International Journal of Pharmaceutics 433 (2012) 149–156

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

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

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

Iman Asghari*, Feridun Esmaeilzadeh

School of Chemical and Petroleum Engineering, Shiraz University, Shiraz, Iran

ARTICLE INFO

Article history:
Received 4 November 2011
Received in revised form 1 May 2012
Accepted 3 May 2012
Available online 11 May 2012

Keywords:
Nanoparticles
Iron chelator
Deferasirox
RESS process
SC-CO_2
Taguchi

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

* Corresponding author.
E-mail address: Asghari.iman@gmail.com (I. Asghari).

0378-5173/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ijpharm.2012.05.005

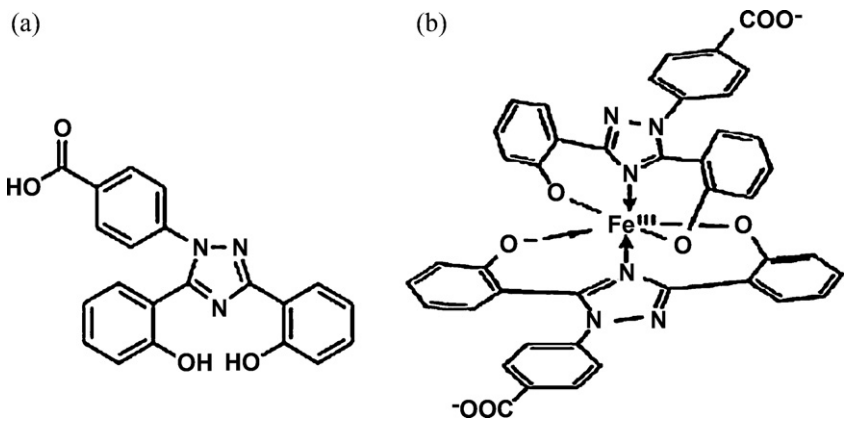

Fig. 1. (a) Molecular structure of deferasirox and (b) function of deferasirox.

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.

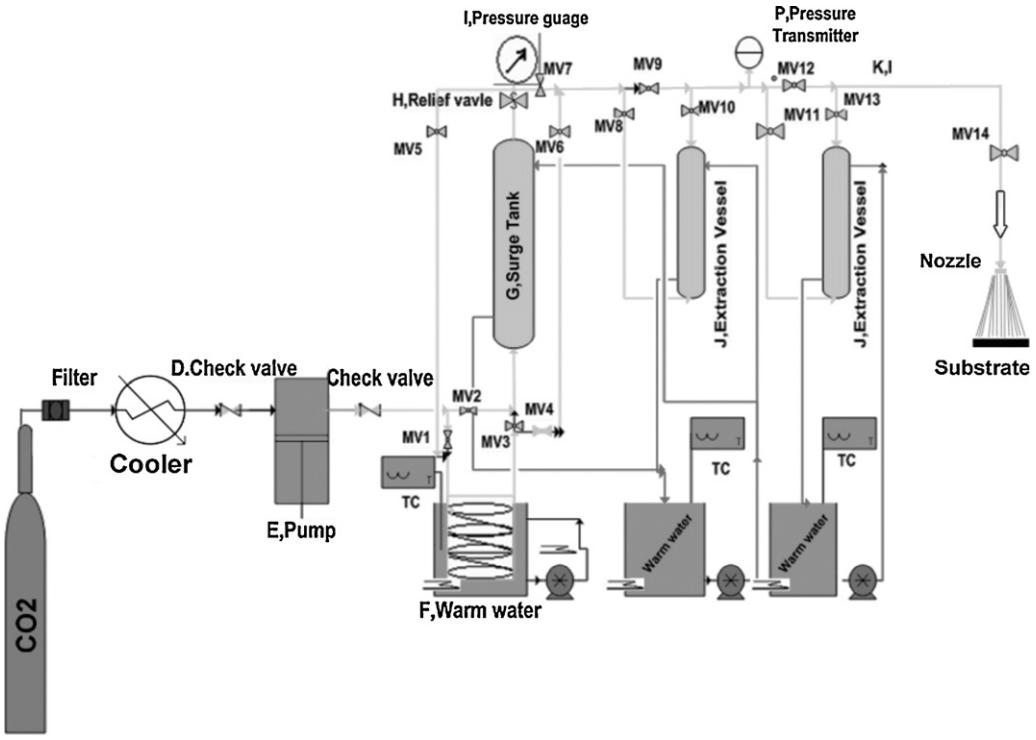

Fig. 2. Schematic diagram of RESS apparatus.

