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International Journal of Pharmaceutics 308 (2006) 190–199
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

Formation of phenytoin nanoparticles using rapid expansion of supercritical solution with solid cosolvent (RESS-SC) process

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Received 6 July 2005; received in revised form 22 September 2005; accepted 3 November 2005
Available online 13 December 2005

Abstract

Nanoparticles are of significant importance in drug delivery. Rapid expansion of supercritical solution (RESS) process can produce pure and high-quality drug particles. However, due to extremely low solubility of polar drugs in supercritical CO_2 (sc CO_2), RESS has limited commercial applicability. To overcome this major limitation, a modified process rapid expansion of supercritical solution with solid cosolvent (RESS-SC) is proposed which uses a solid cosolvent. Here, the new process is tested for phenytoin drug using menthol solid cosolvent. Phenytoin solubility in pure sc CO_2 is only 3 μmol/mol but when menthol solid cosolvent is used the solubility is enhanced to 1302 μmol/mol, at 196 bar and 45 °C. This 400-fold increase in the solubility can be attributed to the interaction between phenytoin and menthol.

Particle agglomeration in expansion zone is another major issue with conventional RESS process. In proposed RESS-SC process solid cosolvent hinders the particle growth resulting in the formation of small nanoparticles. For example, the average particle size of phenytoin in conventional RESS process is 200 nm whereas, with RESS-SC process, the average particle size is 120 nm, at 96 bar and 45 °C. Similarly at 196 bar and 45 °C, 105 nm average particles were obatined by RESS and 75 nm average particles were obtained in RESS-SC process. The particles obtained were characterized by Fourier-transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), dynamic light scattering (DLS) and differential scanning calorimetery (DSC) analyses. Phenytoin nanoparticle production rate in RESS-SC is about 400-fold more in comparision to that in RESS process.

Keywords: RESS; RESS-SC; Supercritical; Nanoparticle; Phenytoin

1. Introduction

The dissolution of poorly water-soluble drugs is a major concern for pharmaceutical industry, specially for the drugs whose dosage requirement is near their toxicity limits. The particle size reduction is one of the methods which can achieve desired bioavailability of poorly soluble drugs, as the dissolution rate can be enhanced by reducing the particle size (Unno et al., 1984; Yakou et al., 1984). Mechanical methods have been used for particle size reduction but broad size distribution and difficulty in commuting are some of the problems associated with these methods. Also, heat-sensitive materials can degrade by milling. To overcome these disadvantages, new methods have been devised including supercritical fluid (SCF)-based particle size reduction methods (Tom and Debenedetti, 1991). These can be divided into two major processes: rapid expansion of supercritical solution (RESS) for CO_2-soluble drugs and supercritical antisolvent (SAS) process for CO_2-insoluble drugs.

In RESS process, the desired solute is solubilized in SCF and then resulting solution is expanded through a nozzle to cause a sudden decrease in the solubility and hence, particle formation (Tom et al., 1994; Turk et al., 2002). Homogenous nucleation in RESS is caused by supersaturation and several mathematical models have been presented to explain this process theoretically (Kwauk and Debenedetti, 1993; Shaub et al., 1995; Helfgen et al., 2003). In SAS process, the desired solute is dissolved in an organic solvent and then injected inside SCF media causing small particle formation by volumetric expansion and removal of solvent (Luna-Barcenas et al., 1995; Werling et al., 2000; Elvassore et al., 2001; Reverchon et al., 2001). RESS is simpler and less expensive when compared to SAS process. But the solubility of most polar drugs is almost negligible in supercritical CO_2 (sc CO_2) which makes RESS process unviable for practical application. Due to this reason, other less benign

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doi:10.1016/j.ijpharm.2005.11.005

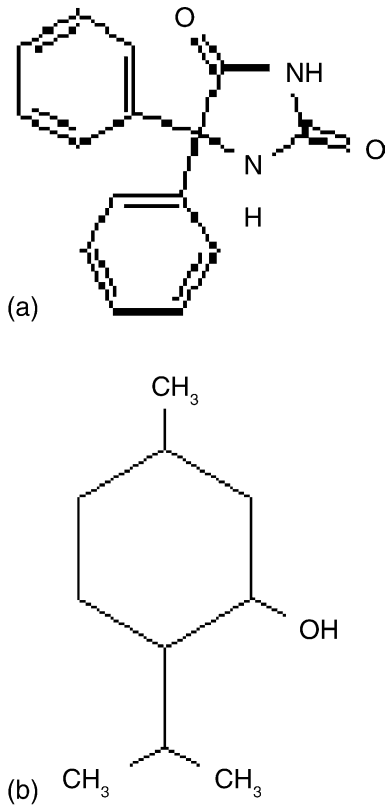

Fig. 1. Chemical structure of phenytoin (5,5-diphenyl-2,4-imidazolidinedione) (a) and menthol (b).

