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Understanding the mechanism of indomethacin-saccharin co-crystal formation using in-line monitoring system with focused beam reflectance measurement and particle vision measurement

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The co-crystal approach has attracted enormous attention in attempts to improve critical pharmaceutical attributes such as the solubility and stability of drug substances. In 2016, the US FDA reclassified the pharmaceutical co-crystals as a special case of solvates and hydrates where the second component, the coformer, is nonvolatile, modifying their earlier viewpoint as a drug product intermediate (DPI) or as an in-process material in 2013. In the 2016 guidance, the FDA describes: “co-crystals can be tailored to enhance drug product bioavailability and stability and to enhance the processability of APIs during drug product manufacture”. In-line monitoring technology is not only a significant tool for processes with high risk such as crystallization but also conforming to the global quality systems for pharmaceutical products. In this study, we attempted to clarify the formation of transient Indomethacin (IMC) meta-stable form as well as Indomethacin-Saccharin (SAC) co-crystal particles with the addition rate of anti-solvent as critical process parameter and in-line monitoring tools. Among various in-line monitoring instruments, we employed FBRM (focused beam reflectance measurement) and PVM (particle vision measurement). The characterization of in-process and post-process particles was performed via PXRD (powder X-ray diffraction) and DSC (differential scanning calorimeter). It was observed that the pathway to the final IMC-SAC co-crystal was greatly affected by the anti-solvent addition rate and process conditions to obtain high-quality co-crystal powder effectively were established. Accordingly, it is concluded that in-line monitoring based on FBRM and PVM can be a very useful PAT tool for QbD implementation.

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