International Journal of Pharmaceutics 499 (2016) 395–402

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Continuous preparation of polymer coated drug crystals by solid hollow fiber membrane-based cooling crystallization

Dengyue Chen[a], Dhananjay Singh[a], Kamalesh K. Sirkar[a,*], Robert Pfeffer[b]

[a] Otto York Department of Chemical, Biological and Pharmaceutical Engineering, New Jersey Institute of Technology, University Heights, Newark, NJ 07102, USA

[b] School for Engineering of Matter, Transport and Energy, Arizona State University, Tempe, AZ 85287, USA

ARTICLE INFO

Article history:
Received 15 September 2015
Received in revised form 2 December 2015
Accepted 4 January 2016
Available online 6 January 2016

Keywords:
Polymer coating
Drug crystals
Membrane-based cooling crystallization
Solid hollow fiber

ABSTRACT

A facile way to continuously coat drug crystals with a polymer is needed in controlled drug release. Conventional polymer coating methods have disadvantages: high energy consumption, low productivity, batch processing. A novel method for continuous polymer coating of drug crystals based on solid hollow fiber cooling crystallization (SHFCC) is introduced here. The drug acting as the host particle and the polymer for coating are Griseofulvin (GF) and Eudragit RL100, respectively. The polymer's cloud point temperature in its acetone solution was determined by UV spectrophotometry. An acetone solution of the polymer containing the drug in solution as well as undissolved drug crystals in suspension were pumped through the tube side of the SHFCC device; a cold liquid was circulated in the shell side to rapidly cool down the feed solution-suspension in the hollow-fiber lumen. The polymer precipitated from the solution and coated the suspended crystals due to rapid temperature reduction and heterogeneous nucleation; crystals formed from the solution were also coated by the polymer. Characterizations by scanning electron microscopy, thermogravimetric analysis, laser diffraction spectroscopy, X-ray diffraction, Raman spectroscopy, and dissolution tests show that a uniformly coated, free-flowing drug/product can be obtained under appropriate operating conditions without losing the drug's pharmaceutical properties and controlled release characteristics.

1. Introduction

Polymers are of great importance in controlled release of drugs (Bernkop-Schnürch et al., 2000; Bhattacharyya et al., 2012; Cui et al., 2014; Fluri et al., 2008; Ghebaur et al., 2012; Kakizawa et al., 2010; Laga et al., 2012; Li et al., 2014; Mei et al., 2012; Nahrup et al., 2004; Paulsson and Edsman, 2002; Ramyadevi and Rajan, 2015; Sundaresan et al., 2014; Wulff and Leopold, 2014). A few of the common techniques employed to achieve controlled release of drugs are as follows (Langer, 1990). Diffusion of a drug takes place from a drug reservoir through a polymer layer surrounding the reservoir. Alternately, the drug is dispersed in a polymeric matrix through which it diffuses. The matrix can also ultimately swell or is degraded leading to controlled release of the drug. In the first technique, drugs such as proteins and peptides are protected from degradation by stomach acids by the polymeric coating. Coated with a layer of polyethylene glycol, drug nanoparticles have been found to penetrate a compromised blood-brain barrier (Nance et al., 2012) or overcome a mucous barrier (Lai et al., 2008). Here we are therefore concerned with a continuous fabrication technique involving development of a polymeric coating around the drug particle/crystal.

Methods for developing a polymeric coating around micron-size, submicron particles and nanoparticles may be classified (Wang et al., 2004) as dry or wet, batch or continuous. Techniques studied extensively over the last 20 years e.g., Rapid Expansion of Supercritical Solutions (RESS) (Tsutsumi et al. 1995; Kim et al. 1996), compressed anti-solvent (Falk et al., 1997), Supercritical Anti-Solvent (SAS) (Wang et al., 2004), and Gas Anti-Solvent (GAS) processes, are very demanding due to the very high pressure often involving supercritical CO_2 and the low solubility of the polymers in such fluids. Further, these are batch processes as in all industrial crystallization techniques whether they employ cooling, evaporation or anti-solvent to bring about crystallization from a solution.

Conventional crystallization devices containing impeller mixing-based equipment (Myerson, 2002; Tavare, 1989) invariably suffer from poor mixing resulting in extreme variations in the crystallized products. In processes utilizing anti-solvent

* Corresponding author. Fax: +1 973 642 4854.
E-mail addresses: dc224@njit.edu (D. Chen), ds64@njit.edu (D. Singh), sirkar@njit.edu, kamalesh.k.sirkar@njit.edu (K.K. Sirkar), Robert.Pfeffer@asu.edu (R. Pfeffer).

http://dx.doi.org/10.1016/j.ijpharm.2016.01.008
0378-5173/

crystallization, the impinging-jet mixer (Midler et al., 1994) employing two jet streams meeting head to head generates nuclei/crystals which undergo growth subsequently in a well-mixed vessel or a tubular precipitator. The shortcomings of this technique have been summarized (Zarkadas and Sirkar, 2006).

To overcome most of the deficiencies of previous techniques, we have adapted the solid hollow fiber cooling crystallization (SHFCC) method developed earlier (Zarkadas and Sirkar, 2004). In the SHFCC, a solution of the drug to be crystallized flows in the bore of a solid hollow fine fiber whose wall is impervious; a cold liquid flows on the shell side of this hollow fine fiber in a countercurrent direction setting up a rapid and highly efficient heat exchange (Song et al., 2010) leading to cooling-based crystallization of the solute in the lumen-side liquid.

