Continuous Production of Polymer Coated Drug Crystals, Submicron Particles, and Nanoparticles by Hollow Fiber Membrane-based Cooling and Anti-solvent Crystallization

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ABSTRACT

Currently, no technique is available to continuously film coat fine and nano-sized drug particles with a polymer to produce large amounts of free-flowing coated particles. We have adapted both the solid hollow fiber cooling crystallization (SHFCC) and the porous hollow fiber membrane-based anti-solvent crystallization (PHFAC) techniques to continuously produce polymer-coated micro-particles, nanoparticles, and drug crystals. Controlled cooling or addition of an anti-solvent allows for polymer nucleation on the surface of the particles and the formation of a thin polymer film around the particles, the thickness of which can be varied depending on the operating conditions. Furthermore, scale-up of both techniques can be easily accomplished by using a larger SHFCC or PHFAC module containing a larger number of solid or porous hollow fiber membranes (HFMs).

Keywords: continuous polymer coating of particles, nanoparticles and drug crystals, hollow fiber membranes, cooling crystallization, anti-solvent crystallization

1. INTRODUCTION

A common strategy for controlled release of drugs involves a thin polymer coating on the drug particle/crystal. Polymeric coating also provides protection for fragile drugs from hydrolysis and degradation; polymer coated nanoparticles (NPs) can traverse the physiological human mucous and blood–brain barriers. The processes employed now to achieve these goals are primarily batch in nature. They involve techniques such as, Rapid Expansion of Supercritical Solutions [1], Supercritical Anti-Solvent [2] and Gas Anti-Solvent [3] processes: these require very high pressure and suffer from low polymer solubility in the solvents employed. Our goal is to continuously produce large amounts of free-flowing polymer-coated particles: the particles may be nanoparticles, submicron particles or micron-sized particles.

Two novel crystallizers, SHFCC [4] and PHFAC [5] were adapted to continuously coat host particles, e.g., submicron and NPs of silica, and micron-sized Griseofulvin (GF) drug crystals with different polymers (PLGA and Eudragit RL 100) [6-10]. The silica submicron particles and nanoparticles were suspended in an acetone-polymer solution and served as nucleation sites for polymer precipitation in the SHFCC or PHFAC device producing film coated particles. The GF crystals were either dissolved or suspended in the acetone-polymer solution; GF crystals precipitated first from solution and were then coated by the polymer which precipitated later with the crystals being nucleation sites. For polymer-coated drug crystals, the surface morphology, particle size distribution, and polymer coating thickness were characterized by scanning electron microscopy (SEM), scanning transmission electron microscopy (STEM), laser diffraction spectroscopy (LDS) and thermogravimetric analysis (TGA). To study the properties of the coated drug crystals, x-ray diffraction (XRD), Raman spectroscopy, and drug dissolution tests were implemented. Coated silica particles were analyzed after vacuum drying using SEM, STEM, energy dispersive spectrometry, LDS and TGA.

2. POLYMER COATED GF DRUG PARTICLES

2.1 Solid hollow fiber cooling crystallizer (SHFCC)

Figure 1(a) shows a single polymeric HFM serving as an efficient heat exchanger: the feed solution flowing in the tube side is cooled down rapidly by the cold liquid circulating counter-currently on the shell side. The solid HFM of polypropylene (PP) has considerable pH, chemical and solvent resistance. This nonporous HFM wall has a smooth surface minimizing clogging inside the HF. Figure 1(b) illustrates a SHFCC device having a few hollow fibers (HFs) in the cylindrical shell. The HF number is adjusted according to scale-up needs. In Figure 2(b) (SEM micrograph), a thin polymer coating can be seen on each GF crystal. Compared to Figure 2(a) in which the GF drug particles were crystallized without any polymer, the surface morphology around the drug crystals also appears to be different which suggested that the polymer successfully coated the GF drug particles via the SHFCC process. Drug particles were evenly coated by the polymer precipitated from an acetone solution inside the SHFCC module. Tests using XRD, Raman and DSC concluded: polymer coating around GF crystals did not affect the drug [10].

