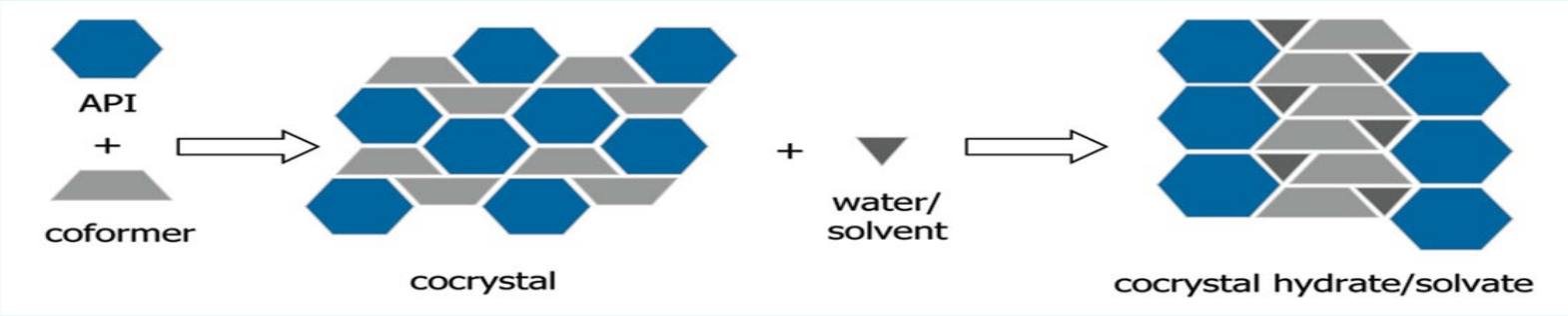
IMPROVING STABILITY OF PHARMACEUTICAL COCRYSTALS THROUGH CO-BLENDING VIA HOT MELT EXTRUSION.

Steven Ross

Introduction: matrix-assisted cocrystallization

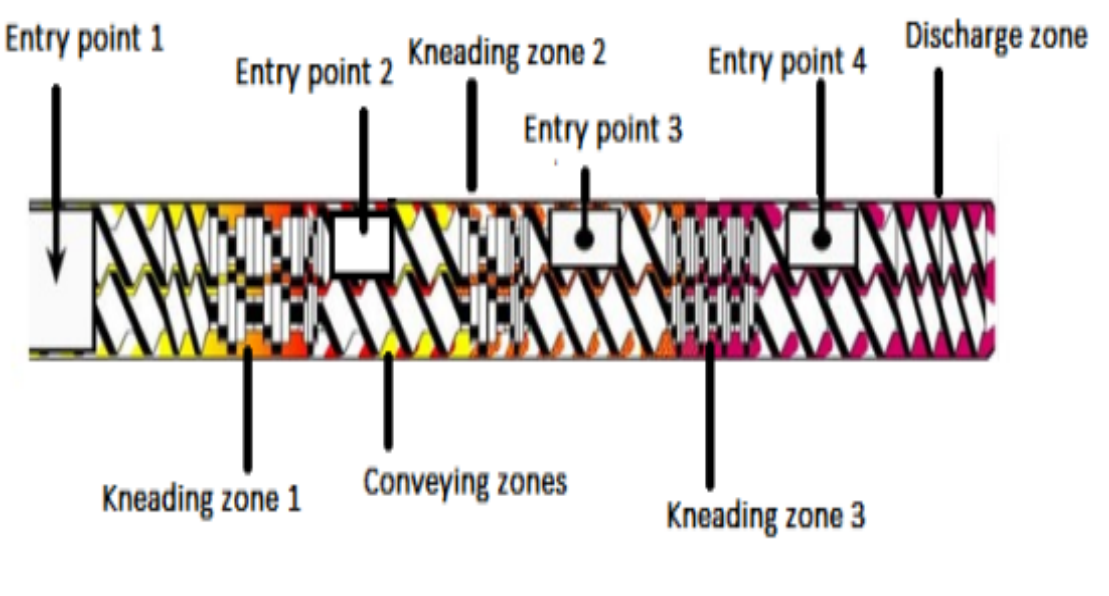
- Cocrystallization offers and expedient way to alter the physicochemical properties of APIs including dissolution rate, intrinsic solubility, melting point, hygroscopicity, compressibility, bulk density and friability.
- Matrix-Assisted Cocrystalization (MAC) describes co-processing pharmaceutical API alongside added excipients To achieve this he added excipient must be:
    - Inert
    - Non-miscible.
    - low melting viscosity
    - solidify quickly upon cooling
- Previous attempts at utilizing MAC with hot-melt extrusion (HME) have failed [1]
    - This is due to the increased interactions in the extruder barrel due to high-shear kneading zones causing dispersive mixing between Cocrystal pair and excipient, leading to amorphous content in cocrystal.



1 Eddleston M, Thakuria R, Aldous B, Jones W. An Investigation of the Causes of Cocrystal Dissociation at High Humidity. Journal of Pharmaceutical Sciences. 2014;103(9):2859-2864.

