311a Antisolvent Crystallization and Mixing in Porous Hollow Fiber Devices

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This paper examines antisolvent crystallization under a new perspective and in a flow environment much different from that available in currently used industrial devices, namely, the unique environment offered by porous hollow fiber membrane devices. The latter are compact, extremely efficient on a volumetric basis, easy to scale up and control. Their inherent characteristics promote the creation of homogeneous concentration conditions on a scale considerably smaller than existing industrial crystallizers without the necessity of a large energy input, properties that are desirable but rarely achieved in industrial crystallizers.

The nature of antisolvent crystallization, namely, mixing of two miscible liquids/solutions, initiated the study of porous hollow fiber devices as mixers. Our studies showed that upon proper rating porous hollow fiber devices can create typical supersaturation levels needed in antisolvent crystallization. Moreover, supersaturation is created uniformly due to the large number of feed introduction points, the membrane pores. In addition, radial mixing is substantial in contrast with traditional tubular devices and the characteristic time involved in this process is comparable to the device residence time.

Porous hollow fiber antisolvent crystallization was tested for a well studied biological molecule, L-asparagine monohydrate. The process proved to be successful despite the fact that the geometrical design of the membrane hollow fiber crystallizers used was not optimal. Mean crystal sizes between 34-86 μm and 33-40 μm were obtained respectively in standalone membrane hollow fiber crystallizers (MHFC) and their combinations with completely stirred tanks. The CSD was confined below 150 μm for the former and 70 μm for the latter, levels that are sufficient for most pharmaceutical crystalline products, for which bioavailability and formulation concerns dictate the desired CSD. In addition, porous hollow fiber devices achieved 1-5 orders of magnitude higher nucleation rates compared to batch stirred crystallizers. Considerable improvements can be obtained by carefully designing membrane hollow fiber crystallizers.