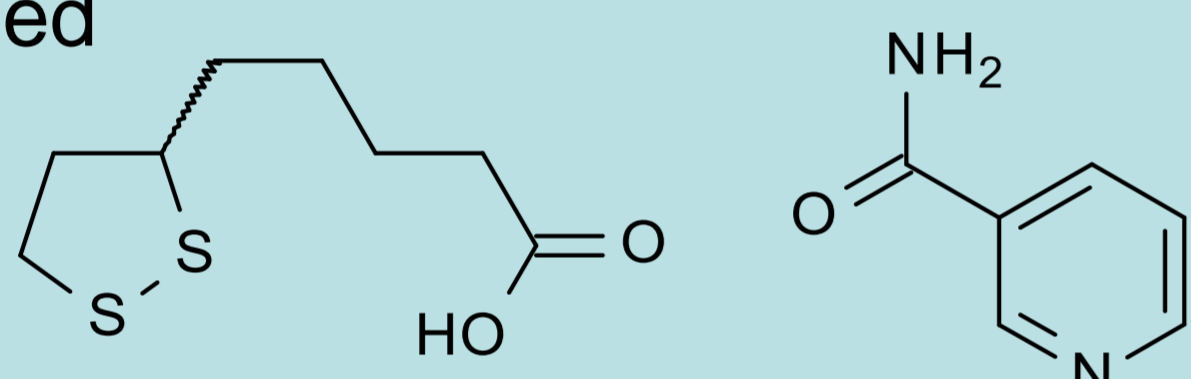
4. Small scale co-crystallisation trials

Choose co-formers



Small scale trials utilised:

- Liquid-assisted grinding
