Materials Science and Engineering C 33 (2013) 2864–2870

Contents lists available at SciVerse ScienceDirect

Materials Science and Engineering C

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

Modified supercritical antisolvent method with enhanced mass transfer to fabricate drug nanoparticles

Mitali Kakran [a,b], Nanda Gopal Sahoo [a,b], Maria N. Antipina [b], Lin Li [a,*]

[a] School of Mechanical and Aerospace Engineering, Nanyang Technological University, 50 Nanyang Avenue, Singapore 639798, Singapore
[b] Institute of Materials Research and Engineering, Agency for Science Technology and Research (ASTAR), 3 Research Link, Singapore 117602, Singapore

ARTICLE INFO

Article history:
Received 3 December 2012
Received in revised form 25 January 2013
Accepted 1 March 2013
Available online 14 March 2013

Keywords:
Quercetin
Nanoparticle
Supercritical antisolvent
Mass transfer
Dissolution

ABSTRACT

The main aim of this study was to modify the supercritical antisolvent precipitation method to enhance the mass transfer in order to prepare smaller nanoparticles of drugs. The supercritical antisolvent apparatus was customized by introducing a titanium horn in the precipitation chamber for generation of the ultrasonic field for enhanced mass transfer and the method was called supercritical antisolvent with enhanced mass transfer (SAS-EM). The effects of flow rate, ultrasonic amplitude, drug concentration and flow time on the particle size were investigated. The results showed that increasing the flow rate, incrementing the ultrasonic power up to an optimum point, decreasing the drug concentration and reducing the flow time helped to achieve smaller quercetin particles in the range of 120–450 nm. It is also shown that there is a tradeoff between the particle size and the yield; therefore the process parameters can be selected based on the particle size requirement. DSC studies suggested that the crystallinity of SAS-EM prepared quercetin nanoparticles decreased as compared to original quercetin powder. The dissolution of SAS-EM prepared nanoparticles increased significantly in comparison with the original quercetin powder. However, there was no significant difference in the dissolution of various quercetin nanoparticles samples prepared by the SAS-EM process. The best dissolution percent achieved was 75% for the smallest size sample prepared at the flow rate of 5 ml/min, power supply of 200 W, drug concentration of 10 mg/ml, and flow time of 4 min.

1. Introduction

The poor solubility and low bioavailability of drugs are two increasing concerns that have emerged during the development of new drugs. Studies have revealed that more than 40% of drugs exhibit very poor water solubility which limits their absorption [1]. Poor water solubility becomes a challenge when formulating them in conventional dosage means. Due to low water solubility, conventional formulations are associated with irregular absorption in the gastrointestinal tract [2]. Hence, an increase in dissolution rate will have a positive influence on the bioavailability of drugs with poor water solubility. Physical modifications to increase the surface area of the drug particles result in an enhanced dissolution rate. Micro/nanonization is the most common method for increasing the surface area of the drug by reduction of the particle size. The supercritical fluid based techniques have been used to produce nanoparticles in order to take advantage of some specific properties of these fluids, mainly the very fast (gas-like) mass transfer [3], and the reduction of organic solvents used in traditional methods [4]. The most commonly used supercritical fluid is carbon dioxide (CO_2) because it is cheap, non-polluting and its critical temperature and pressure parameters are simple to be obtained in an industrial apparatus; and the mild process temperature conditions are compatible with the thermal stability of many organic thermolabile compounds to be used in food, pharmaceutical and cosmetic industries [3]. The most used process is the supercritical antisolvent (SAS) precipitation [5], that has been successfully used to process pharmaceuticals, superconductors, coloring matters, explosives, polymers and biopolymers [6,7]. This technique involves dissolving the solute in a suitable organic media and spraying the solution into supercritical fluid. The supercritical fluid acts as an antisolvent, resulting in supersaturation of liquid droplets and instantaneous precipitation of the solute as fine particles. After the removal of the solvent, the pressure of the carbon dioxide (CO_2) rich solution is then normalized to atmospheric pressure. The collection of particles is then done at the bottom of the chamber. The precipitation chamber is continuously purged with supercritical CO_2 to dry the particles. In this process, the particle shape and size distribution are dependent on droplet formation, mass transfer rate between the solvent and antisolvent phases, pressure, temperature and the flow rates at which fluids are added to the precipitation chamber [8]. In recent years, the supercritical antisolvent (SAS) precipitation process has been modified to generate smaller particles of controllable size which have a narrower size distribution. The modified technique, better known as supercritical antisolvent precipitation with enhanced mass transfer (SAS-EM) still uses supercritical carbon dioxide as the antisolvent but the solution jet is atomized into micro droplets by

* Corresponding author. Tel.: +65 67906285; fax: +65 67904062.
E-mail address: mlli@ntu.edu.sg (L. Li).

0928-4931/$ – see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.msec.2013.03.002

utilizing a surface vibrating at an ultrasonic frequency [9], which provides a velocity component that greatly enhances mixing and turbulence within the supercritical phase. This results in high rates of mass transfer between the two fluids. The SAS-EM technique helps to achieve the production of small particles due to the combined effects of tiny solution droplets due to jet atomization and rapid mixing rate between the solution and anti-solvent [10]. Enhancement of the miscibility of the solvent and anti-solvent phases can influence particle size by improving the rates of mass transfer between the solution and supercritical phase and also preventing agglomeration of the particles [11].