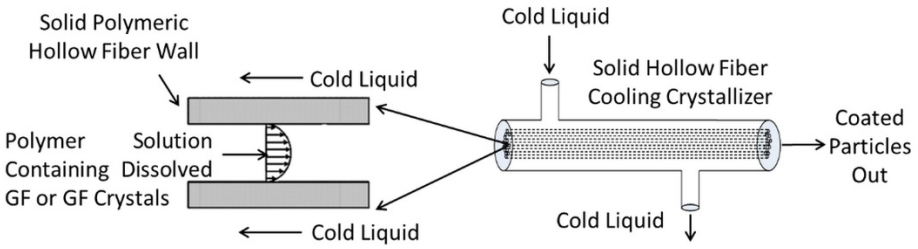
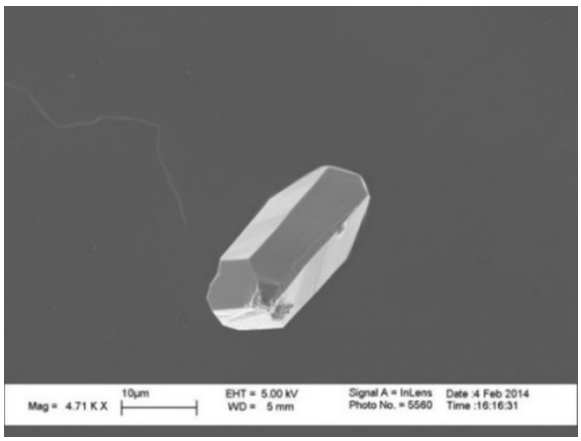
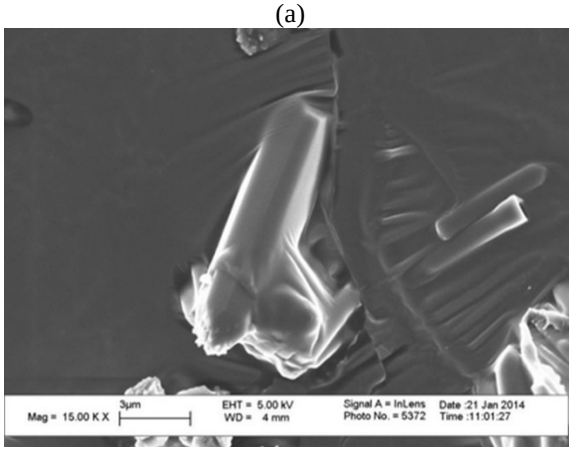


Figure 1. (a) Single solid hollow fiber heat exchanger/crystallizer; (b) Solid hollow fiber membrane based cooling crystallizer module (Adapted from [10])



(a)



(b)

Figure 2. SEM micrographs of (a) GF drug crystal after precipitation in a SHFCC unit without any polymer and (b) polymer coated GF drug crystals after precipitation (from [10]).

This process was studied [6,7,10] using two polymers Eudragit RL 100 and PLGA and submicron silica particles (Cosmo 55, 550 nm) [7] and silica nanoparticles (12 nm) [6], respectively. However these processes were carried out for no more than 5-10 minutes. Jin [11] has demonstrated via thermogravimetry analysis (TGA) that the coating thickness on the submicron silica particles (550 nm diameter) was quite uniform even when the experiment was continued for 60-120 minutes. Results from his studies for 60 minutes are reproduced in Table 1 below. This study by Jin [11] shows that the SHFCC method is stable in operations running for an extended period. The characterization of the products at different times during the operation indicated a stable product consistent with uniform and fine spherical shape; the coating thickness of the samples was essentially identical as the process was continued for 60 min (Table 1). This implies that, as a novel coating/encapsulation technique, the SHFCC method is stable and reliable for an extended duration coating process and produces consistent and integrally coated products.