HME Processing

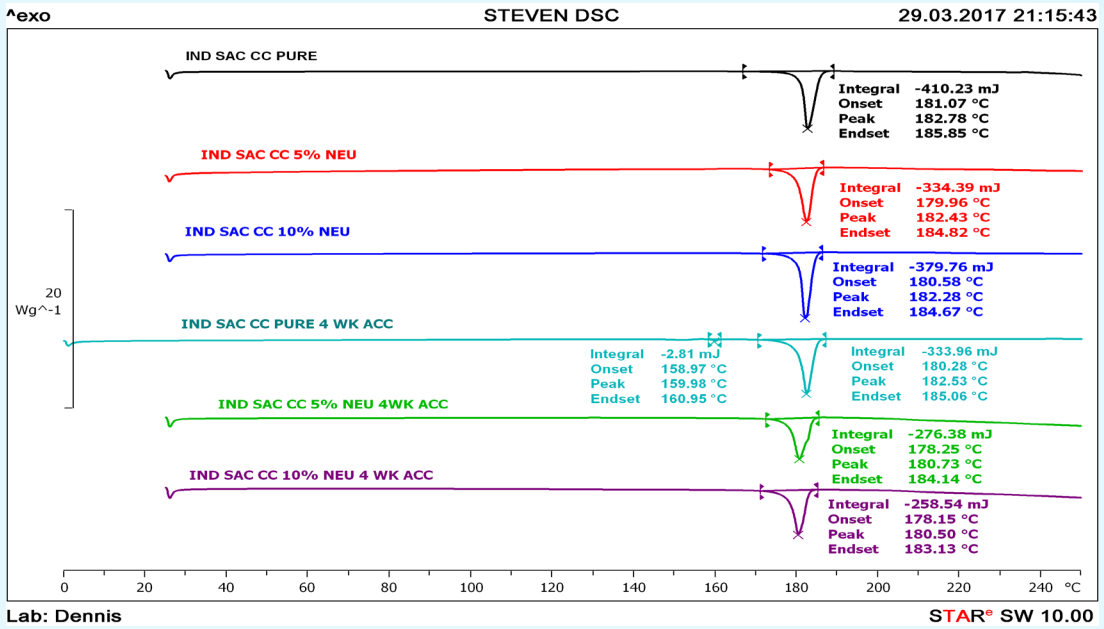
- Here, a selection of excipients are co-processed alongside indomethacin (IND)-saccharin (SAC) cocrystals HME with the aim of improving long term physical stability
- To avoid previously reported issue, a second feeder was placed above entry point 4, into the screws conveying zone, to avoid high-shear mixing in the kneading zones.
- Neusilin, HPMC and PEG 6000 were used as added excipients and fed into the extruder via the second feeder at entry point 4.
- Further analysis was performed on the pure and excipient blended samples after 4 and 6 months of stability testing under accelerated conditions of 40 ± 1 °C and 75 ± 1.5% RH as per ICH guidelines [2]

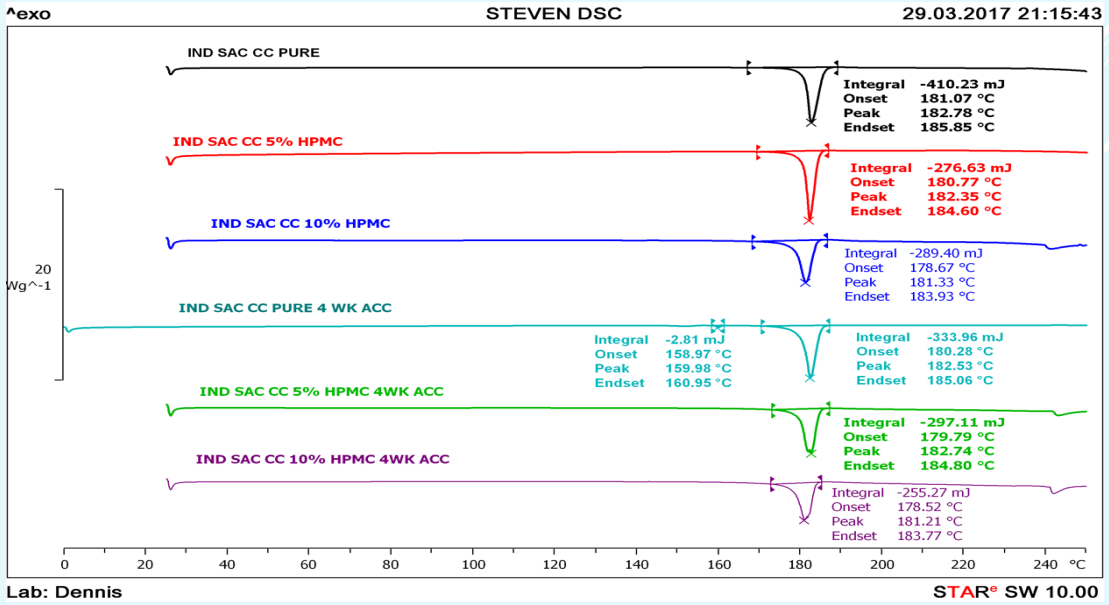


2 Lee M, Chun N, Wang I, Liu J, Jeong M, Choi G. Understanding the Formation of Indomethacin–Saccharin Cocrystals by Anti-Solvent Crystallization. Crystal Growth & Design. 2013;13(5):2067-2074.