- Cooling /evaporative crystallisation in 5 mL vials

Outcome: Novel ALA:nicotinamide co-crystals obtained


5. Analysis

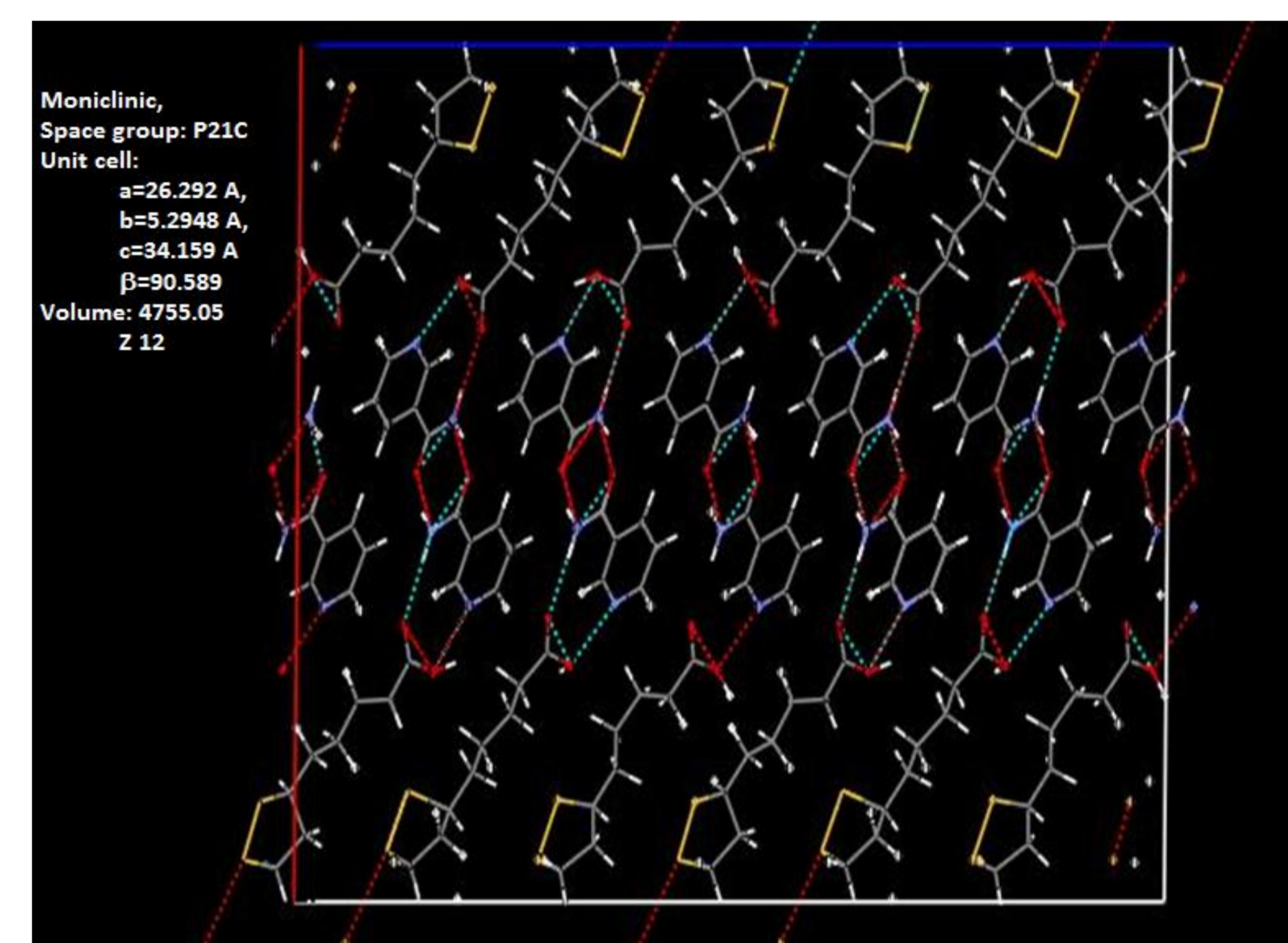
Novel co-crystal forms identified using:

