(241a) Mathematical Modeling and Design of Layer Crystallization in a Concentric Annulus With and Without Recirculation

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In pharmaceutical manufacturing, the drug product is often separated from a liquid phase by crystallization, washing, filtration, and drying—each of which reduce the overall product yield. Poorly filtering crystals can result in bottlenecks in the downstream processing and can affect crystal product purity or reduce yield due to additional washes. These observations have motivated efforts to design continuous crystallization processes that are reliable for manufacturing a product that meets purity, yield, shape, and size requirements, and at the same time ensures efficient downstream processing.

One way to avoid slurry handling is to constrain crystal growth to occur on fixed surfaces so that the amount of solid particles in the bulk is minimized. Layer crystallization has been characterized as being a process in which coherent crystal layers grow on cooled surfaces of a specially designed tube or plate heat exchanger.[1,2] Layer crystallization from melts has been widely applied for the purification of organics and inorganics such as sucrose and milk fat, and in seawater desalination.[3-6] For layer crystallization, the liquid phase is always at a higher temperature than the solid phase, so that in melts, the temperature is required to be higher than the melting point, but layer crystallization from solutions can be operated at much lower temperatures with less energy consumption.[7]

This work proposes a layer crystallization process from a solution in a concentric annulus that avoids the need for washing, filtration, and drying.[8] A continuous flow of drug product could be generated by employing multiple cyclic annular crystallizers in parallel. Many past studies on mass[9-12] and heat transfer[12,13] in annular reactors have concentrated on obtaining correlations of dimensionless number, but these methods are limited by the configurations and operating conditions[13,14] and they are not able to predict the entire concentration or temperature field that is important for crystallization. To our knowledge, this work for the first time thoroughly examines heat and mass transfer of a crystallization process with solid-layer growth in an annulus with and without recirculation. The mass and/or heat transfer model with solid-layer growth on a cylindrical surface can be employed for many other applications, such as fouling in heat exchangers,[15] biofilms in petroleum pipelines,[16] and melt layer crystallization in a tank.[17,18]

A dynamic model is developed in the form of coupled partial differential equations to (1) predict the crystal layer thickness as a function of time and axial position, (2) update the nonuniform boundary temperature at the solid-liquid interface, which is affected by the local thickness of the crystal layer, and (3) calculate the temperature and concentration fields in the annulus. The model predictions are shown to closely track experimental data that were not used in the model's construction, and also compared to an analytical solution that can be used for quickly obtaining rough estimates when there is no recirculation loop. The effects of modifying the operating conditions are investigated, including variation in initial solute concentrations, cooling liquid jacket temperature, inlet solution velocities, core liquid temperature, and extent of mixing in the recirculation loop. The model can be used to optimize product yield and crystal layer thickness uniformity, with constraints on the

supersaturation to avoid bulk nucleation by adjusting cooling temperatures in the core and jacket. Additionally, the model could be extended to predict molecular purity of the crystal layer, by considering more components.

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