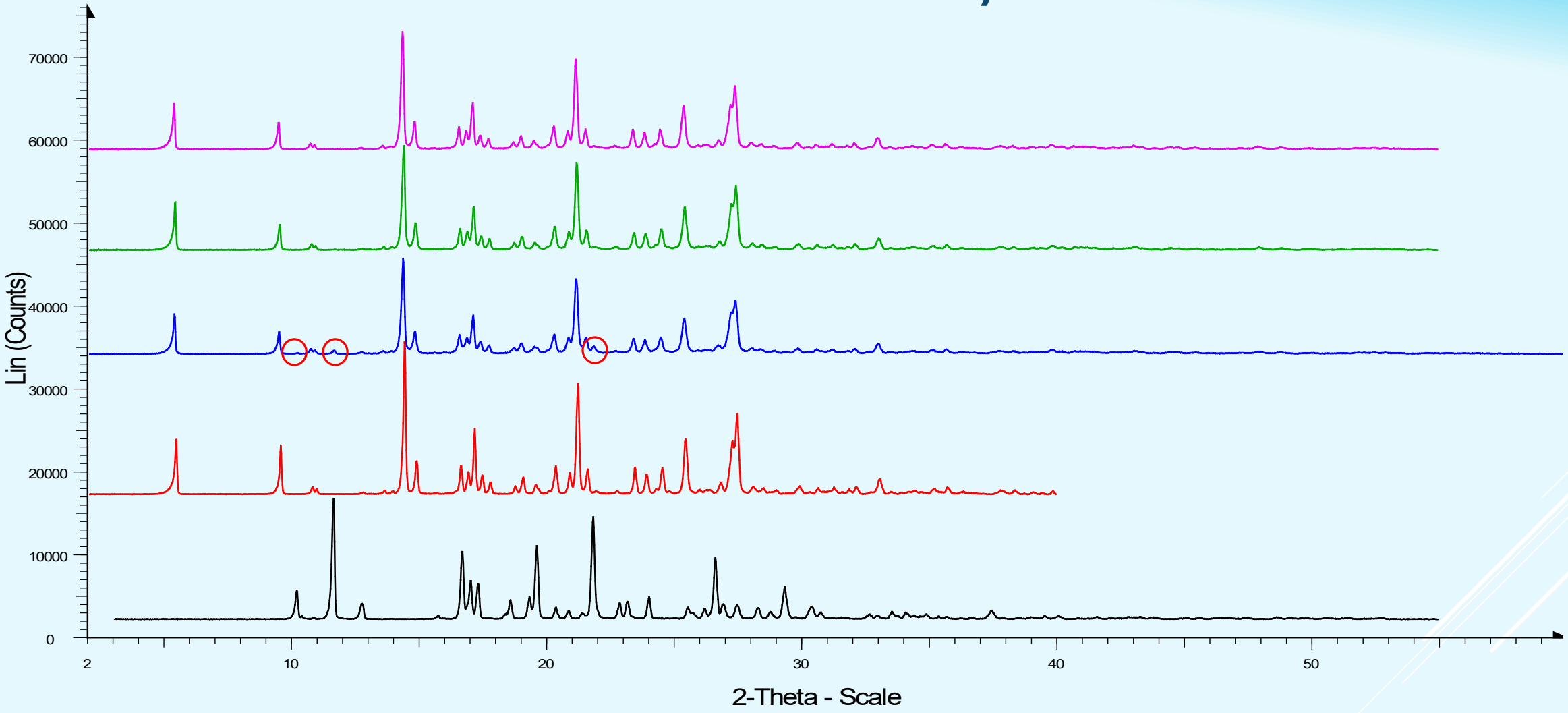
Results: DSC – IND/SAC NEU

- DSC analysis revealed after a 6 month period under accelerated conditions, the pure IND/SAC cocrystal displayed an additional endotherm at 159°C.
- Meanwhile, the excipient coated cocrystals display no such endotherm, indicating they have maintained their physical stability
- For HPMC coated cocrystals a small endotherm can be seen at 242°C, though this can be attributed to the polysaccharides degradation behaviour
- Peak at 159 °C Likely due to coformer solubilisation rarther than hydrate formation.





Results: XRPD- NEUSLIN after 4 month stability



Pure IND
IND/SAC CoXL
IND/SAC CoXL 4 ACC
IND/SAC CoXL 5% NEU ACC
IND/SAC CoXL 10% NEU ACC

Results: XRPD

- Diffractograms of the pure cocrystals revealed the emergence of new peaks at 10.15 $^{2}\theta$, 11.61 $^{2}\theta$ and 21.8 $^{2}\theta$.
- These peaks correlate with that of indomethacin, further indicating the disassociation via solubilisation of saccharin, leaving recrystallized indomethacin samples.
- Diffractograms of cocrystals blended with excipients did not display these peaks, demonstrating improved physical stability.

Results: XRPD- TOPAS crystal structure Day: 1

- Cocrystal structure was determined from the XRPD data by Rietveld refinement with favourable residual variances.

- Table below displays the residual experimental and weighting pattern, Goodness of fit and the percentage of which our sample matched published data collected from the Cambridge structural database [3].

