Microfluidic Systems for Continuous Crystallization of Small Organic Molecules

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Abstract

This thesis presents one of the first demonstrations of continuous crystallization in microfluidic devices, and illustrates their use for various applications related to crystallization of small organic molecules. Crystallization is an important process in a number of industries, including specialty chemicals, food, cosmetics, nutraceuticals and, most importantly, pharmaceuticals. Most small molecule pharmaceuticals are isolated in crystalline form, and more than ninety percent of all pharmaceutical products are formulated in particulate, mainly crystalline form. However, crystallization is not a completely understood process. The sensitivity of the process to synthesis conditions gives rise to serious reproducibility issues. The traditional batch crystallizers suffer from non-uniform process conditions across the reactor, and chaotic, poorly controlled mixing of the reagents, often resulting in polydisperse crystal size distribution and impure polymorphs. This makes it difficult to obtain reliable information on the process kinetics that can be used for scale-up, as well as to study the fundamentals of the process.

Microfluidic systems offer a unique toolset for crystallization because of well-defined laminar flow profiles, enhanced heat and mass transfer, better control over the contact mode of the reagents, and optical access for in situ characterization. The better control over the synthesis conditions gives rise to the potential for controlling the crystal size, as well as the polymorphic form. In addition, low consumption of reagents makes it an attractive research tool for expensive pharmaceutical compounds. Some of the advantages of microfluidics have been demonstrated for crystallization in micro-batches, but so far not in continuous devices. Continuous crystallization is difficult to achieve in microchannels as uncontrolled nucleation, crystal growth, agglomeration and sedimentation of crystals easily clog the small channels. The interaction of crystals with channel walls may also contribute to channel plugging in these devices.

This thesis has developed microfluidic devices for continuous crystallization of small organic molecules for the first time. We have decoupled nucleation and growth, the two key steps of crystallization, using reaction engineering principles, and have developed two separate continuous devices, one for each of these two processes. We have used seeded crystallization and reactor design to achieve controlled growth, as well as to suppress secondary nucleation, agglomeration and sedimentation of crystals. In addition, we have eliminated any significant interaction of crystals with channel walls by controlling the properties of channel surfaces. We have also integrated microscopy and spectroscopy tools with the device for in-situ characterization of crystal size and polymorphic form. We have illustrated the use of these devices to extract growth kinetics data for crystals of various shapes, including high aspect ratio systems such as that with acicular or plate-like habits. The reproducibility and control in our devices have allowed
us to elucidate the growth mechanism and fundamentals of the growth process for difficult crystal systems. In addition, we have demonstrated that continuous microfluidic devices offer a unique advantage over the current state-of-the-art technology to measure the size, size distribution and growth kinetics of high aspect ratio crystal systems more accurately.

Moreover, we have demonstrated the use of microfluidic devices for understanding crystal habit modification in the presence of impurities. We take advantage of the high spatiotemporal resolution of microfluidic devices to study the evolution of crystal habit over time, and to obtain information on the kinetics of habit modification in the presence of different impurities. We have developed an understanding of the habit modification mechanism for alpha glycine in the presence of alpha amino acids. Such information may not only provide insights into impurity-crystal interactions, but also serve as a powerful tool for the design of impurities that can be deliberately added to improve the crystallization process.

Furthermore, we have designed and developed a second microfluidic device for continuous supercritical crystallization for the first time. Using supercritical fluid as an antisolvent, we have demonstrated continuous spontaneous nucleation of acetaminophen. We have shown the ability to produce micron-sized crystals, which may be useful for increasing the bioavailability of drugs with lower solubility, as well as for inhalable and highly potent drugs with stringent size requirements. The developed platform can also be used as a high-throughput device for safely screening crystallization conditions in the supercritical domain. We have demonstrated such use by screening the effects of pressure and various solvents on the habit, size and polymorphic form of acetaminophen crystals.

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