Journal of Membrane Science 564 (2018) 682–690

Contents lists available at ScienceDirect

Journal of Membrane Science

journal homepage: www.elsevier.com/locate/memsci

Continuous production of drug nanocrystals by porous hollow fiber-based anti-solvent crystallization

Xinyi Zhou[a,1], Xuan Zhu[a,1], Bing Wang[b], Jingchao Li[c], Qiuhong Liu[a], Xuemin Gao[a], Kamalesh K. Sirkar[d,*], Dengyue Chen[a,*]

[a] School of Pharmaceutical Sciences, Xiamen University, Xiamen, Fujian 361102, China
[b] Key Laboratory of Urban Pollutant Conversion, Institute of Urban Environment, Chinese Academy of Sciences, Xiamen, Fujian 361021, China
[c] College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, China
[d] New Jersey Institute of Technology, Otto York Department of Chemical, Biological and Pharmaceutical Engineering, Newark, NJ, USA

ARTICLE INFO

Keywords:
Drug nanocrystals
Griseofulvin
Anti-solvent crystallization
Porous hollow fiber membrane

ABSTRACT

Nanotechnology is being utilized to develop advanced concepts in drug delivery systems including production of nanodrugs such as, nanocrystals and nanosuspensions. Continuous crystallization methods are of increasing interest and porous hollow fiber membrane (HFM) based modules have been recently utilized as an anti-solvent crystallizer. The porous hollow fiber anti-solvent crystallizer (PHFAC) based method has been modified here to produce continuously nanocrystals of Griseofulvin (GF). In the PHFAC device, deionized water introduced from the HFM bore into the shell side is used as the anti-solvent; acetone containing dissolved GF is introduced into the shell side of the HFM module as the drug solution. Water, the anti-solvent, mixed vigorously with the drug solution leading to drug crystallization and the drug crystals were separated by vacuum filtration and freeze-dried. The experimental conditions were varied to control the particle size, size distribution and the appearance of the nanoparticles. The properties of the drug nanocrystals were characterized via Transmission Electron Microscopy (TEM), Scanning Electron Microscope (SEM), Dynamic Light Scattering (DLS), Raman Spectroscopy, Energy Dispersive X-rays Spectroscopy (EDX), *Differential Scanning Calorimetry (DSC),* FT-IR Spectrometer, *X-ray Diffraction (XRD);* drug dissolution tests were *also* implemented. Drug nanocrystals as small as 86.4 nm were produced under modest pressure and temperature conditions in a controllable and continuous manner.

1. Introduction

Due to their small size, nanoparticles possess unique capabilities, such as volume effect, quantum size effect, surface effect, macroscopic quantum tunneling effect and so on and are therefore widely used in various fields. In pharmaceutical area, drug nanoparticles have attracted increasing interest from researchers and industry for their distinct advantages. For instance, they can be passively targeted on liver, spleen, bone marrow and other organs and tissues to cure the disease. Nanoparticle drugs sized under 100 nm have biological permeability through tumor vascular walls and hence are able to achieve a curative effect. Moreover, nanoparticles can increase the efficacy of antibiotics and enhance the potency of antifungal and antiviral agents in the treatment of intracellular bacterial infections.

For drugs with poor water solubility and dissolution rate, the stability and bioavailability of oral preparations can be drastically improved with drug nanoparticles for the purpose of protecting peptides, vaccines and other drugs from clearance in the digestive tract [1]. Due to rapid development of nanoscience and nanotechnology, synthesis of drug nanocrystals has been widely applied to drug delivery system (DDS) [2]. Nanonization of the drug is a desirable method to improve bioavailability and efficacy in order to enhance their therapeutic effect [3]. A number of size reduction techniques were developed or optimized to produce stable drug nanocrystals [4].

