Role of Crystallography in Pharmaceutical Solid Form Development

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Crystallography plays a crucial role in pharmaceutical drug discovery as well in development. At drug-discovery stage, it is widely used during hit/lead optimization stage to improve potency as well as to optimize ADME properties by taking advantage of the structure ligand complex. During drug development, small molecule crystallography plays a crucial role starting from solid form discovery to all the way to solid form selection of a selected candidate molecule and as well as in establishing control strategies during development and beyond. Late discovery of thermodynamically more stable solid form for marketed drug product can have serious implications for pharmaceutical company as well as for the patients taking the drug. In case of Ritonavir (Norvir ®), a thermodynamically more stable polymorph suddenly appeared two years after its launch, causing slowed dissolution of marketed dosage form and compromising oral bioavailability. This led to recall of marketed dosage form and substantial efforts went into understanding of both polymorphs and reformulating the drug product with the newer polymorph. To avoid this kind of situation, lots of resources are spent early on during development for solid form discovery (anhydrous/salt/co-crystal) as well as for derisking the selected solid form via exhausted experimental polymorph screening as well as via using computational tools where knowledge of 3-D crystal structure information can play a crucial role. Recent development of structural informatics tools utilizing over 1 million crystal structures in Cambridge Structural Database (CSD) have demonstrated their predictive capabilities for solid form discovery and derisking. Due to immense pressure to shorten development timelines, these structural informatic tools arising from knowledge of available crystal structures are of greater importance to complement resource extensive physics based computational and experimental methods. In this presentation, different aspects of pharmaceutical solid form development will be presented and in addition, the evolution of crystallography from absolute structure determination of a molecule to gain insights into its 3-D packing, and properties arising from that 3-D arrangement and to design new solid forms with better properties will be discussed.