- From this we can conclude the added excipient causes no change to cocrystal structure.

Formulation	Rexp	Rwp	GoF	Percentage Cocrystal (%)	Percentage impurities (%)
Pure cocrystal	3.67	7.71	2.10	100	0
NEU 5%	4.01	8.77	2.19	100	0
NEU 10%	4.01	8.77	2.19	100	0
HPMC 5%	3.84	9.11	2.37	100	0
HPMC 10%	3.75	9.44	2.51	100	0
PEG 6000 5%	4.02	9.02	2.24	100	0
PEG 6000 10%	4.16	9.45	2.43	100	0

3 Basavoju S, Boström D, Velaga S. Indomethacin–Saccharin Cocrystal: Design, Synthesis and Preliminary Pharmaceutical Characterization. Pharmaceutical Research. 2007;25(3):530-541.

Results: XRPD- TOPAS crystal structure: 4 Month stability studies

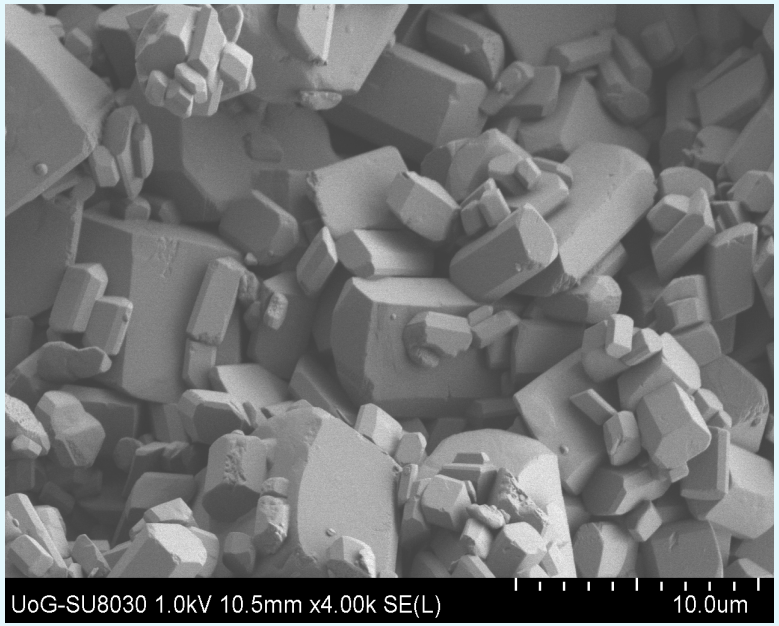
- Results on Table below indicate that the addition of added excipient generally provides protection from degradation under accelerated conditions with no change in crystallinity for cocrystals blended with NEU, HPMC, and 5%PEG 6000.
- The pure cocrystal sample was found to have only a 95.4% match to CSD structural data.
- Unmatched peaks were found to fit to CSD data for indomethacin, indicating dissociation had occurred under accelerated conditions
- Recrystallisation of SAC occurred in 10% PEG6000 blended cocrystals

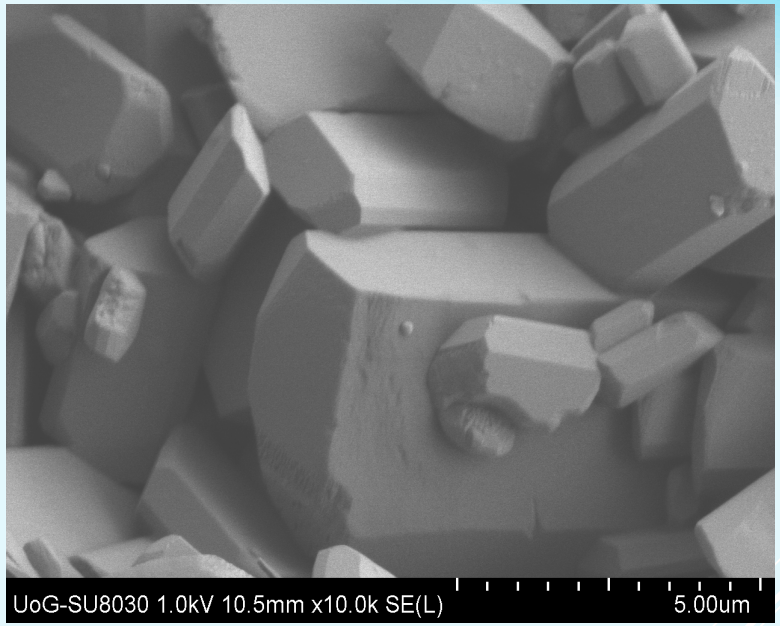
Formulation	Rexp	Rwp	GoF	Percentage Cocrystal (%)	Percentage impurities (%)
Pure cocrystal	3.95	8.10	6.18	95.40	4.60 (IND)
NEU 5%	4.06	8.22	2.03	100	0
NEU 10%	4.00	8.38	2.09	100	0
HPMC 5%	3.88	9.18	2.37	100	0
HPMC 10%	3.74	9.50	2.54	100	0
PEG 6000 5%	3.94	8.63	2.19	100	0
PEG 6000 10%	3.95	9.04	2.29	96.33	3.67 (SAC)