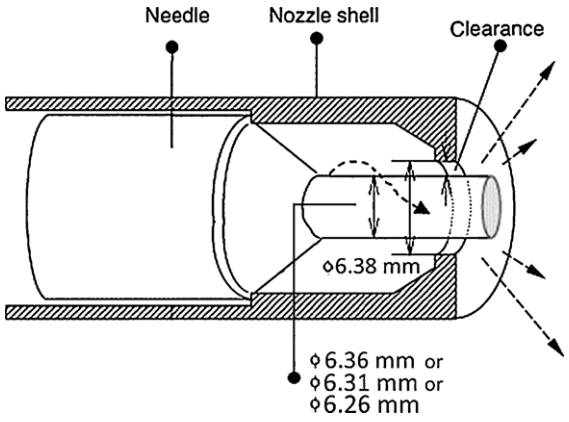

Fig. 3. Nozzle configuration.

2.4. XRD analysis

Verification for the crystal structures is done through XRD. The micronized deferasirox, forming a weighted dispersion on a glass slide, was evaluated using an X-ray powder diffractometer (Bruker, D8 ADVANCED, Germany). The sample was irradiated using a Cu target tube, and exposed to all lines. A monochromator was used to select the K_1 line ($\lambda = 1.54056$). The scanning angle ranged from 5° to 100° of the diffraction angle (2θ), and the counting time used was 1 s/step in steps of $2\theta = 0.05°$. The scanning rate used was 3°/min. The excitation current used was 40 mA and the excitation voltage used was 30 kV.

3. Results and discussion

In the present study, the influences of RESS parameters such as extraction temperature (308–318 K), extraction pressure (140–200 bar), effective nozzle diameter (500–1200 μm) with and without cosolvent were investigated on the mean particle size of the micronized deferasirox particles which are expressed below. In addition, the Taguchi method was used to arrange the experimental conditions of micronization of deferasirox particles based on L-9 array.

3.1. Design of experiments (DOE) and the Taguchi approach

There are many ways to design a test, but the most frequently used approach is a full factorial experiment. However, for full factorial experiments, there are 2^f possible combinations that must be tested (f = the number of factors each at two levels). Therefore, it is very time-consuming when there are many factors (Ross, 1989). In order to minimize the number of tests required, fractional factorial experiments (FFEs) were developed. FFEs use only a portion of the total possible combinations to estimate the effects of main factors and the effects of some of the interactions. Taguchi developed a family of FFE matrices which could be utilized in various situations. These matrices reduce the experimental number but still obtain reasonably rich information. The conclusions can also be associated with statistical level of confidence (Cox and Reid, 2000; Peace, 1993; Ryan, 1988).

Taguchi methods have been widely used to optimize the reaction variables by formulating a minimum number of experiments. This approach helps to identify the influence of individual factors and establish the relationship between variables and operational conditions (Dasu et al., 2003).

A Taguchi orthogonal array design was applied to identify the optimal conditions and to select the parameters having the most principal influence on the precipitated particle size of deferasirox. In this paper Taguchi's L-9 orthogonal array table was used to carry out RESS experiments by choosing 4 parameters at 3 levels (Table 1). Table 2 shows the structure of Taguchi's orthogonal array