- XRPD, single crystal diffraction
- DSC/TGA
- FT-IR
- 1 H-NMR
- Microscope/SEM

Stability tested by DSC and HPLC

 New form is a *thermally stable*, 1:1 co-crystal of ALA and nicotinamide.

6. Crystal structure



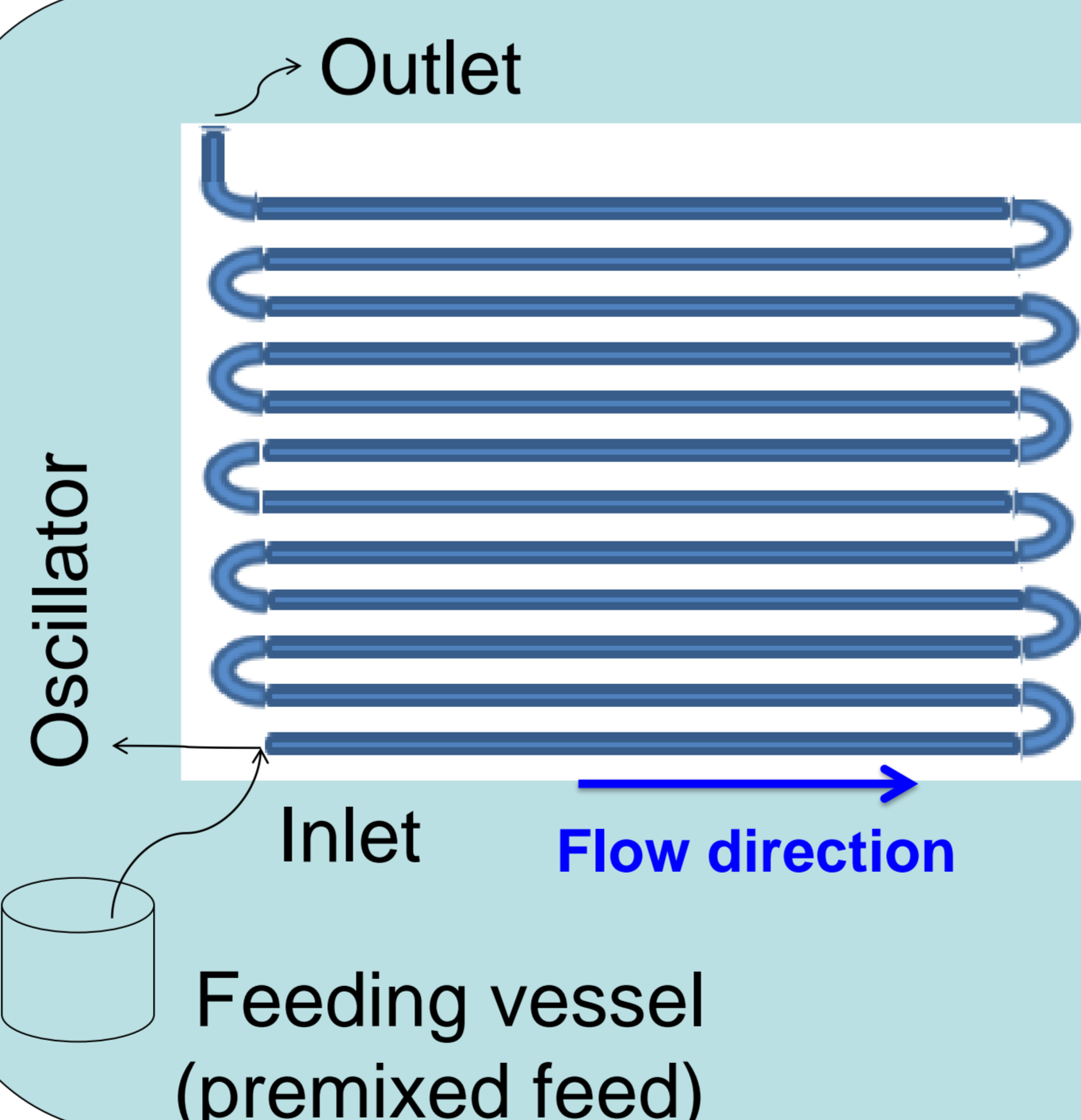
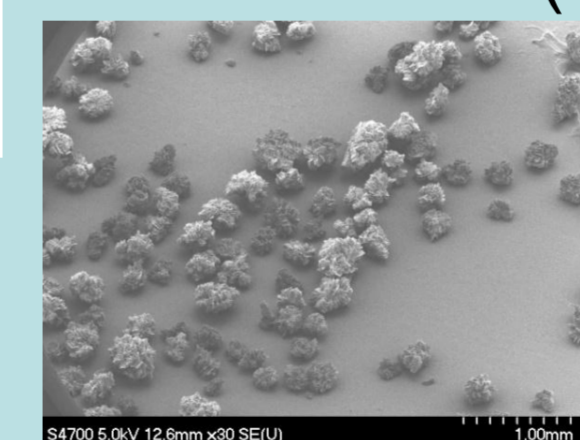
7. Scale-up co-crystallisation process