SCFs been used to produce polar particles using RESS method (Reverchon et al., 1995). Also, organic compounds tend to agglomerate due to their adhesive nature, resulting in agglomeration which generally produces bigger particles. Both challenges are addressed in this work by improving the drug solubility in sc CO_2 and also producing sub-100 nm particles by reducing the particle growth. Here, the new concept is tested for phenytoin drug.

Phenytoin (5,5-diphenyl-2,4-imidazolidinedione; Fig. 1) is widely used as anticonvulsant and antiepileptic drug. As phenytoin is a blocker for inactivated sodium channels, it is also used as antiarrhythmic drug for treatment of heart rhythm disturbances (Dylag et al., 2004). The side effects of phenytoin include nausea, insomnia and other central nervous system disorders (Page et al., 2002; Reynolds, 1982). Phenytoin is a highly crystalline compound having high melting point of 295–298 °C due to the strong intermolecular hydrogen bonding. Phenytoin solubility in water is as low as 80 μmol/l (Stella et al., 1999). For better bioavailability, low melting prodrugs have been proposed which later on convert to phenytoin (Stella et al., 1999). Also, some excipients have been added to phenytoin to obtain better dissolution (Hashim and El-Din, 1989). For example, β-cyclodextrin–phenytoin complexation has been used for enhancing phenytoin bioavailability (Tsuruoka et al., 1981). Most common route of phenytoin exposure is oral, though parenteral mode is used intravenously in *status epilepticus*.

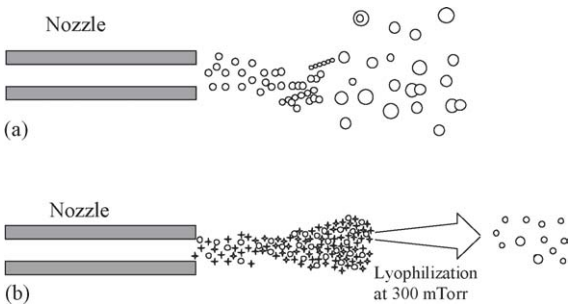

Fig. 2. Schematic of RESS (a) and RESS-SC (b) process.

Due to the high polarity it is difficult to solubilize phenytoin in sc CO_2. At 196 bar and 45 °C, phenytoin solubility in sc CO_2 is only 3 μmol/mol. With this low solubility RESS is not economically viable for industrial production. Earlier, micrometer-sized phenytoin particles were formed by supercritical-assisted atomization process after dissolving in methyl alcohol (Reverchon, 2003). To overcome the limitation of low solubility, this work proposes the addition of a solid cosolvent to enhance the phenytoin solubility in sc CO_2.

Though the mathematical modeling of RESS predicts particles of size less than ∼20 nm at the tip of the nozzle, particles experimentally obtained are in the range of 200–1000 nm (Helfgen et al., 2003). In conventional RESS process, each particle is surrounded by same kind of particles in the expansion zone which results in larger particles due to coagulation (Fig. 2a). So far various solvents and techniques have been used for phenytoin crystals modifications (Nokhodchi et al., 2003). A new method, rapid expansion of supercritical solution with solid cosolvent (RESS-SC), has been proposed which overcomes this particle growth in expansion zone resulting in smaller nanoparticles. In RESS-SC, phenytoin particles are surrounded by a solid cosolvent, avoiding surface to surface interaction to other phenytoin particles, hence hindering the particle growth. RESS-SC concept is shown in Fig. 2b. The cosolvent is simply removed by sublimation using a lyphilizer, which is carried out after the particle recovery from the expansion chamber.

1.1. Choice of cosolvent

The choice of cosolvent is very important as it needs to provide polar interaction to enhance solubility in CO_2. Polar cosolvents including acetone, ethanol have been tried so far which are liquid at operating and exit conditions and can cause particle dissolution (Dobbs et al., 1987; Dobbs and Johnston, 1987; Liu et al., 2000; Jin et al., 2004). In this work, solid cosolvent is proposed which should have following properties:

- sufficiently high vapor pressure for easy removal by sublimation;
- solid at nozzle exit conditions (typically −5 to 25 °C, observed experimentally);
- appreciable solubility in sc CO_2;
- non-reactive with desired solute or sc CO_2;