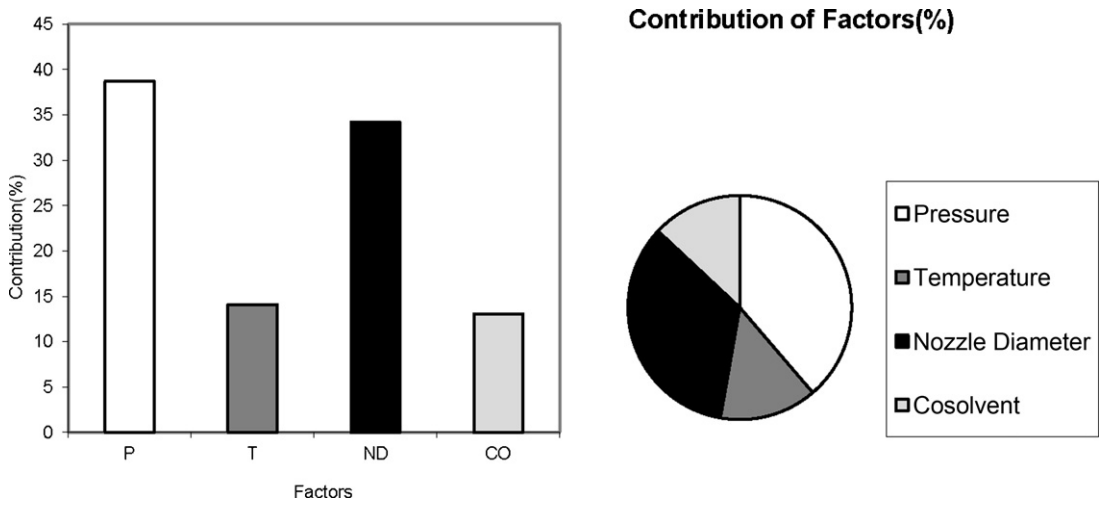

Fig. 4. The contribution of factors.

Table 1
Parameters and their levels.

Parameters	Level 1	Level 2	Level 3
Pressure (bar)	140	170	200
Temperature (°C)	35	40	45
Nozzle diameter (μm)	500	900	1200
Cosolvent	–	Sol1	Sol2

Sol1 = acetone, Sol2 = isopropanol.

Table 2
Taguchi L9 orthogonal array for deferasirox precipitated particles.

Run	*P*	*T*	ND	CO	Average size (μm)
1	140	35	500	–	1.5
2	140	40	900	Sol1	0.82
3	140	45	1200	Sol2	0.65
4	170	35	900	Sol2	0.73
5	170	40	1200	–	0.30
6	170	45	500	Sol1	0.55
7	200	35	1200	Sol1	0.39
8	200	40	500	Sol2	0.63
9	200	45	900	–	0.80

Sol1 = acetone, Sol2 = isopropanol.

Table 3
Contribution of each factor.

Factor	Percent (%)
P	38.704
T	14.066
ND	34.175
CO	13.043

design and the results of measurement by Sigma scan Pro (Image analyzer software). Table 3 and Fig. 4 show the contribution of each factor based on Qualitek-4 software. For Taguchi design the statistical software namely Qualitek-4 was applied. The average particle size versus levels for all 4 factors is listed in Table 4.

Table 4
Levels versus average particle size for all 4 factors.

Factor level	Pressure	Temperature	Nozzle diameter	Cosolvent
Level 1	0.989	0.873	0.893	0.866
Level 2	0.526	0.583	0.783	0.586
Level 3	0.606	0.666	0.446	0.670

3.2. Interpretation of SEM images

The SEM images of original and precipitated deferasirox are given in Fig. 5. As can be seen in Fig. 5, great reduction in the size of the precipitated particles of deferasirox compared with the original particles is clear. Moreover, a slight change into spherical form was observed for the precipitated particles of deferasirox, while the original particles were irregular in shape.

The results based on Qualitek-4 Software which were obtained by mean particle size via Sigma Scan Pro Image analyzar Software show that the optimum pressure, temperature, nozzle diameter and cosolvent are 170 bar, 313 K, 1200 μm and acetone as cosolvent respectively (Fig. 7). It should be mentioned that in all 9 runs the deferesirox particles were precipitated by 1 cm spraying distance. In other words, since the spraying distance could not cause a significant change in the particle size and morphology of deferasirox, it was considered as a constant parameter which was 1 cm from the end of the nozzle.

Spherical deferasirox particles were precipitated in runs 5, 6, and 7. On the contrary, agglomerated deferasirox was precipitated in runs 1, 2, and 9. Fig. 6 illustrates the SEM images of these conditions (a and b: spherical; c and d: aggelomorated particle). Fig. 7 shows the precipitated deferasirox particles via RESS process at optimum condition.

