In Situ Synchrotron Wide-Angle X-ray Diffraction as a Rapid Method for Cocrystal/Salt Screening
P. Dong, L. Lin, Y. Li, Z. Huang, T. Lang, C. Wu, M. Lu
Sun Yat-Sen University

Purpose
Cocrystal/salt formation is very important for solubilization or properties modification in pharmaceutics. Current cocrystal/salt screening methods, including solution-based method, grinding, DSC and Kofler contact method, have many disadvantages such as environment-pollution, low efficiency and miss detection. The present study was aimed to explore in-situ synchrotron wide-angle X-ray diffraction (WAXD) as an rapid and effective method for cocrystal/salt screening.

Methods
Physical mixture of drug and conformer (molar ratio 1:1) was sealed in a Kapton film bag and fixed on a Linkam CSS 450 hot stage. In-situ synchrotron WAXD was employed to record the phase transformation of drug-coformer physical mixture during heating process at the heating rates of 2, 10 and 30 °C/min. Synchrotron radiation provided X-ray with ultra-high intensity and time resolution, which passed through the sample through the Kapton window. 2D detector collected the scattered signal, which reflected structure changes during phase transformation. Thermal behaviors of physical mixture during heating process were recorded by differential scanning calorimetry (DSC). The WAXD results were compared with the DSC data to get more detailed and accurate information about the mechanism of cocrystal/salt formation.

Results
Synchrotron WAXD can in-situ detect the formation of caffeine-saccharin cocrystal, carbamazepine-saccharin cocrystal and lamotrigine-saccharin salt during heating process, even at a very rapid heating rate (30 °C/min). Based on its high sensitivity and time resolution, in-situ synchrotron WAXD can accurately attribute the complicated thermal events in DSC curves and provide useful information to guide cocrystal/salt preparation by hot melt extrusion or melting method.

Conclusion
In-situ synchrotron WAXD provides an attractive opportunity for high-throughput screening of cocrystal and salt. This paper is an encore presentation, which has been presented in AAPS-NUS 9th PharmSci@Asia Symposium (5-6 June 2014, Shanghai China) and awarded the Best Podium Presentation Award.