Results: SEM

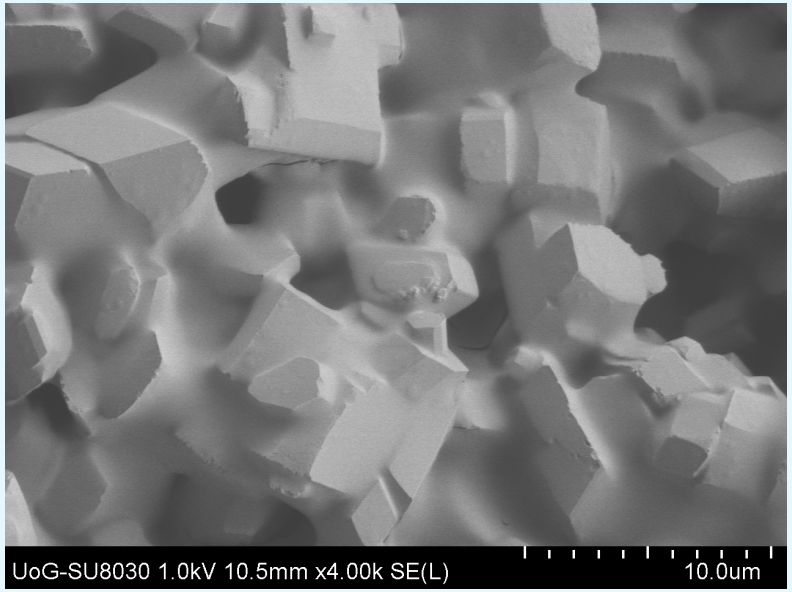
- A marked morphological difference can be seen between Cocrystals blended with excipients and those that were not.
- In the NEU and HPMC blended cocrystals a protective matrix has formed around the cocrystals.
- The matrix can prevent uptake of water molecules preventing hydrate formation and coformer solubilisation.
- Limited interaction between API and coformer preventing dissociation.

