Regrowth behaviour in pharmaceutical crystals – A case study on Paracetamol

Isha Bade[1*], Vivek Verma[1], Ian Rosbottom[1], Jerry Y. Y. Heng[1]
*lead presenter: isha.bade16@imperial.ac.uk
1 Imperial College London, United Kingdom

Although mechanical breakage is a common occurrence in industrial crystallizers, there exists limited knowledge on the consequent growth of broken crystals. Owing to this, process modelling attempts rarely account for specific post-breakage growth kinetics resulting in unreliable predictions of crystal shape and size. Considering that breakage along the cleavage plane is most probable when a crystal is under pressure [1] , understanding the growth behavior post cleavage is highly crucial to accurately predict the end crystal properties and improve their downstream processibility. This work reports for the first time an unconventional 'regeneration' phenomenon in paracetamol crystals following breakage along the cleavage plane (010) [2] . The broken part was observed to regrow on the parent crystal hence returning to the pre-breakage shape before demonstrating overall growth (figure 1).

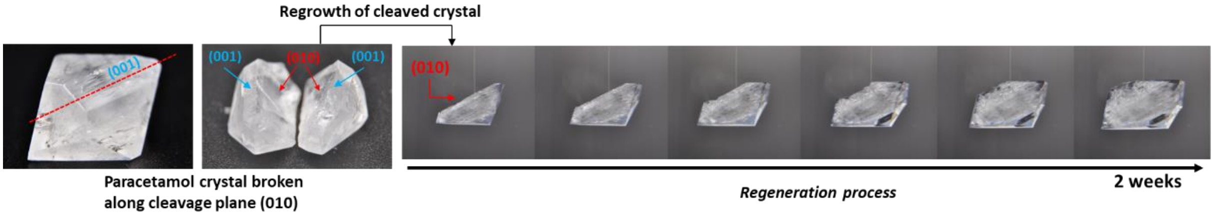

Figure 1. Regeneration process observed in a macroscopic paracetamol crystal broken along the cleavage plane (010)

This unique behavior was investigated with large single crystals of paracetamol using slow evaporation of a saturated ethanolic solution at room temperature. With the aid of macrophotography for single crystal imaging, regrowth kinetics were obtained by measuring the linear growth rate of two characteristic lengths of the growing crystals, one parallel (length b) and one perpendicular to the cleavage plane (length a) over a period of 1-2 weeks depending on the crystal size. Growth of length a was approximately 1.5 times faster (0.045 mm hr^{-1}) than the growth in the same direction of a whole crystal (0.024 mm hr^{-1}). This behaviour was seen to be dependent on the direction of breakage with reference to the cleavage plane irrespective of the initial crystal size; cuts parallel to the cleavage plane exhibited regeneration as opposed to perpendicular ones.

The regeneration phenomenon contradicts well-established morphology prediction theories that suggest slow growth of low attachment energy facets, usually the cleavage planes. It was speculated that this anomaly in the growth behaviour is due to a combination of surface energetics and the surface chemistry of the solid crystal as well as the solute-solvent interactions which need to be investigated further. This phenomenon comes at a time when 'dynamic' organic crystals are gaining increasing traction due to their unusual behavioral responses to external stimuli via transitions in their molecular packing, previously only reported in hard materials like polymers. Therefore the growth kinetics and molecular mechanism of the regeneration process can provide a new direction to crystal engineering.

References

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2. Bade I, Verma V, Rosbottom I, Heng JYY. Crystal regeneration – a unique growth phenomenon observed in organic crystals post breakage. Materials Horizons. 2023; DOI: 10.1039/d2mh01180h