Cocrystal formation and thermal behaviors based on binary phase diagrams

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Cocrystal is defined as a crystalline material which comprises two or more unique solid components in a stoichiometric ratio. An interest has increased in cocrystals in pharmaceutical industry recently because those crystals may improve physicochemical properties, including solubility, physical stability, mechanical properties, and bioavailability. A variety of methods for preparing cocrystals have been reported such as solution crystallization, slurry conversion, evaporation, co-grinding, and ultrasound crystallization. In some cases, a physical mixture of two components was heated to prepare a cocrystal. Although it is possible to form a cocrystal by heating a physical mixture, the details of heat-induced cocrystal formation have not been examined yet. The purpose of this study was to clarify the thermal behavior of a physical mixture and cocrystal formation in reference to a binary phase diagram.

Also, some applications to improve physicochemical properties by cocrystal formation will be introducing in this presentation.

Physical mixtures were prepared using an agate mortar. They were heated at heating rates of 2, 5, 10, 30 °C/ min using differential scanning calorimetry (DSC). Some of them were further analyzed using X-ray DSC and polarization microscopy. Indomethacin and tenoxicam were used as a model of active pharmaceutical ingredient (API). Physical mixtures of an API and 42 kinds of coformers were analyzed using Differential Scanning Calorimetry (DSC) and simultaneous measurement of X-ray-DSC.

When a physical mixture of two components capable of cocrystal formation was heated using DSC, an exothermic peak associated with cocrystal formation was detected. In some combinations, several endothermic peaks were detected and associated with metastable eutectic melting, eutectic melting, and cocrystal melting. In contrast, when a physical mixture of two components incapable of cocrystal formation was heated using DSC, one endothermic peak which was associated with eutectic melting was detected. In order to elicit these kinds of behavior in accordance with the binary phase diagrams, homogeneously-mixed fine particles were crucially important. Although cancelation of endothermic and exothermic peaks occurred depending on heating rate and an exothermic peak associated with cocrystal formation was not necessarily confirmed, it was possible to detect the exothermic peak by changing a heating rate. These experimental observations clarified the relation between the thermal behavior of a physical mixture and cocrystal formation.