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Formation of ultrafine deferasirox particles via rapid expansion of supercritical solution (RESS process) using Taguchi approach

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ABSTRACT

The poor water solubility of many drugs is a challenge in pharmaceutical research. Recently, there have been great interests in finding environmentally friendly methods producing fine particles of pharmaceutical products for applications in pharmaceutical engineering. A promising method to improve the bioavailability of pharmaceutical agents is the rapid expansion of supercritical solutions. Deferasirox (DFS), a tridentate chelator, requires two molecules for iron (III) coordination. The bioavailability (the percentage of the drug absorbed compared to its initial dosage) is limited by this insolubility. The effect of four different RESS parameters including, extraction temperature (308–318 K), extraction pressure (140–200 bar), effective nozzle diameter (500–1200 μm), with and without cosolvents were investigated on the size and morphology of the precipitated particles of deferasirox based on Taguchi design. The results show great reduction in the size of the precipitated particles of deferasirox (50 nm–5 μm) via RESS process compared with the original particles of deferasirox (5–500 μm).

1. Introduction

In recent years, significant effort has been devoted to developing drug formulation and delivery systems for issues such as targeting and controlled release (Mainardes and Silva, 2004; Rabinow, 2004; Del Valle and Galan, 2005). In fact, the solubility is a serious limitation in drug development and related requirements for bioavailability and normal absorption pattern. According to the established statistics, about a third of the drugs listed in the United States Pharmacopeia are poorly water-soluble or insoluble and more than 40% of new drug development has failed because of poor biopharmaceutical properties (Lipinski, 2002; Muller et al., 2001). The nanosizing of drug particles has been identified as a potentially effective and broadly applicable approach. For example, smaller-diameter particles correspond to a faster dissolution rate, hence potentially higher activity and easier absorption. Other distinct advantages include tissue or cell specific targeting of drugs, longer circulating capacity in the blood, higher stability against enzymatic degradation, and the reduction of unwanted side effects (Leuner and Dressman, 2000; Kayser et al., 2005). Several conventional techniques are used for reduction of particle size such as crushing, grinding, milling, spray drying, freeze-drying and recrystallization of the solute particles from solutions using liquid antisolvents. But all these techniques have got several disadvantages. Some substances are unstable under milling conditions, and in recrystallization process the product is contaminated with solvent. In addition, there are thermal and chemical degradation of products due to high temperatures, high-energy requirements, large amount of solvent use, solvent-disposal problems, and broad particle size distributions. Due to their several drawbacks, the use of supercritical fluids has increased rapidly over the last few years, and several processes for particle formation have been studied (Kayrak et al., 2003a). Supercritical fluid processing techniques have been applied to the particle formation in drug formulation (Stanton et al., 2002; Fages et al., 2004). The methods of fine particles formation using supercritical fluids are: rapid expansion of supercritical solutions (RESS), anti-solvent processes (gas anti-solvent (GAS), supercritical anti-solvent (SAS), aerosol solvent extraction system (ASES), solution enhanced dispersion by supercritical fluids (SEDS)) and particles from gas saturated solutions/suspensions (PGSS) (Jung and Perrut, 2001). The RESS process consists of extraction and precipitation unit. A substance is solubilized in a supercritical fluid (SCF) at the extraction unit, then the supercritical solution is suddenly depressurized in a nozzle causing fast nucleation and fine particle formation. Due to the rapid expansion of supercritical solution through a nozzle, a large decrease in density occurs which leads to decreasing the SCF solvating power. The solute becomes supersaturated and then precipitated. The driving force of the nucleation process is supersaturation. Higher supersaturation leads to an increase in the nucleation rate, and tends to decrease the particle size. Advantages of RESS process are that nano or microparticles are produced, providing a solvent-free product and controllable

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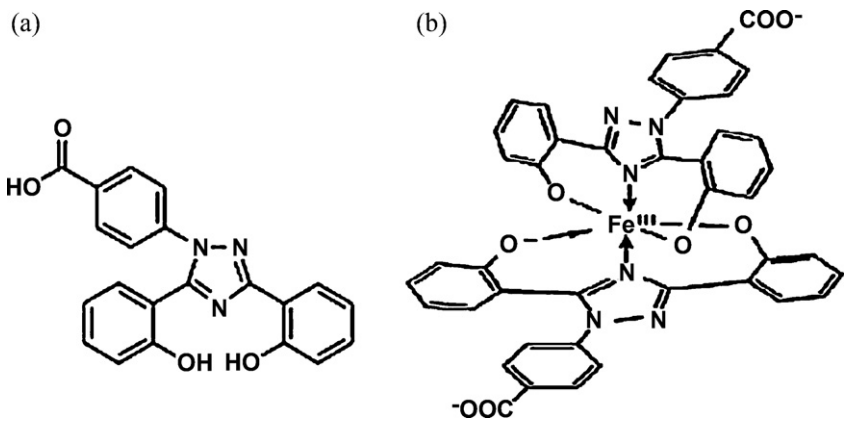