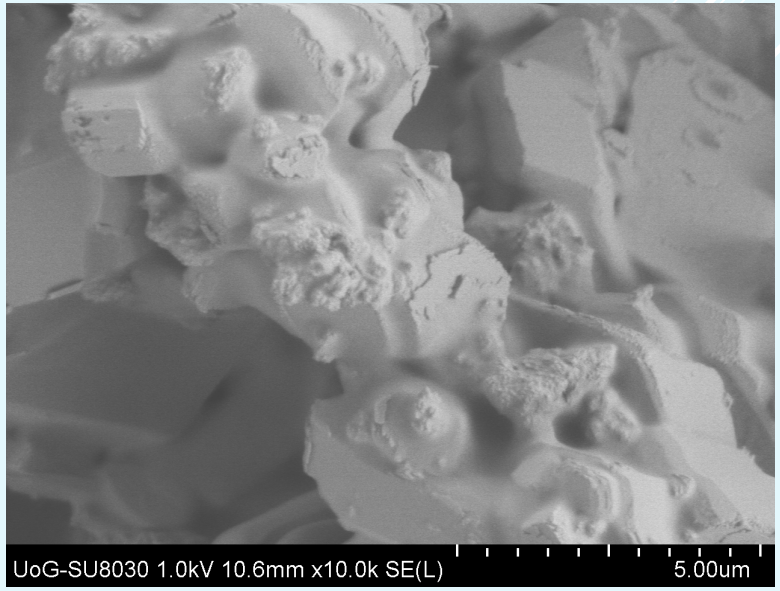
Base CoXL





NEU

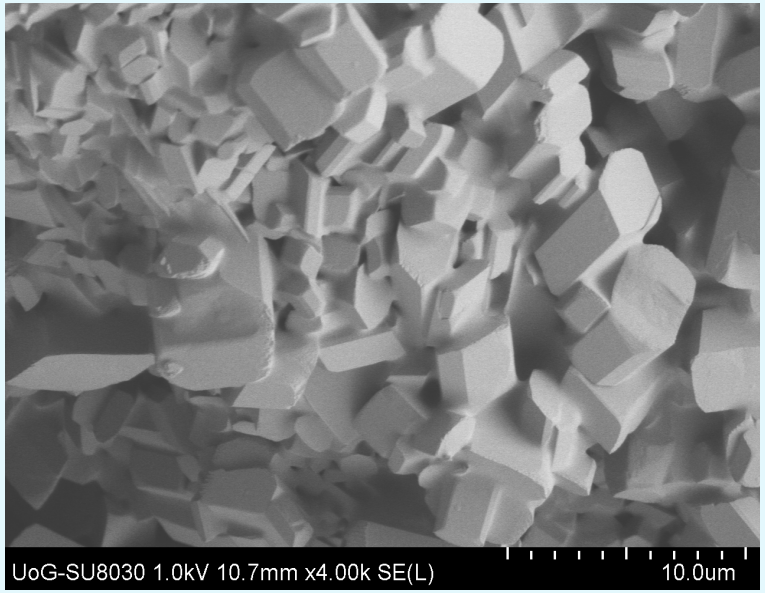


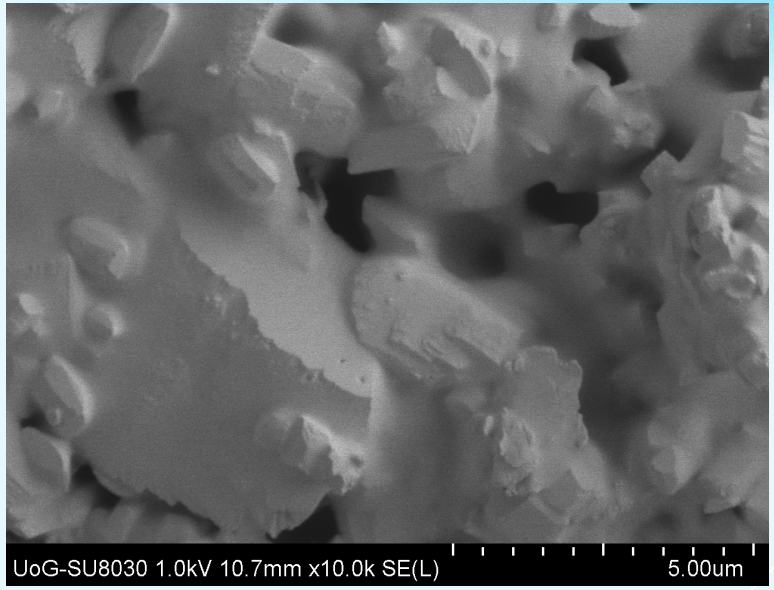


Results: SEM- PEG 6000

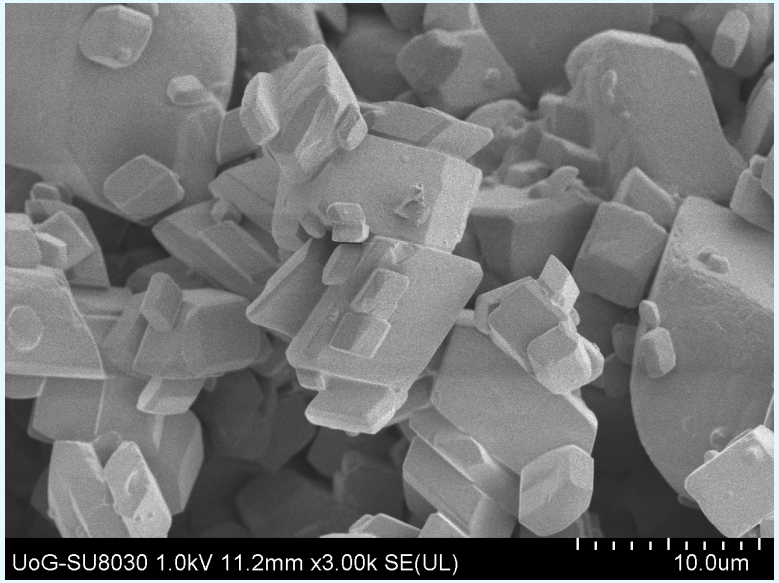
- The cocrystals blended with PEG 6000 do not display an the matrix as seen in the NEU and HPMC blended cocrystals
- This can be attributed to the fact that PEG 6000 is crystalline while NEU and HPMC are amorphous in structure.
- This could potentially explain why reduced crystallinity was observed in the PEG 6000 blended cocrystals after stability testing.
- Uptake of water molecules or solubilisation of either component would cause decrease in structure crystallinity