Scale-up in a batch OBC

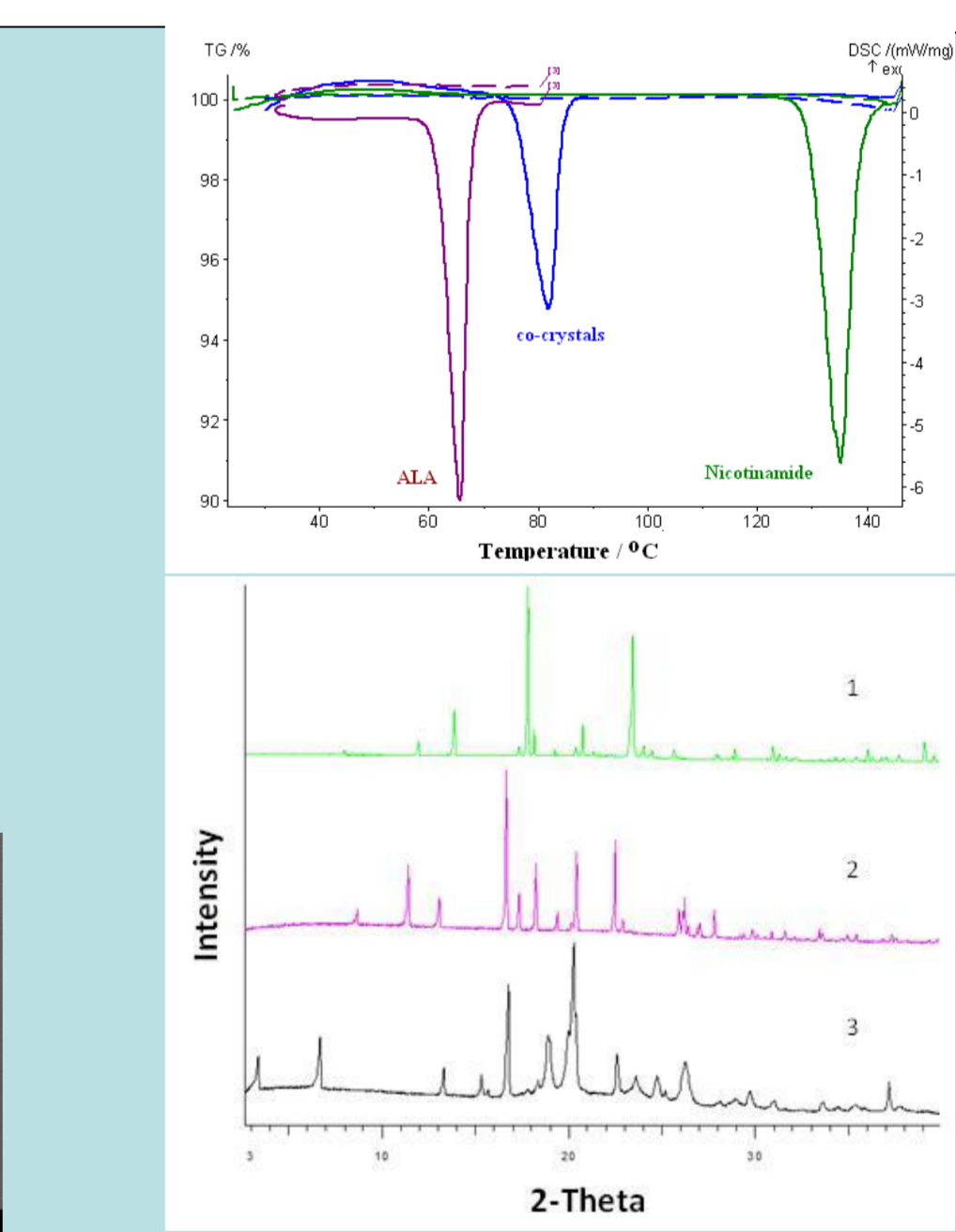
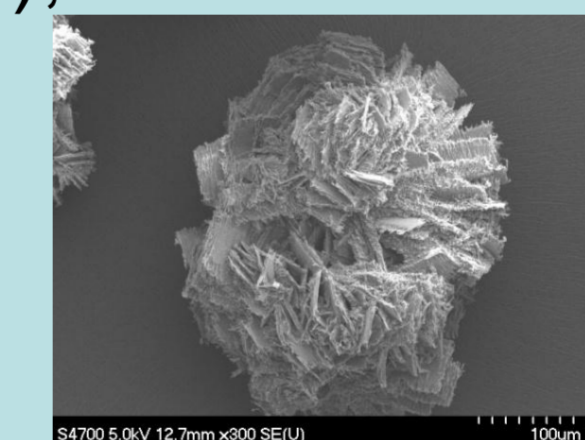


- Co-crystallisation process scaled-up in a 500 mL batch OBC to identify:
- Suitable solvent system
- Cooling profile
- Key parameters for continuous process (oscillation intensity/concentration)

Scale-up in a COBC


 COBC: 15 mm ID jacketed length: 25 m
 Volume: 4.2 L
 Flow rate: 71 mL/min
 Oscillation: 1Hz, 30mm
 Run Time: 2 ~ 3 hrs per trial
Solid produced: > 1kg (330g/hr)
 Yield: ~70% (w/w); RT: ~1hr