Fig. 1. (a) Molecular structure of deferasirox and (b) function of deferasirox.

particle size. The morphology and size distribution of the precipitated material is related to pre-expansion and expansion conditions, extraction parameters, spray distance and nozzle design (Hirunsit et al., 2005). Carbon dioxide is commonly used as a supercritical fluid because it is non-toxic, non-flammable, and cheap. It also has a low critical temperature and pressure (T_c = 31.1 °C and P_c = 73.8 bar) that allow for low temperature processing. From a pharmaceutical point of view, supercritical carbon dioxide has several advantages, including being solvent-free, and being able to be used in a single-stage process and at moderate processing temperatures. Hereditary hemochromatosis (HH) is an autosomal recessive disorder characterized by progressive iron overload through increased intestinal absorption. Phlebotomy, the preferred treatment, can prevent or reverse some complications of iron overload, such as hepatic damage; however, compliance is variable and some patients are poor candidates because of underlying medical disorders and/or poor venous access. Thus, if an oral iron chelator such as deferasirox (Exjade) proves to be tolerable and effective, HH patients will have an alternative treatment option. Iron-chelation therapy is essential in iron-overloaded patients. Iron chelation is a key feature in the management of transfusion dependent anaemias—such as b-thalassaemia major, b-thalassaemia intermedia, sickle-cell disease and myelodysplastic syndrome—to prevent end-organ damage and improve survival. Exjade is supplied as a tablet that is dispersed in water or juice. Deferasirox (Exjade, ICL670) belongs to a novel class of tridentate iron chelators, the N-substituted bis-hydroxyphenyl triazole. Two molecules of deferasirox are needed to form a soluble complex with one Fe^{3+} ion (Fig. 1b). The active substance is a white to slightly yellow and not hygroscopic powder. It has a good permeability and it is practically insoluble in water and in acid medium, the solubility increasing with pH. Therefore, the particle size is likely to be important to the rate and possibly to the extent of absorption (Hershko et al., 2001; Nick et al., 2003; Piga et al., 2003). Poor aqueous solubility represents a major hurdle in achieving adequate oral bioavailability for a large percentage of drug compounds in drug development nowadays. Nanosizing refers to the reduction of the active pharmaceutical ingredient (API) particle size down to the sub-micron range, with the final particle size typically being 100–200 nm. The reduction of particle size leads to a significant increase in the dissolution rate of the API, which in turn can lead to substantial increases in bioavailability (Noyes and Whitney, 1897). Several authors have reviewed the applications of RESS on the preparation of fine and ultra fine particles. Formations of anthracene fine particles have been evaluated by Nagahama and Liu in 1997. Kröber et al. in 2000 reported an investigation of RESS for synthesis of small organic particle. In this research, deferasirox was used as a model drug and the experiments were carried out to investigate the effect of extraction temperature (308–318 K) and pressure (14–20 MPa), effective nozzle diameter (500–1200 μm) without and with cosolvents on the size and morphology of the precipitated deferasirox particles (see Fig. 1).

2. Materials and methods

2.1. RESS set-up

The RESS pilot plant is shown in Fig. 2. At first, the gaseous CO_2 from a cylinder capsule was passed through a filter and then entered into a refrigerator to make liquid CO_2.The liquid CO_2 was then pumped by a reciprocating high pressure pump into a surge tank. The surge tank dampened the pressure fluctuations produced by the operation of the pump. At the outlet of the surge tank a bourdon gauge in the range of 0–250 bar was placed. The pressurized CO_2 then entered into an extraction vessel. It should be noted that the surge tank and the extraction vessel are surrounded by a regulating hot water jacket. The basket which is packed by sample and glass wool was placed into an extraction vessel. For each condition the extractor vessel was held for 2 h to ensure equilibrium has been obtained. The equilibrated solution was then expanded by a preheated fine needle valve into a nozzle. The precipitated deferasirox particles were collected on the stub and analyzed by a SEM to monitor the particle size and its morphology. A new type of nozzle (Fig. 3) was designed and fabricated to achieve ultrafine nanosize particles.

2.2. Material

The solute used during this study, deferasirox, was prepared from Pharmaceutical Arasto Company and carbon dioxide (99.9% < purity) was purchased from Abughadareh Gas Chemical Company.

2.3. Particle characterization

Precipitated deferasirox particles were analyzed by scanning electron microscopy (SEM) (S360-CAMBRIDGE). Before the SEM analysis, both the processed and the original samples must be coated by a sputter-coater (SC-7640-Polaron) with Pd–Pt under the presence of argon (99.9% < purity) at the room temperature for a period of 100 s under an accelerating voltage of 20 kV. The mean particle size was calculated by a Sigma Scan Pro Image Analyzer Software.