394b Polymorph Screening Using Microfluidics

Venkateswarlu Bhamidi, Guangwen He, Paul J. A. Kenis, and Charles F. Zukoski

Materials often crystallize into solid phases that are chemically identical but differ widely in morphology and physical properties. The different forms of the crystals of the same compound are referred to as polymorphs and they may result from differences in the conformation of the molecule and / or packing arrangement of the molecules in the lattice. Polymorphs of the pharmaceutical compounds vary significantly in solid-state properties like crystal shape, density, dissolution rate etc., which influence not only the ease of process handling in manufacturing, but also the efficacy and shelf-life of the drug. Thus, the pharmaceutical industry is often faced with the challenge of discovering and characterizing the various crystalline forms of the active pharmaceutical ingredients (API). Existing screening protocols often use anti-solvent crystallization and evaporation / cooling of the solution with little or no control over the mixing of anti-solvent and the rate of solvent evaporation.

A significant interest exists in the pharmaceutical industry for rapid polymorph screening techniques that reduce the time, effort and material consumed. Towards that end, we are developing a microfluidic solution for high throughput polymorph screening. Microfluidic technology provides a methodology to actively regulate the rapid micromixing at micron length scales. By using a combinatorial approach, several screening experiments can be performed simultaneously and the material consumption can be minimized.

In this work, we will discuss a ‘first generation' microfluidic mixer design that effects anti-solvent crystallization. The solution and anti-solvent flow inside a microfluidic channel and the mixing of the liquids is due only to diffusion. Also, the rate of mixing and the composition of the liquid phase can be varied by changing the flow rates and concentrations, thus influencing the polymorph selectivity. We present the results of our experiments on some model systems and discuss the applicability of the concept towards the development of a high throughput microfluidic device for rapid polymorph screening.