3.3. Effect of extraction pressure

Generally, the variation of the extraction pressure brings about a change in the concentration of deferasirox. The pressure studied here varies from 140 to 200 bar. An increase in extraction pressure from 140 bar to 170 is observed to induce decrease in the average particle size. Similar results were reported by Hezave and Esmaeilzadeh (2010). The reason for this is that an increase in the solute solubility results in higher supersaturations in the fluid upon expansion. According to the classical theory of nucleation, higher supersaturation causes higher nucleation rate and the particle volume is inversely proportional to the nucleation rate. Our above results appear to agree with simple theoretical predictions. Similar results have also been reported for other organic solutes. But the finest average particle size and the smallest particle size distribution are observed at 170 bar. In other words, a further increase of extraction pressure till 200 bar yields a marked increase of the particle size, which may suggest a decoupling of the two processes of nucleation and growth. Perhaps at high deferasirox concentrations (i.e., high extraction pressure), the particle growth may be

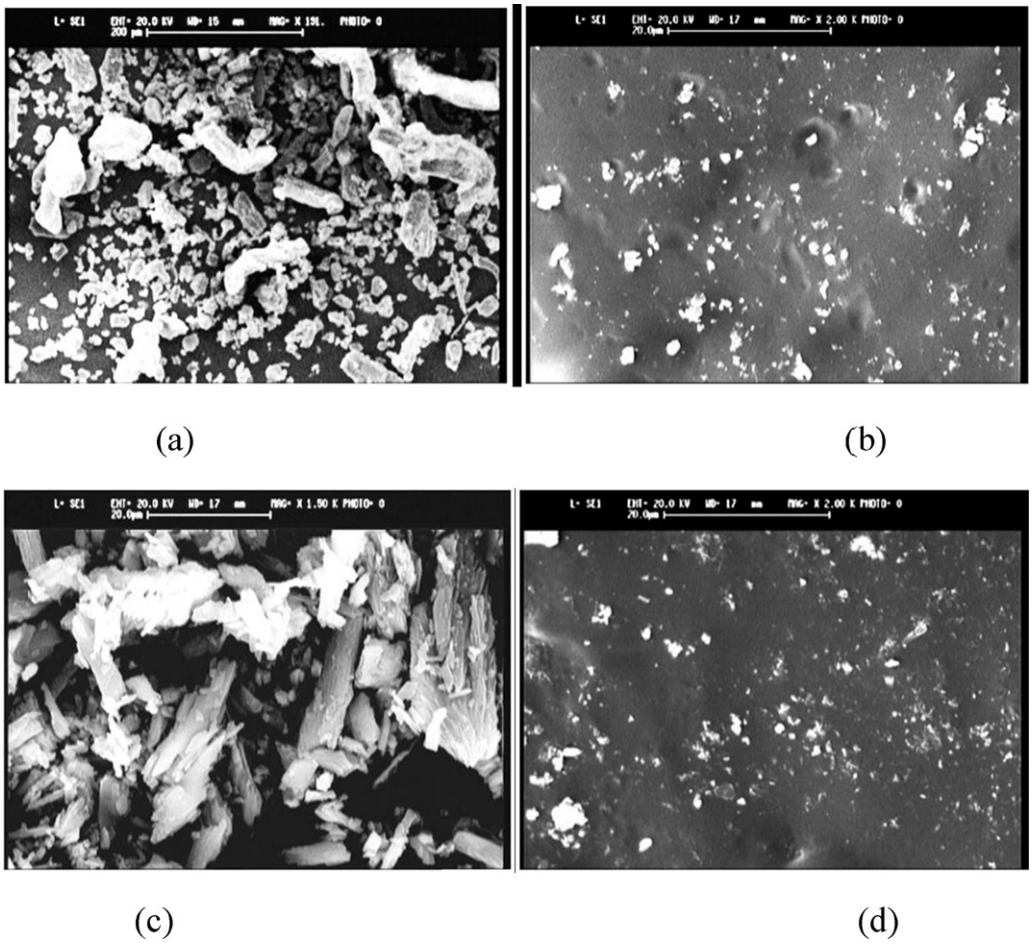

Fig. 5. The SEM images of (a and c) unprocessed deferasirox particles and (b and d) processed deferasirox.

dominant or a particle may include several nuclei during the growth process. Therefore, large particles seem to be readily produced and a broad particle size distribution may be obtained. Similar results have been reported for formation of aspirin by Huang et al. (2005). Fig. 8 illustrates the average particle size of precipitated deferasirox versus pressure levels.