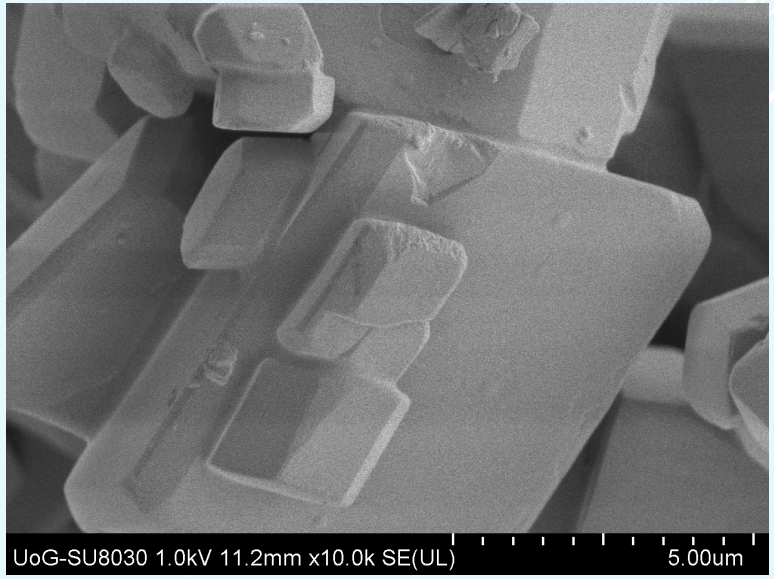
HPMC





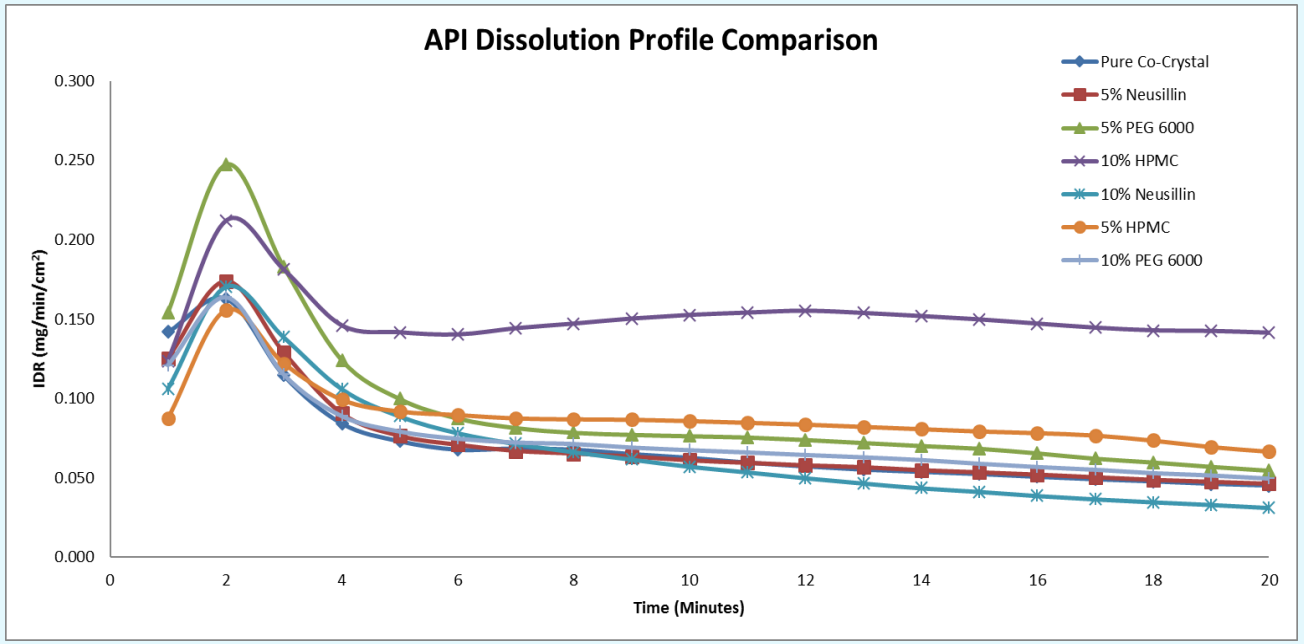
PEG 6000

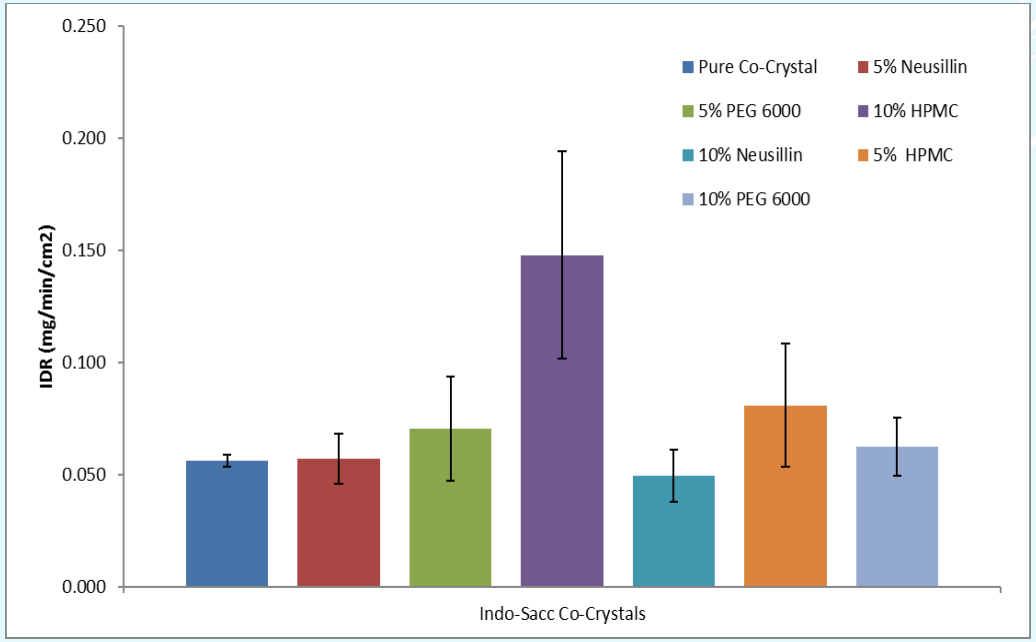




Results: Dissolution studies

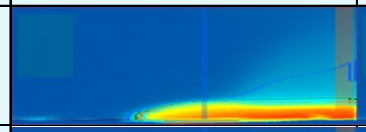
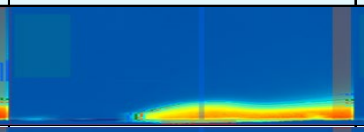
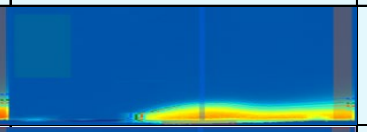
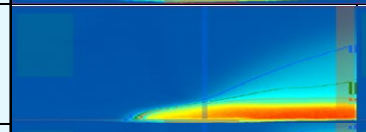
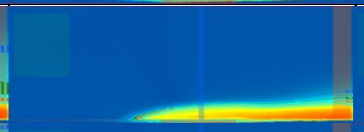
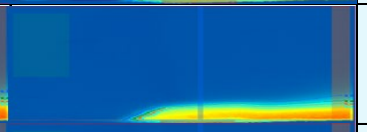
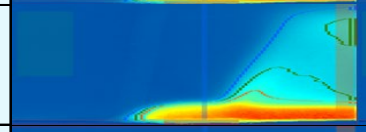
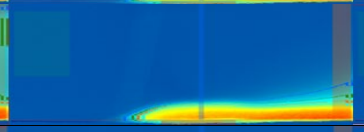
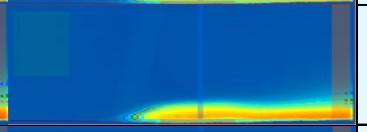
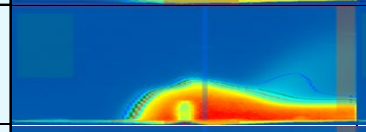
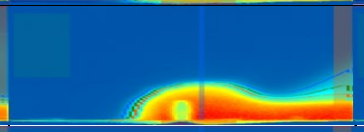
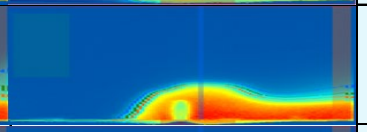
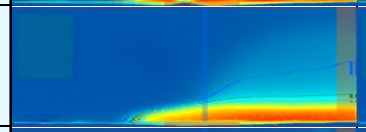
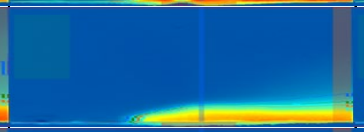
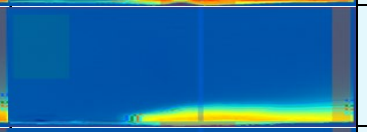
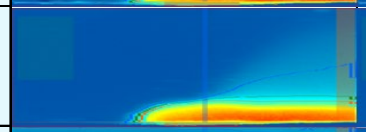
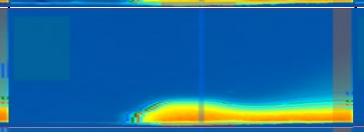
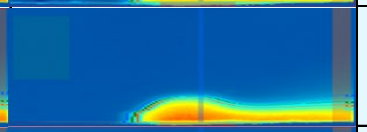
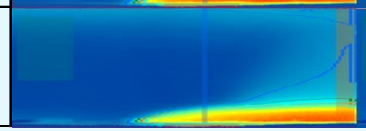
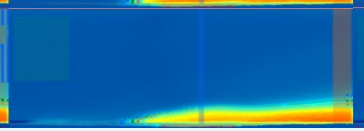
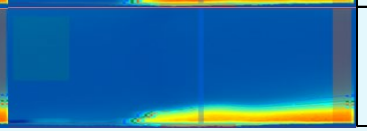
- The excipient coated cocrystals show similar dissolution rates to the pure cocrystal despite the additives.
- This is due to low concentration of excipient in the mix and that as the polymer is only added to the extrusion process after the last mixing zone.
  - the excipient is not interspread throughout the crystal lattice and instead acts as mealy a protective coating
- As the selected polymers are water soluble they do not negatively effect the dissolution of the cocrystal.
- The only exception to this trend is the HPMC loaded samples





Results: Dissolution studies- Surface Dissolution imaging (SDI)