Table 1. Polymer Coating Thickness* on Submicron Silica Particles from a 60 min Process**

Process time	3 min	14 min	28 min	39 min	55 min
$\frac{m_{polymer}}{m_{silica}}$	0.138	0.158	0.161	0.166	0.162
Coating thickness	27.6 nm	31.2 nm	31.7 nm	32.6 nm	31.9 nm

*Thickness of polymer Eudragit RL 100 obtained from TGA measurements;** From Jin [11].

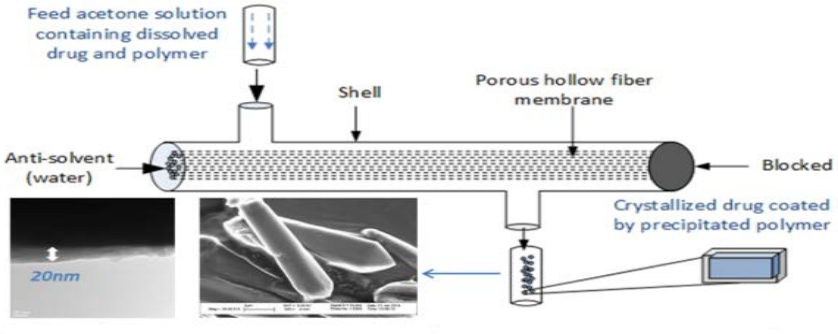
2.2 Porous hollow fiber anti-solvent crystallization (PHFAC)

The porous hollow fiber anti-solvent crystallization technique [5,8] (PHFAC) has also been utilized successfully to produce continuously polymer-coated drug crystals. The anti-solvent water was pumped from one end of the tube side of the porous HFs while the other end of the HFs was blocked (Fig.3); this ensured that the water stream will be forced to penetrate though the pores in the fiber wall to the shell side due to the pressure difference. In the shell side, an acetone solution of the drug GF and the polymer Eudragit RL 100 was flowing. The introduction of the anti-solvent through numerous pores generated very high supersaturation in the shell-side solution leading to drug crystallization followed by polymer precipitation on the drug crystals acting as nuclei for polymer precipitation [8]. The porous

HFs employed were of nylon (600 µm ID). Figure 3 illustrates the schematic of such a PHFAC device and the process for synthesis of polymer-coated drug crystals. Coated drug particles were automatically flushed out of the system along with the shell-side solution-suspension.

Figure 4 shows dissolution tests of the as received, uncoated, and Eudragit coated GF drug particles via the PHFAC technique [8]: the polymer coated GF only dissolved about 20% after 50 min whereas both the as-received and uncoated particles were completely dissolved by that time indicating that the polymer coating was achieving controlled release of GF. A similar behavior was observed for GF crystals coated by the SHFCC technique [10

Figure 3. Synthesis of polymer coated drug crystals in a porous hollow fiber anti-solvent crystallizer (PHFAC) [8].



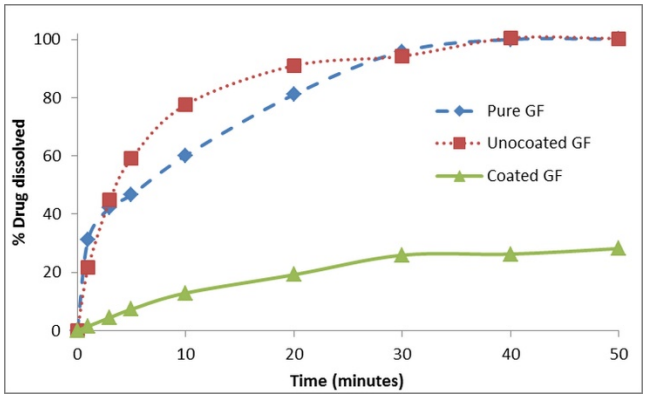


Figure 4. Dissolution tests of as received, uncoated, and Eudragit coated GF drug particles [8].