3.4. Effect of extraction temperature

The extraction temperature for deferasirox in this study ranges from 308 to 318 K. Increasing the extraction temperature leads to a decrease in the density of CO_2 and a concurrent increase in the solute's vapour pressure. The decrease of the solvent density causes a decrease of the solvent strength. On the other hand, a concurrent increase in the solute's vapour pressure leads to an increase in the deferasirox solubility. An increase of extraction temperature from 308 to 313 K leads to the increase of the supersaturation and nucleation rate as a result of increased solute concentration. The increase of nucleation rate leads to a reduction in the deferasirox particle growth time, and consequently the smaller particle is obtained. However, continuously increasing temperature (at 318 K) caused an increase in the average particle size because a rise in the temperature leads to an increase in the deferasirox concentration. During the expansion, high deferasirox concentration brings about the increase of the particle size, as a consequence of coagulation among particles. Similar results have also been reported in the literature (Huang et al., 2004). Fig. 9 illustrates the average particle size of precipitated deferasirox versus temperature levels.

3.5. Effect of nozzle diameter

It was expected that the nozzle diameter and its dimension in the RESS process would highly affect the particle formation. In this study, the effect of the effective nozzle diameter was investigated (500–1200 μm). The results of the experiments show the average particles sizes can be reduced by lowering the diameter of nozzle. In other words, the particle size increases with increasing the nozzle diameter. Several studies have been reported in which the change of the nozzle diameter can play an important role in processing materials (Tom et al., 1994). Fig. 10 illustrates the average particle size of precipitated deferasirox versus nozzle diameter levels.

3.6. Effect of cosolvent

The results from the SEM images and analysis of variance (ANOVA) indicate that Cosolvent-saturated $SCCO_2$ can solubilize higher amount of deferasirox, at the given pressure and temperature. The large solubilities are attributed to the resultant chemical interaction forces (hydrogen bonding) and an increase in dispersion forces in these systems upon the addition of co-solvents. The higher solubility enhancement is achieved with the addition of acetone as compared to that with the addition of an equal amount (by weight) of isopropylalcohol to carbon dioxide. Deferasirox solubility is low in SC-CO_2, because CO_2 is a nonpolar compound.

