Olanzapine crystals grow by association of preformed solute dimers

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The classical mechanisms of crystallization assume that crystals nucleate and grow by sequential association of single solute molecule. Recent results have highlighted deviations from the accepted models whereby preformed nanostructures facilitate crystal nucleation and integrate into growing crystals. Here we explore non-classical pathways for crystallization and crystal form transitions of the antipsychotic drug olanzapine; olanzapine is known to assemble into 60 distinct polymorphs and crystal solvates. We demonstrate the presence of mesoscopic solute-rich clusters in olanzapine solutions. The clusters constitute a unique phase comprised of domains whose size is insensitive to the solution thermodynamics, yet the amount of olanzapine captured in the clusters increases exponentially with the solute chemical potential. We show that the clusters host the nucleation of crystal forms of increased stability. In contrast to their role in nucleation, the clusters do not integrate into growing crystals, but instead incorporate as unstructured occlusions. The majority of the known olanzapine solid forms are comprised of centrosymmetric dimers. NMR and Raman spectroscopies demonstrate the presence of olanzapine dimers as a minority component in solutions in water-ethanol mixtures. Analyses of the crystal growth kinetics from a monomer/dimer mixture predict a parabolic correlation between the step velocity v and the total olanzapine concentration C for the case where the crystal grows by dimer association. The kinetics of layer spreading reveals a congruent v(C) in a broad C range, suggesting that the olanzapine dimer is the preferred growth unit. Models of olanzapine association in the tested solvent suggest that precursory dimerization eliminates ethanol and water molecules strongly bound to monomers. As solvent dissociation from kinks and incoming solutes constitutes the rate determining step in crystal assembly, strongly bound solvent would significantly retard monomer association. The residual weakly bound solvent, associated to the dimers, contributes to a lower kinetic barrier and faster rate of crystallization via the dimer pathway. To our knowledge, these results represent the first definitive evidence of crystal growth by oligomer association.

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