- SDI analysis was carried out to visually observe surface dissolution behaviours
- From this data, we can observe that gelling was present in the 10% HPMC blended sample
- The formation of the gel leads to an inflated IDR as the gel traps the drug and then forms through the IDR zone.
- The 5% HPMC coated cocrystals also displayed some gelling behaviour, however this occurred later in the dissolution

Batch	1 minute	10 minutes	20 minutes	Avg. IDR (mg/min/cm2)	St.Dev	% St.Dev
Pure Co-Crystal				0.0562	0.0027	4.75
5% Neusillin				0.0569	0.0112	19.62
5% PEG 6000				0.0706	0.0232	32.85
10% HPMC				0.1478	0.0461	31.16
10% Neusillin				0.0495	0.0114	23.11
5% HPMC				0.0808	0.0275	34.07
10% PEG 6000				0.0624	0.0131	21.02

Conclusions

- Co-processing inert polymer or inorganic excipients alongside cocrystals will allow the formation of a protective matrix in between cocrystal particles depending on the crystallinity or amorphicity of the specific excipient.

- This has been shown to enhance stability of IND/SAC cocrystals both under accelerated conditions and at room temperature.

- Amorphous excipients are a superior option to crystalline excipients due to the formation of a more viscous and protective matrix

- The addition of the excipient has no negative effect on the dissolution or crystallinity of the cocrystal structure, due to the fact it is added in the extruder conveying zones and is not reacted with the bulk cocrystal components.

- **This approach can be applied to any cocrystal system and can be used as an industrial platform for cocrystal commercialization.**

ACKNOWLEDGMENTS

THANKS FOR YOUR ATTENTION...!!!