Current approaches in production of drug nanoparticles involve either top-down or bottom-up methods [5]. For top-down methods, drug particles are broken down to lower size particles by methods, such as pearl milling, high pressure homogenization etc.; these have greater utility for drugs having a high degree of crystallinity [6–8]. For bottom-up methods of direct particle formation, a classical precipitation process of 'via humida paratum' (VHP) is developed where drug dissolved in a solvent is precipitated by mixing with a non-solvent. This method

* Corresponding authors.
E-mail addresses: sirkar@njit.edu (K.K. Sirkar), dchen@xmu.edu.cn (D. Chen).
[1] X. Zhou and Dr. X. Zhu contributed equally to this work and should be considered as co-first authors.

https://doi.org/10.1016/j.memsci.2018.07.082
Received 10 April 2018; Received in revised form 12 July 2018; Accepted 27 July 2018
Available online 29 July 2018
0376-7388/

succeeds in producing crystalline drug nanoparticles while requiring strict control of the process [9]. One of the common methods, supercritical fluid (SCF) technology, solubilizes the solute in the supercritical fluid first and subsequently precipitates it via supersaturation through rapid expansion to obtain virtually contaminant-free particles [10,11]. In another technique, the spray freeze drying (SFD), the method involves the steps of droplet generation, freezing and sublimation drying [2,12,13]. However, high expenditure, intensive labor, demand of material and risks of dust explosion are disadvantages of these techniques [14]. Confined liquid impinging jets (CLIJ) has been used to produce particles in the submicron to nano range where precipitation takes place when a jet of drug solution impinges a jet of anti-solvent from two opposing nozzles [15]. But secondary crystallization and further growth may be induced by incomplete depletion of solute during nucleation and crystal growth. A precipitation technique named as in situ micronization has been developed to produce the drug nanoparticles in a relatively simple and modest way [16]; however, it may result in larger particles and poor control of crystal size. The frequently utilized method of rapid expansion of supercritical solutions (RESS) enables particle formation due to rapid supersaturation by applying rapid phase change of supercritical fluids. Supercritical Anti-Solvent (SAS) method [17–19] induces precipitation/crystallization of solutes by saturating the polar liquid solvent with carbon dioxide under supercritical conditions [11]; such a process would require critical experimental conditions such as the generation of high pressure condition for supercritical CO_2. Moreover, this method is a batch process with low output levels and questionable stability of the drug quality, which are against the requirements for modern pharmaceutical production. Nano spray drying invented by Büchi® employs a vibration mesh spray technology for fine droplet generation and is ideal for heat-sensitive biopharmaceutical products [20].

Meanwhile, porous hollow fiber membrane-based techniques were being developed to implement continuous phase-change processes. A continuously flowing solution of $BaCl_2$ on the shell-side permeated into a solution of K_2SO_4 flowing in the tube-side of a hollow fiber membrane device to achieve precipitation of $BaSO_4$ particles via chemical reaction [21–23]. This configuration is prone to the possibility of plugging of the hollow fiber bore unless special designs are made and precautions are taken. Instead of a chemical reaction-based precipitation, Zarkadas [24], Zarkadas and Sirkar [25] utilized hollow fiber devices to implement anti-solvent crystallization. They found that it was more useful to implement crystallization in the shell-side of the module so that chance of flow-passage blockage was much less due to many directional freedoms of flow. The specific configuration was adopted in which drug-containing feed solution flowing in the hollow fiber bore permeated into the shell side where the anti-solvent was flowing; thus crystallization took place in the shell-side.

Recently, Chen et al. [26] reported a convenient anti-solvent crystallization technique to synthesize continuously polymer-coated drug particles using a porous hollow fiber membrane device. Interestingly, the first part of this study [26] described PHFAC-based continuous crystallization of micron size GF crystals depending on various conditions that produced GF crystals with the median size from 1.61 μm to 11.83 μm. They had used an alternate arrangement for shell-side crystallization: the anti-solvent water was introduced from the hollow fiber bore into the shell-side having the flowing GF-in-acetone solution (Fig. 1(a)). The introduction of the anti-solvent water through tiny membrane pores into the acetone-based drug solution in the shell-side of the HFM module ensured a high-mixing zone in the microenvironment, which further provided a suitable condition for the crystallization of small drug particles.