Such a technique was employed recently by us (Chen et al., 2014a) to generate a thin coating of the polymer Eudragit RL 100 or poly(D,L-lactide-co-glycolide) (PLGA) from its solution in acetone on 550 nm submicron silica particles; the silica particles were in suspension which was flowing continuously through the bore of the hollow fine fibers. The polymer coating thickness could be varied by changing the operating conditions. By using two different hollow fiber modules having different numbers of hollow fibers, we demonstrated facile scale-up yielding essentially the same polymer coating thickness on the silica particles at two different production rates. Continuous and reproducible polymer coating of silica nanoparticles of 12 nm diameter in suspension in an acetone solution of the polymer Eudragit RL 100 (Chen et al., 2014b) was also demonstrated. The polymer-coated submicrometer or nano-sized particles were recovered to produce free-flowing particles.

These silica particles were acting as surrogates for drug particles. There are a few other factors to be considered when drug crystals are to be coated continuously by a polymer by the SHFCC technique. For example, the drug may be in solution or it may be present as crystals/particles in suspension or the drug may be present simultaneously in solution as well as in a suspension depending on its solubility. Whenever the drug is present in a solution, it is often a challenge to prevent co-precipitation of the drug and the polymer. For example in the SAS process, there are quite a few examples where co-precipitation took place (co-precipitation of ethyl cellulose and ampicillin (Montes et al., 2012); co-precipitation of polyvinylpyrolidone and diflunisal (Zahran et al., 2014); poly-ε-caprolactone co-precipitated with green tea polyphenols (Sosa et al., 2011)).

The SHFCC technique will always have the polymer in solution in a given solvent. If the drug crystals are introduced into the polymer solution, there is a possibility that the drug may have limited/low solubility in the solvent. On the other hand, if we have a solution of the drug, the polymer may be introduced into the solution and completely dissolved into it. Therefore the most general situation will have both the drug and the polymer in solution; but if the drug has limited solubility, some drug may be present as a suspension. Here we have a solution of the coating polymer which contains in addition a solution of the drug to be crystallized as well as a suspension of micron-sized drug crystals flowing in the solid hollow fine fiber bore. The drug under consideration is Griseofulvin; the polymer used to coat the drug crystals is Eudragit RL 100. The goal of this work is to introduce a facile cooling-based method for continuous polymer coating of drug crystals/particles when the drug is present in a solution as well as in a suspension and the polymer is in solution.

It is useful to identify another hollow fiber membrane-based method for continuous crystallization, the porous hollow fiber-based anti-solvent crystallization (PHFAC) (Zarkadas and Sirkar, 2006). The PHFAC technique has also been employed to develop continuously a suspension of polymer-coated drug particles/crystals from a solution of the drug and the polymer in the solvent by exposure to an anti-solvent (Chen et al., 2015). In this technique, the acetone solution of the drug and the polymer flows on the shell side of a porous hydrophilic hollow fiber. Water acting as the anti-solvent is introduced from the tube side of the hollow fiber through the pores in the hollow fiber wall into the hollow fiber shell side where the acetone solution of the polymer and the drug is flowing. Very high supersaturation is created instantaneously by this process leading to rapid crystallization of the drug first followed by nucleation/precipitation of the polymer around the drug crystals.

However, in the PHFAC technique of Chen et al. (2015), both the drug and the polymer were in solution whereas here the drug is present in solution as well as in suspension. It would also be of interest to determine how the results of the PHFAC process compare with what we propose here employing simple cooling without the complexities of an anti-solvent system.

1.1. Solid hollow fiber cooling crystallizer

A single polymeric solid hollow fiber is shown in Fig. 1(a). This solid hollow fiber serves as a typical heat exchange tube except the dimensions of the solid hollow fine fiber are orders of magnitude smaller than those of a conventional heat exchange tube. The feed liquid flowing into the hollow fiber lumen is an acetone solution of the drug and the polymer at say, 45 °C. This solution contains a suspension of GF microcrystals as well. As this solution-suspension is pumped through the hollow fiber lumen, it is rapidly cooled down by the cold liquid circulating on the shell side of the hollow fiber module after introduction at −9.1 °C. The temperature of the liquid exiting the hollow fiber lumen is around 5 °C. The cooling leads to crystallization of the dissolved drug as well as polymer precipitation around the preexisting drug crystals in suspension and the rapidly forming drug crystals which allow heterogeneous nucleation of the polymer around them.

The hollow fine fiber was made of polypropylene (PP); it has considerable pH, chemical and solvent resistance as well as mechanical strength. The nonporous fiber wall has a relatively smooth surface which minimizes the possibility of clogging

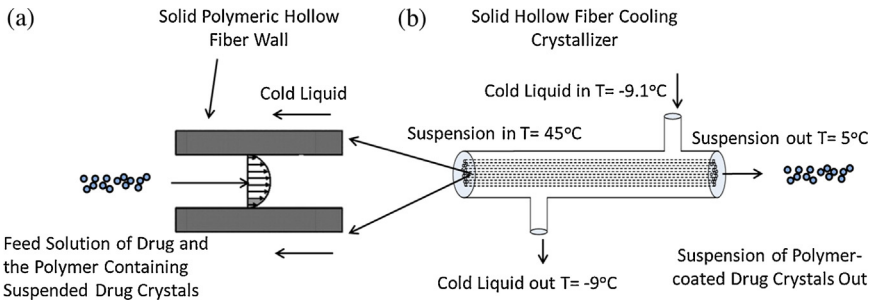

Fig. 1. (a) Single solid hollow fiber heat exchanger; (b) Solid hollow fiber membrane based cooling crystallizer module.