The novel SHFCC and PHFAC crystallization-based techniques provide alternate methods to continuously coat drug particles with polymers. When the solubility of the coating polymer is sensitive to temperature change, the SHFCC technique is useful. However, the extent of coating polymer utilization is likely to be less than that in the PHFAC technique. This is due to the fact that normally the polymer cannot precipitate entirely from the solution since the temperature reduction achieved is limited in a not-too-long device. The PHFAC technique can be used in situations where the coating polymer is quite sensitive to the anti-solvent but the control over the precipitation might be weaker than that in the SHFCC method. Depending on different conditions and requirements, one can choose to apply either technique to coat drug particles. Both techniques are economical, practical, easy to scale-up and do not require demanding operating conditions needed for conventional coating techniques which are primarily batch processes.

3. POLYMER COATED SUBMICRON AND NANOPARTICLES

Both The SHFCC and the PHFAC techniques have been used to successfully film coat submicron [7, 9] and nano-sized [6, 9] silica particles with Eudragit and/or PLGA. Figure 5 shows STEM micrographs of an uncoated and polymer coated 500 nm silica particle via the SHFCC technique. The bright area is the silica submicron particle; the dark grey ring is the polymer coating. Based on the scale bar, the thickness of the coating around the 500 nm particle can be estimated to be about 25 nm. Figure 6 shows an EELS 2-D map of a Eudragit coated 12 nm silica particle [6]. Since the polymer contains no silica and the silica contains no carbon, the figure clearly shows that the nanoparticle was uniformly coated with polymer. From the scale bar, the coating thickness can be estimated to be about 3 nm.

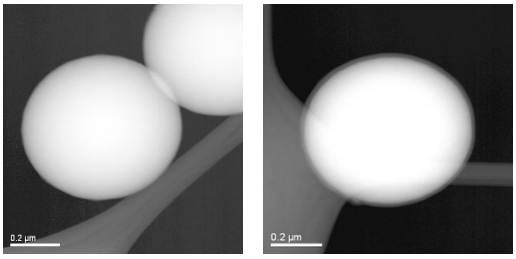
(a)  (b)

Figure 5. STEM micrographs of uncoated (a), and coated silica particle with Eudragit (b) [7].

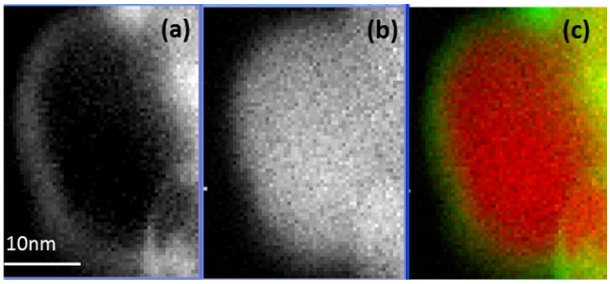


Figure 6. EELS 2D elemental map of (a) carbon K-edge, (b) silicon L3,2–edge and (c) colorized map, carbon in green and silicon in red [6].

4. CONCLUDING REMARKS

Two novel hollow fiber membrane-based crystallization methods have been developed for continuously synthesizing polymer coated drug crystals and producing continuously polymer coated submicron and nano-sized silica particles. A solution of GF and polymer in acetone resulted in rapid formation and growth of GF crystals which were then coated with a thin layer of polymer. Using a PHFAC technique, the crystal growth and coating thickness can be varied by changing operating conditions such as the flow rates of the GF/polymer solution and anti-solvent and the geometry of the module. Scale-up of both methods is relatively easy by simply adding more hollow fibers to the modules. The basic SHFCC and PHFAC techniques are covered by two issued US patents [12] and [13] respectively. Continuous polymer coating of particles and crystals of various sizes by the SHFCC method is described in a recently issued US patent [14]. An application for a US patent for continuous polymer coating of particles and crystals of various sizes by the PHFAC method has also been filed.

5. ACKNOWLEDGEMENTS

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