This PHFAC technique and the HFM device were also used successfully to produce polymer-coated submicron as well as nanoparticles of silica in a controllable way [27]. These successes suggested the possibility of production of even smaller drug nanocrystals by controlling the nucleation and growth condition of crystals as well as the hydrodynamic optimization of the module [28].

To downsize the production of micron size GF drug crystals into nanocrystals of GF, we have redesigned the membrane module and investigated the hydrodynamic and crystallization conditions to achieve controlled and continuous synthesis of drug nanocrystals of GF at ambient pressure and temperature. The GF nanocrystals produced have been characterized extensively and the enhancement of their dissolution characteristics was also explored.

2. Experimental methods

2.1. Materials

Griseofulvin (purity 99.2%) was obtained from Yuanchenggongchuang Technology Co. Ltd (Wuhan, Hubei, China). Acetone (analytical purity) was purchased from Xilong Chemical Co. Ltd (Guangzhou, Guangdong, China). Deionized water was produced by multi-function ultrapure water system (Unique-R20, Ruisijie Water-purification Technology Co. Ltd, Xiamen, Fujian, China). All reagents were of analytical grade and used as received.

2.2. Apparatus and procedures

The experimental apparatus schematically shown in Fig. 1(b) was designed for anti-solvent induced precipitation. The PHFAC system, fabricated to perform the experiment, consisted of three sections: inlet system; crystallization system; vacuum filtration system. The inlet system had two parts, with the first part generating the drug solution stream and the other part generating the anti-solvent stream. The solution containing GF was prepared by stirring a suspension of the as-received GF crystals in acetone in a conical flask on a magnetic stirring apparatus until the drug was fully dissolved in the solvent. Upon complete dissolution, the GF solution was passed into the shell side of the crystallization system by a peristaltic pump (YZ1515x, Shenchen Pump Industry Co. Ltd, Baoding, Hebei, China). Meanwhile, water, the anti-solvent, was pumped into the lumen side of the PHFAC system by another peristaltic pump at a fixed flow rate at a slightly earlier time. In the PHFAC system, the left end of the tube side (shown in Fig. 1(b)) was blocked by epoxy resin. This prevented water from flowing out from the tube side end and created the pressure difference between the tube and the shell side to push the drug solution out to the shell side bulk from the outside of the hollow fiber membrane surface. The PHFAC module shell side was formed by a fluorinated ethylene propylene (FEP) tubing with an outer diameter (OD) of 19 mm and an inner diameter (ID) of 17 mm. The effective tube length was 26 cm, which was also the length of each of the 14 polyvinylidene fluoride (PVDF) porous hollow fiber membranes (pore size 0.1–0.15 μm; porosity, 0.75) having an OD of 2.5 mm and ID of 1.8 mm. As shown in Fig. 1(b), PHFAC module was placed at an angle of 15° to the horizontal to maximize the contacting area for the drug solution and anti-solvent in the shell side along the fiber length direction.

The perspective view of a single porous hollow fiber membrane shown in Fig. 1(a) illustrates the precipitation process in the drug solution flowing on the shell-side induced by the anti-solvent. In the shell side, the drug solution contacted uniformly with the anti-solvent which penetrated out from the pores (0.1–0.15 μm) in the hollow fiber walls. The drug crystals along with the excess solution flowed out to the outlet of the device continuously and subsequently to the vacuum filtration system (1000 mL, Tianjin Jinteng Experimental Equipment Co. Ltd, Tianjin, China); this system allowed collection of the particles through 0.1 μm pore-sized membrane filters (VVLP04700, Merck Millipore Ltd, County Cork, Ireland), which were freeze-dried prior to various characterization steps.