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Micronization of chitosan via rapid expansion of supercritical solution

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ABSTRACT

In this study, rapid expansion of supercritical solution (RESS) was used to micronize the chitosan particles. Design of experiment was implemented with response surface methodology (RSM) using Mini Tab software 17. The operating temperature (30–70 °C), pressure (7–22 MPa) and effective nozzle diameter (500–1200 μm) were considered as the range of operating variables while spraying distance (1 cm) and nozzle length (5 mm) were held constant. The characterization (size and morphology) of the precipitated particles of chitosan was determined by scanning electron microscopy (SEM). The results show great reduction in the size of the precipitated particles of chitosan compared with the original particles. A decrease in the particle size of chitosan was found with increasing extraction pressure and temperature along with a decreasing of nozzle diameter. Response surface analysis verified that R^2 and modified R^2 of the model for 500 μm effective nozzle diameter were 97.19% and 95.18%, respectively.

1. Introduction

Chitosan is a partially deacetylated polymer of Nacetyl glucosamine which can be obtained through alkaline deacetylation of chitin that is commonly found in the shells of insect and crustacean and cell walls of some fungi. Chitin is known as the second most abundant natural polysaccharide followed by cellulose [1]. Deacetylation of chitin is obtained through boiling chitin from crab and shrimp shells in sodium hydroxide after decolorization by potassium permanganate [2,3]. Chitosan consists of a β-(1,4)-linked-D-glucosamine residue with the amine groups randomly acetylated. The amine and —OH groups give chitosan many special properties that make it applicable in many areas and conveniently available for chemical reactions [4].

Useful characteristics of chitosan have been widely demonstrated, including biocompatibility [5], biodegradability, low toxicity [6], cell affinity [7], antimicrobial [8], antioxidant activities [9] and low production costs. Chitosan is used in various fields, such as pharmaceuticals [10,11], biotechnology [12,13], agriculture [14], textiles [15] and paper [16].

It has been reported that chitosan is very good for nano and micro particles preparation for controlled drug release. Chitosan nanoparticles has attracted more attention as a drug delivery carrier due to their low toxicity, simple and mild preparation methods, better stability and versatility of administration [17]. Chitosan extensively used for development of self-assembled nanoparticles which could enhance the drug oral bioavailability [18] and also for pharmaceutical carriers for sustained drug release [19].

Conventional methods for chitosan microparticles production are: spray drying [21] coacervation [11], suspension cross linking [22], reverse micelles formation [20], ionotropic gelation of chitosan molecular chains [23] emulsion–solvent extraction [24] and processes based on cavitation, attrition, high shear and impaction [25,26]. These processes have several limitations and drawbacks like the use of organic solvents and the need for further processes to reduce solvent residue levels to safe limits and the difficulty of surfactants separation. Moreover, these kinds of processes often have negative effects include thermal and chemical degradation and broad size distribution. Replacing traditional organic solvents with more environmentally friendly materials could eliminate the disadvantages of conventional micronization methods [27]. Versatile operating conditions and exceptional properties like gas-like diffusivities and viscosities, gas-like to liquid-like densities that are possible with supercritical fluids provide the flexibilities in controlling the size of the particles.

Rapid expansion of supercritical solutions (RESS), particle generation from gas saturated solution (PGSS), gas anti-solvent (GAS) and their modifications are the primary techniques for particle formation using SCF [28].

The RESS process is an appropriative, innovative and promising technology for production of certain pharmaceuticals due to small particles, narrow particle size distribution, solvent-free products and controllable particle size. In this process the particle size distribution and morphology of precipitated particles is dependent to

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pre-expansion and expansion conditions, extraction parameters, spray distance and nozzle design [29].

Several other advantages of RESS process are: High products purity, environmentally acceptable technology, crystal polymorphism control, possibility of thermo-labile molecules processing, single-step, easy downstream processing and processing of chemically and shock-sensitive materials [30].

Because of relatively low critical pressure (7.39 MPa) and temperature (304.2 K) of carbon dioxide (CO_2) and environmentally benign, inexpensive, non-flammability and non-toxicity, it is the most common solvent in the RESS process. The low polarity is the only major drawback of CO_2 that leads to low extraction of chitosan. Thus co-solvents can be used to change the polarity of SC-CO_2 and increase its solvation power to desired analyte [31].

The aim of this study was to determine the parameters influencing the particle characteristics in order to be able to control particle size and distribution of chitosan particles by implementation of response surface methodology (RSM). The RSM is useful for modeling, problem analysis and optimization when a response (i.e., particle diameter) is influenced by several variables such as pressure and temperature [32–34].

