Stoichiometric Diversity of Cocrystallization in Batchelor Flow

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The cocrystal is formed by a stoichiometric combination of active pharmaceutical ingredient (API) with coformers via non-covalent interactions such as hydrogen bonding, ionic interactions, van der Waals interactions and π-interactions. So, the physical or chemical properties of the cocrystal, such as solubility, chemical stability, structure etc are dramatically different from those of API or conformer. As such, a poorly water-soluble API could be modified to a good water-soluble cocrystal and API would be stabilized via a formation of cocrystal. Thus, the cocrystallization is recently drawing a great attention in the pharmaceutical industry for exploitation to improve the physical or chemical properties of drugs.

In the present study, a new cocrystallization method was developed for stoichiometric diversity of cocrystals by using a periodic Batchelor flow. The Batchelor flow was generated in gap between two disks where the one disk was rotating and the other one was stationary, which was called as rotation disk (RD) crystallizer. Then, the cocrystallization in the RD crystallizer was compared to that in the conventional mixing tank (MT) crystallizer, in which a random turbulent eddy flow was generated by the impeller. According to the cocrystallization of caffeine (API) and maleic acid (coformer), the metastable form of (2:1) cocrystals was initially formed and then slowly transformed into the stable form via the induction of (1:1) cocrystals and reconstruction of (2:1) cocrystals to (1:1) cocrystals in MT crystallizer, as usual in Ostwald's Rule of Stage to polymorphic nucleation and phase transformation, over 10 hrs. However, in RD crystallizer the stoichiometric nucleation of cocrystal was completely different. As such, the stable form of (1:1) cocrystal was directly nucleated in the period Batchelor flow, indicating the significant influence of fluid motion on the stoichiometric diversity of cocrystallization. So, the cocrystallization was completed within an hour in the RD crystallizer. This result was supposed due to the molecular alignment effect of the periodic Batchelor flow on the nucleation of cocrystals. This effect of the Batchelor flow was amplified as increasing the rotation speed of the disk, resulting in the significant reduction of the induction time for cocrystal nucleation.

In the cocrystallization of the caffeine (API) and 4-hydroxybutyl acrylate (conformer), different stoichiometric diversities of cocrystallization in the RD and MT crystallizers were found. The (2:1) cocrystals were initially nucleated, then shifted to the (1:2) cocrystals and finally transformed into the (1:3) cocrystals in the MT crystallizer. A different pathway of the stoichiometric diversity of the cocrystallization was exhibited in the RD crystallizer. The mixture of (2:1), (1:2) and (1:3) cocrystals was initially formed, and then directly transformed to (1:3) cocrystals due to the effect of the periodic Batchelor flow. Such pathway in the RD crystallizer was varied with the rotation speed of the disk and initial supersaturation, whereas it was independent of the operating parameters in MT crystallizer.

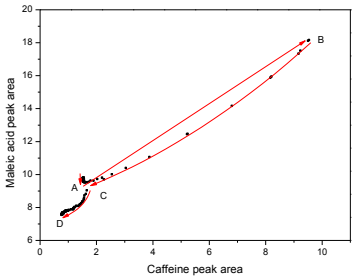

Fig. 1. Pathway of cocrystallization in RD crystallizer

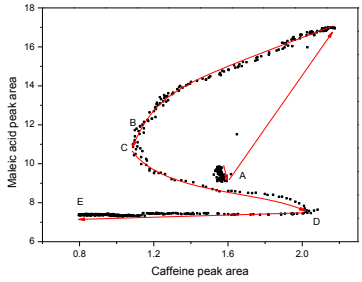

Fig. 2. Pathway of cocrystallization in MT crystallizer.