Magnifying Nano-/Meso- Structural Information of Amorphous Pharmaceutical Solids Through Small Angle X-Ray Scattering

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Amorphous state is intentionally (eg. amorphous solid dispersion) or unintentionally (induced by processing) present in solid pharmaceutical intermediates and/or finished dosage forms.[1] In either case, in-depth characterization of the structural properties of amorphous states is an important step towards prediction and control of the quality of final products such as dissolution performance and physical and chemical stability. Likewise, a thorough structural analysis of inherently amorphous macromolecule drugs (eg. protein) and polymeric excipients is inevitable to ensure their desired functionality.

Powder X-ray diffraction (pXRD) is one of the most used quantitative tools for the analysis of crystalline phases and crystallinity of pharmaceuticals[2] and recently for the characterization amorphous forms.[3] On the other hand, the rich information achievable by small-angle X-ray scattering (SAXS) has gained limited attention for the analysis of pharmaceuticals so for. A particularly useful technique is simultaneous small- and wide-angle scattering (SWAXS)[4], which combines the meso-scale (2-50nm) with the nano-scale (<2nm), i.e. the supramolecular domain structure with the high-resolution atomic/molecular structure and forms the link to pXRD. In this presentation, we describe various nano-/meso-scale structural parameters that can be derived from solid-state SAXS analysis of amorphous pharmaceuticals. This includes the specific inner surface, mean square density fluctuation, domain size, correlation length, etc. The applications will be discussed through some relevant case studies. For amorphous forms of APIs like desvenlofaxine, simvastatin, and sulfamerazine, obtained by milling the SAXS invariant directly provide the information of the degree of nanoscale heterogeneity that was related to physical stability.[5] Furthermore, SAXS parameter enabled the differentiation between the nanostructures of amorphous drug-polymer dispersions obtained via melt quenching and milling. In a case of lyophilized protein formulation exposed to different humidities, the change in specific inner surface obtained by SAXS as a function of water content was found to systemically correlate with their reconstitution kinetics.[6] The extended applications of SAXS methods will be further exemplified for microstructure characterization of excipients.[7]

References:

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