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Novel Crystallization of Pharmaceutical Compounds using Porous Carbon Membranes

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Abstract

Crystallization is a fundamental process in the pharmaceutical industry, as more than 90% of active pharmaceutical ingredients (API) are synthesized as crystalline final products or intermediates [1]. It is essential to consistently produce crystals with specific properties, so controlled processes are desirable. Currently, most crystallization technologies employed are batchwise. Continuous crystallization technologies offer the advantage of improved product quality and control, reduced costs, and increased scalability[2]. Historically, evaporative and cooling crystallization are some of the earliest documented crystallization processes and are widely used. However, these technologies carry some challenges as slow production rates and low crystal properties control [3]. Membrane crystallization technologies have been proposed as a promising strategy to improve process performance and to offer better control over the crystal final properties. These technologies have demonstrated potential in processing high-value products like pharmaceuticals and proteins. However, membrane crystallization inherently results in crystal formation on the feed side of the membrane, which adds two extra processing steps to achieve dry solute (filtration and drying), thereby escalating system intricacy and plant scale [4].

Percrystallization (PerX) is a novel membrane crystallization technology that allows the continuous production of dry crystals in a single step. Unlike conventional membrane technologies, the solution containing a solvent and solute permeates through the porous structure of an inorganic membrane. The inorganic membranes are the result of an impregnation of a carbon precursor solution into a porous α-alumina substrate. In the presence of vacuum, a simultaneous single-step separation of solvent evaporation and solute crystallization occurs on the surface the membrane. The membrane PerX has proved to be effective for processing food compounds, mineral salts, and organic acids. Previous results have shown that by tuning the carbon membrane morphological features it is possible to produce crystals with different particle size and distribution and crystal morphology. [5]

This work reports on the proof of concept of using percrystallization technology for API crystals in pharmaceutical industry and the process optimization. In this novel process, dry ibuprofen crystals (with a solvent content <1500 ppm) are obtained in a single step, avoiding further downstream processes, with outstanding yields exceeding 90%. This is a novelty in the pharmaceutical industry, as currently filtering and drying steps are required to achieve dry crystals. Different operating conditions are used to understand the impact of process operating conditions on solvent evaporation, solute crystallization, dry crystals properties and control polymorphism. The effect of solvent volatility is also studied using different solvent solutions. For this study porous inorganic membranes were prepared by coating a porous substrate with a sugar solution and carbonized at 700ºC. The mean pore size, pore size distribution and pore volumes of the uncoated substrate and modified membranes were quantified using mercury porosimetry technique (MIT). The results indicated a median pore diameter of 0.17 µm and no significant difference between the uncoated substrate and modified membranes. Brunauer-Emmett-Teller (BET) was used to determine the surface area of the characterized membranes. Results showed a slight reduction on surface area in the modified membranes caused by the coating layer on the external and internal surface of the modified membranes. The morphological features of the membranes were obtained using scanning electron microscope (SEM) images. There is a morphology difference of the carbonized carbon membranes in Figure 1b and the pure α-alumina substrate morphology in Figure 1a. The former is characterized by darker coated particles stemmed from the infiltration and carbonization of sugar solutions, while the latter exhibits white rounded shaped α-alumina particles, which aligns with what is found in the literature for this process.

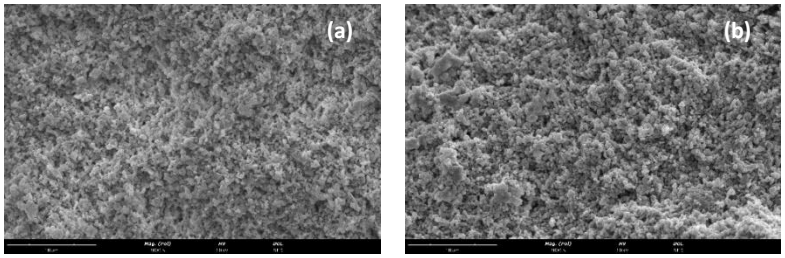

Figure 1 - SEM images of the cross-section layers of (a) the uncoated substrate; (b) the modified membrane

An ibuprofen crystallization rate of 3.1 g/m^{2}·h, equivalent to more than 97 ton/m^{2} per year per year was achieved at the best conditions tested. Using percrystallization technology, the ibuprofen crystal properties were improved by tuning the morphology. As observed in Figure 2 percrystallization lead to a morphology change from needle like particles (Figure 2a) to plate like particles (Figure 2b). This change in morphology results in improved flowability and processability properties, as well as enhanced solubility and bioavailability, which is essential within the pharmaceutical industry. By changing the process operating conditions, it was possible to control crystal particle size and its distribution. This work revealed that higher temperature leads to faster solvent evaporation, so the kinetics of crystal growth is limited by the residence time on the membrane surface. Coupled with lower feed concentration, results suggest mass transfer limitations during crystal growth, thus yielding smaller crystal particles.

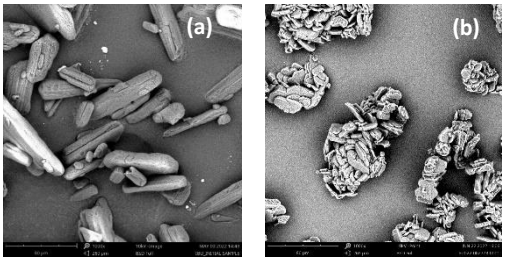

Figure 2 - SEM images of ibuprofen (a) initial sample; (b) percrystallized sample

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