STRATEGIES FOR PARACETAMOL WITH 4’-CHLOROACETANILIDE PURIFICATION AND CRYSTALLIZATION

Leila Keshavarz, Rene Steendam, Lian Blijlevens, Patrick Frawley

The striking ability of impurities to significantly influence crystallization processes is a topic of paramount interest in the pharmaceutical industry. Despite being present in small quantities, impurities tend to considerably change a crystallization process as well as the final crystalline product. In the present work, the effect of two markedly different impurities 4-nitrophenol and 4’-chloroacetanilide on the solubility, nucleation and crystallization of paracetamol are described. In the first part of this work, the fundamentals are outlined and show that although each impurity led to a small increase in solubility of paracetamol, their effect as a nucleation inhibitor was much more pronounced. Induction time experiments were used in conjunction with the classical nucleation theory to show that the impurities did not affect the solid-liquid interfacial energy but instead significantly reduced the kinetic factor, overall resulting in reduced nucleation rates. Intriguingly, both impurities influenced the solubility and nucleation of paracetamol in a similar fashion despite their significant differences in terms of molecular structure, solubility and ability to incorporate into the crystal structure of paracetamol. In the second part of this work, the incorporation of 4’-chloroacetanilide into the solid phase of paracetamol was investigated. The presence of 4’-chloroacetanilide in the solid phase of paracetamol significantly increased the compressibility of paracetamol, resulting in improved processability properties of paracetamol. The compressibility efficiency of paracetamol could be controlled using the amount of incorporated 4’-chloroacetanilide. Therefore, an experimental design space was developed and utilized to select the most important process parameters for impurity incorporation. Intriguingly, the number of carbon atoms in the aliphatic chain of the alcohol solvent strongly correlated to the impurity incorporation efficiency. As a result, it was feasible to accurately control the compressibility and the amount of 4’-chloroacetanilide in the solid phase of paracetamol by simply choosing the required alcohol as the solvent for crystallization. Thus, the present work comprehensively shows how different impurities impact the key crystallization mechanisms and properties of a pharmaceutical product. Rational process control over the incorporation of impurities and additives allows for advanced manufacturing of products with tailored specifications.