Complex Coacervate: Novel Methodology to Crystallize Hydrophobic Drugs

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Unexpected polymorphic transitions occur in over 50% of pharmaceutical drugs as they pack themselves into 2+ distinct lattice arrangements. These differing molecular structures destabilize the intended therapeutic properties of a drug comprising its function and patient safety. This study investigates the use of complex coacervation, a liquid-liquid phase separation technique utilizing oppositely charged polyelectrolytes (polyDADMAC and polyacrylic acid), as a platform for crystallization to preserve the polymorph of any hydrophobic drug (Mefanamic Acid (MFA)). PDADMA-PA coacervate was added to the MFA/DMF system to enable controlled crystallization as coacervate phase transition, from liquid-like to gel-like, occurs. When water diffuses out of the coacervate, MFA supersaturates into sword-like crystals on the coacervate interface in 20 minutes. PDADMA-PA was prepared in various MFA/DMF ratios (4mM-166mM) to conclude that increasing MFA concentration produces progressively larger crystal lattices. XRD confirmed that crystals were preserved in polymorph II, despite it being thermodynamically disfavored (but more bioavailable) compared to polymorph I. Thermogravimetric analysis showed that MFA supersaturates rapidly, as the mass change of water occurs within t=20 hours, making coacervation more efficient than pharmaceutical approaches like extensive medication stability testing under countless stimuli (ex: temperature or mechanical stability) .In fact, confocal z-stack 3D visualization revealed MFA/DMF penetration into pores that contained MFA crystals. Image Intensity segmentation characterized crystal distribution. Results suggest exploring these pores to crystallize drugs of different densities to observe coacervate partitioning or crystallizing hydrophobic drugs.

Awards Won:

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