Therefore, the main objective of this project is to perform supercritical antisolvent precipitation with enhanced mass transfer (SAS-EM) in a controlled and optimized environment to fabricate nanoparticles of the poorly water soluble drug, quercetin. Quercetin is a polyphenolic compound and has attracted attention due to its antioxidant, anticancer and antiviral properties [12]. In spite of this wide spectrum of pharmaceutical benefits, the clinical application of quercetin is limited due to its low hydrophilicity and hence, there is a need to develop a new formulation for quercetin with enhanced dissolution to improve its absorption [13]. We hope to optimize the SAS-EM process to reduce the quercetin particle size to the minimum in order to improve its dissolution properties.

2. Materials and method

2.1. Materials

Quercetin dihydrate was obtained from Sigma Aldrich (Singapore). Ethanol was purchased from Merck (Singapore) and supercritical CO_2 from Soxal (Singapore). All reagents used were of technical grade.

2.2. Fabrication method

The schematic diagram of the supercritical antisolvent precipitation with enhanced mass transfer, SAS-EM (Newton & Stokes, Singapore) apparatus is shown in Fig. 1. The supercritical antisolvent apparatus was customized by introducing a titanium horn (Sonics and Materials) in the precipitation chamber (approximately 390 cm^3 in volume) for generation of the ultrasonic field and jet deflection which greatly enhanced the mixing. The ultrasound was powered by a 500 W, 20 kHz ultrasonic processor. The amplitude of vibration of the horn surface was directly proportional to the input power and was directly controlled by adjusting the power supplied to the ultrasound transducer. The liquid CO_2 was fed into the precipitation chamber from a CO_2 chamber which was connected to the CO_2 cylinder. The liquid feed system with a feed pump (Perkin Elmer Series 2000) was used to inject the drug solution into the precipitation chamber. All the precipitation experiments were carried out at around 79 bar and 36 °C and the frequency of the ultrasonic horn was kept constant at 20 kHz. First of all, the precipitation chamber was filled with CO_2 to obtain the desired pressure. The temperature inside the chamber was maintained by a water bath. Quercetin solution to be injected into the precipitation chamber was prepared in ethanol. The titanium horn, inside the precipitation chamber was then allowed to vibrate at the desired amplitude by adjusting the input power, and the quercetin solution was pumped inside the precipitation chamber by the feed pump. As soon as the solution jet was in contact with the vibrating horn surface, it was atomized into tiny droplets and quercetin particles were formed due to the rapid removal of ethanol by supercritical CO_2 from these droplets. The mass transfer rate between ethanol and supercritical CO_2 was greatly enhanced due to increased mixing caused by the ultrasonic field generated by the horn surface. Increased mixing also led to an increase in particle motion inside the precipitation cell, which prevented agglomeration. Next was the cleaning step in which ethanol left dissolved in supercritical CO_2 was removed by continuously purging with fresh CO_2. The precipitation chamber was then allowed to slowly depressurize until it reached ambient pressure. Finally quercetin particles precipitated were collected for particle analysis. The effects of process variables such as the flow rate, ultrasonic amplitude, drug concentration and flow time on the particle size and dissolution properties of the fabricated quercetin nanoparticles were investigated and analyzed.

2.3. Characterization

The morphology of samples was observed using a scanning electron microscope (JSM-6390LA-SEM, Jeol Co., Tokyo, Japan). The powder samples were spread on a SEM stud and sputtered with gold before the SEM observations. The analysis of the particle size was performed using the UTHSCSA ImageTool program. Differential scanning calorimetric (DSC) measurements were carried out using a TA DSC 200 thermal analyzer in a temperature range of 25–375 °C at a heating rate of 10 °C/min in nitrogen gas. The melting point and heat of fusion were calculated by the DSC software. The melting point and heat of fusion were calculated using the Universal Analysis (TA Q Series Advantage) software. X-ray diffraction (XRD) was measured using the Bruker AXS D8 Advance X-ray diffractometer with Cu Kα—targets at a scanning rate of 0.010 2θ/s, applying 40 kV, and 40 mA, to study the crystallinity of samples. The in vitro dissolution of the samples was determined using the paddle method (USP apparatus II) (Verkin Dissolution Tester DIS 8000) in 100 ml of DI water. The paddle rotation was set at 100 rpm. The temperature was maintained at 37 ± 0.5 °C. The original quercetin and prepared quercetin nanoparticles containing 5 mg of

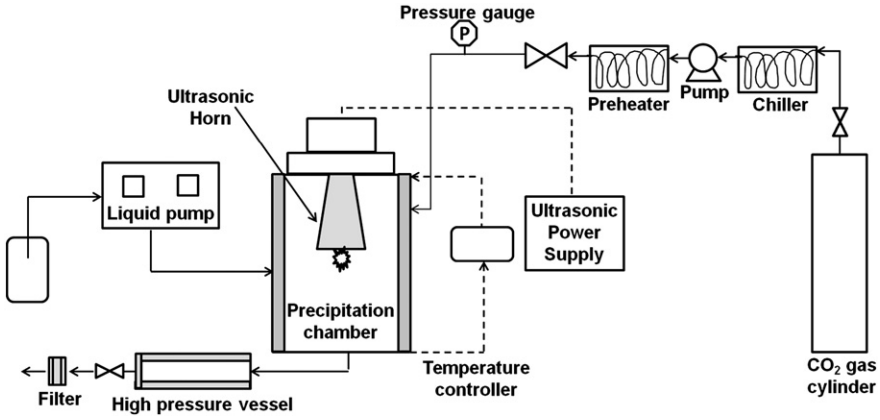

Fig. 1. Schematic of the experimental apparatus used for the SAS-EM process.