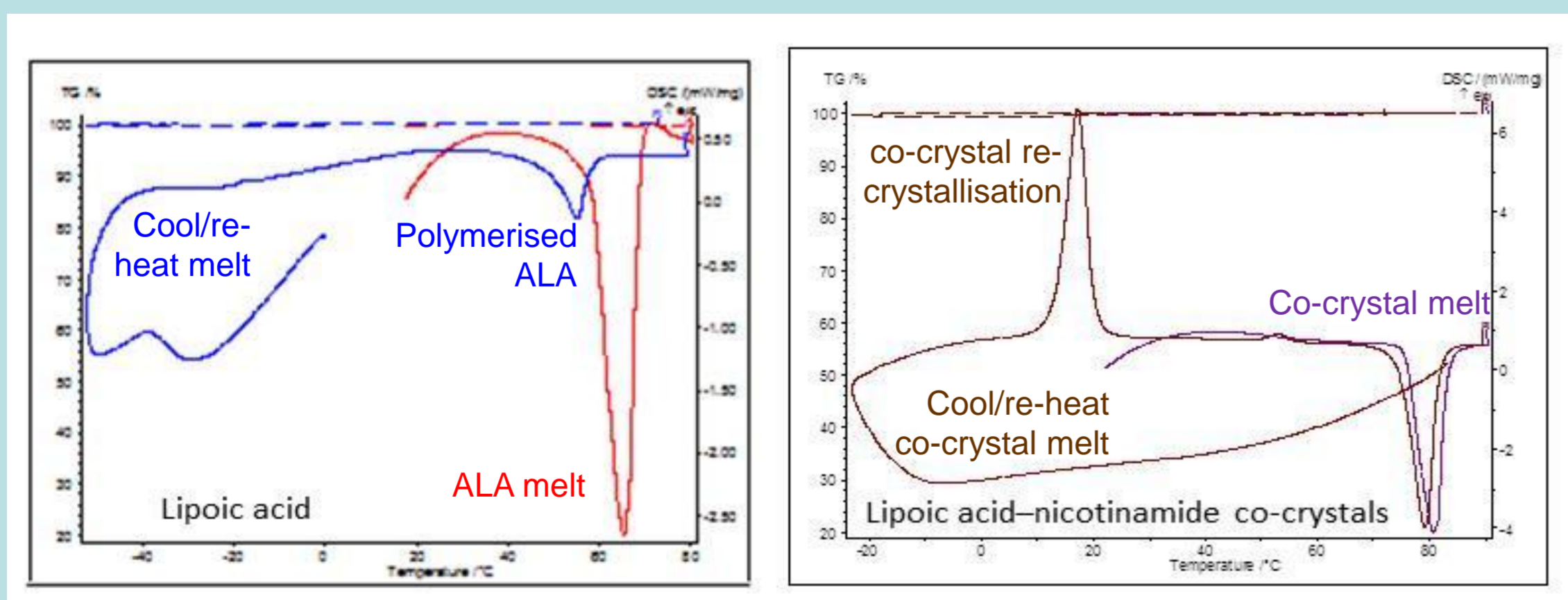
SEM of co-crystals from COBC



DSC & XRPD of co-crystals

8. Stability & Solubility of Co-crystals

DSC of ALA plus ALA nicotinamide co-crystal. Thermal cycling highlights stability of co-crystal



HPLC analysis:

	Original purity	After 30 minutes at 60°C	80°C	Solubility
ALA	99%	61%	18%	2 mg/mL
Co-crystal	99%	99%	99%	10 mg/mL

9. Conclusions

- ALA:nicotinamide co-crystals discovered and characterised.
- Co-crystal composition confirmed via solution NMR plus single crystal XRD structure determination.
- Significant improvement in ALA thermal stability and solubility achieved via co-crystal formation.
- Effective demonstration of scale-up of co-crystallisation process from 0.3g (vial) \rightarrow 30g (OBC) \rightarrow 1kg (COBC).
- Good purity and size distribution achieved in the continuous cooling crystallisation process within the COBC.