1.1. RESS process

The rapid expansion of supercritical solution process consists of extraction and precipitation units. The solutes are dissolved in the SC-CO_2 at the extraction unit. After loading the supercritical fluid with the solute, the supercritical solution is suddenly depressurized in the nozzle causing fast nucleation particle formation. Reduction of the solvent density is the driving force for the nucleation and crystallization of the particles. Decreasing the SC-CO_2 solvating power is obtained through expansion of supercritical solution through a nozzle to atmospheric conditions and then the solute becomes supersaturated and then precipitated. The solubility difference of the solute in supercritical fluids at high and low pressures is the basis of this process. Higher supersaturation leads to enhance the nucleation rate and as a result decreases the particle size [35,36].

The list of pharmaceuticals that were micronized via RESS process is reported in Table 1 [30]. But there is not any published data about micronization of chitosan by this method which is considered to be the novelty of this paper.

Table 1
Summary of pharmaceutical micronization via RESS [30].

Pharmaceutical	Extraction temperature (°C)	Extraction pressure (MPa)	Particle size range (μm)
Ibuprofen	35	13–17	2.85–7.48
Phenytoin	45	19.6	0.105–0.2
Felodipine	30–60	20–40	2–6
Salicylic acid	45–60	15–25	2.24–5.41
Taxol	50	25–35	0.3–19.7
Nabumetone	35–55	15–20	3.3–19.7
Gemfibrozil	35–55	10–22	5.8
Cephalexin	40–60	14–23	0.86–7.22
Digitoxin	45	10	0.068–0.458
Raloxifene	40–80	10–18	0.018
Lynestrenol	45–60	15–30	0.58–0.326
l-Menthol	30–50	20	0.4–1
Carbamazepine	50	15–30	0.22–1.43
Gemfibrozil	22–55	10–25	0.8–2.2
Fenofibrate	35–45	10–20	3.044–7.453

2. Experimental

2.1. RESS setup

To carry out the objectives of this study, the RESS system shown in Fig. 1 was used. The setup consists of two main units of extraction and precipitation (the precipitated particles are collected). For further increasing the CO_2 purity which is stored in the CO_2 cylinder, a column of molecular sieve (Merck, Molecular Sieve 5A-K28751105148) and metal porous filter (Mott Metallurgical, 1003630-01-050) was place next to the cylinder and CO_2 was passed through it. A chiller was used to cool down CO_2 in the range of −10 to −5 °C. A feed pump (reciprocating pump, Jasco, PU-1580, maximum pressure = 35 MPa) was charged the liquefied CO_2 through the needle valve and is fed to the modifier vessel (height = 12.5 cm, inner diameter = 0.9 cm, and outer diameter = 1.3 cm) which is filled with acetone as the modifier and saturated with acetone co-solvent. For damping the pressure fluctuations produced by operation of the pump, the solution was entered to a surge tank after entering to the extraction vessel.

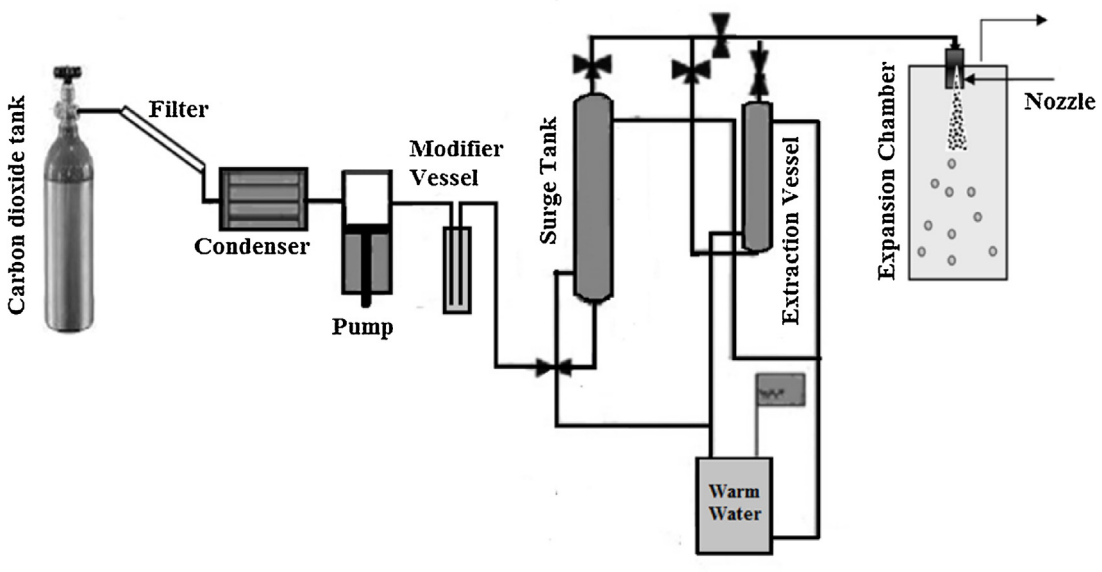

Fig. 1. The schematic diagram of experimental apparatus for the RESS process.