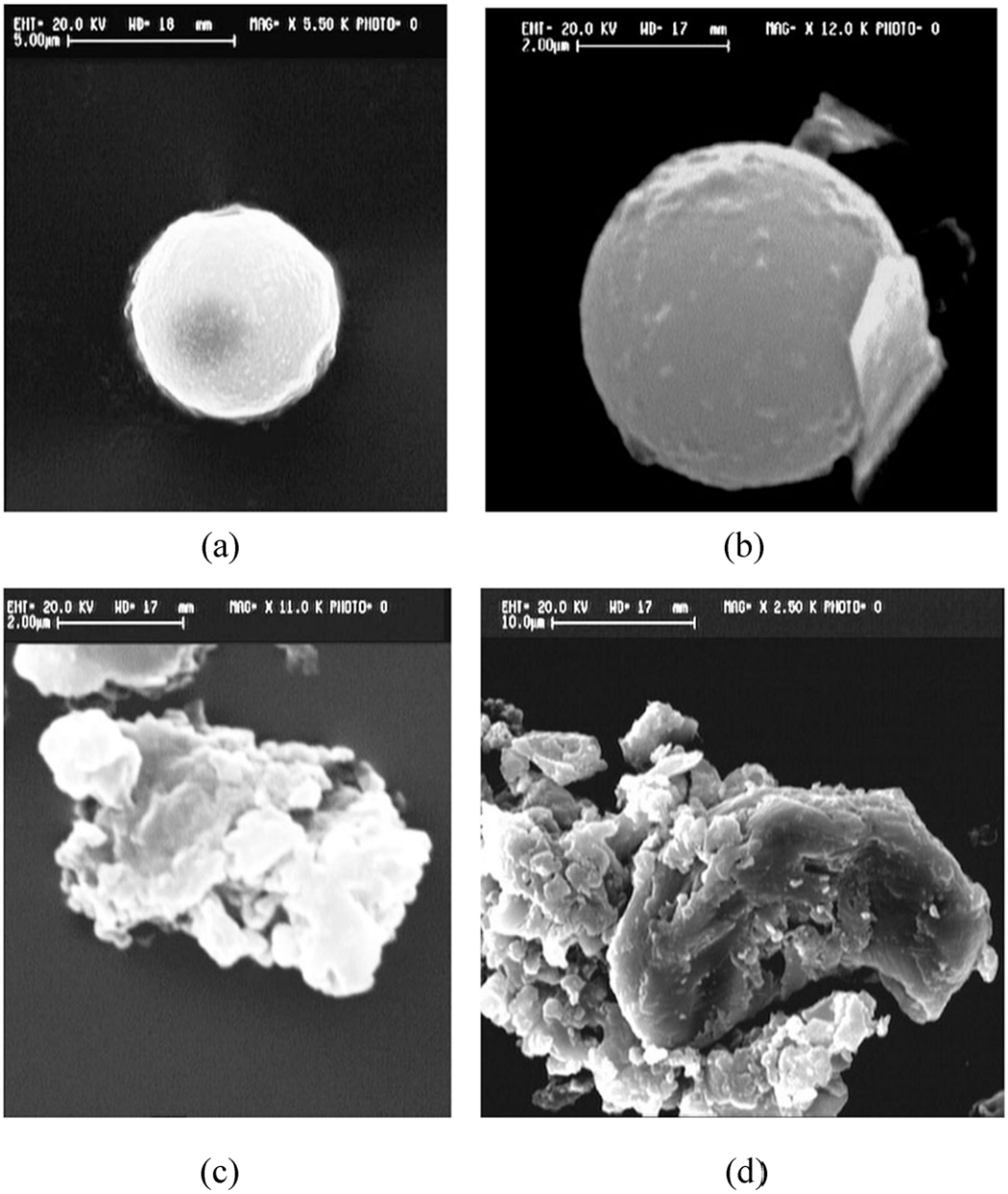

Fig. 6. The SEM images of (a and b) spherical deferasirox particles precipitated via RESS and (c and d) agglemorated deferasirox particles precipitated via RESS.

Therefore, a polar co-solvent such as isopropylalcohol and acetone can be used together with CO_2 to increase the solvating power of CO_2. Similar results have been reported by Yildiz et al. (2007). In other words, the average particle size of deferasirox is decreased in the presence of cosolvent. However, the type of solvent which is used as a cosolvent is related to the chemistry of solute. In this research because of structure of deferasirox, acetone is most effective, but isopropylalcohol as a polar protic solvent is useful as well. In the literature the effect of cosolvent menthol on the 2-aminobenzoic acid (ABA) solubility was investigated by Thakur and Gupta (2006a,b). ABA solubility was enhanced by 118-fold giving solubility as high as 6600 μmol/mol which can be attributed to a high polarity of supercritical CO_2–menthol solution. Polar solvents including acetone and methanol have been used earlier for ABA solubility enhancement (Dobbs et al., 1987; Dobbs and Johnston, 1987). Fig. 11 illustrates the average particle size of precipitated deferasirox versus cosolvent levels.

3.7. XRD analysis

In this study, the XRD patterns for the processed and unprocessed deferasirox particles are given in Fig. 12. The XRD analysis patterns for Fig. 12a and b is nearly at the same angles and the intensity of the peaks is lower for the RESS-SC processed particles of deferasirox. In other words, both the non-micronized and the micronized deferasirox powders showed approximately similar X-ray diffraction patterns (Fig. 12). This implies that the crystalline form of the micronized deferasirox was approximately unchanged by the RESS process which is consistent with those reported in the literature (Kayrak et al., 2003b; Turk et al., 2002; Rehman et al., 2001). However, the intensity of the X-ray diffraction peaks was observed to decrease after RESS process. Finally, the XRD patterns indicated a reduction in the crystallinity of the deferasirox after processing with the RESS.

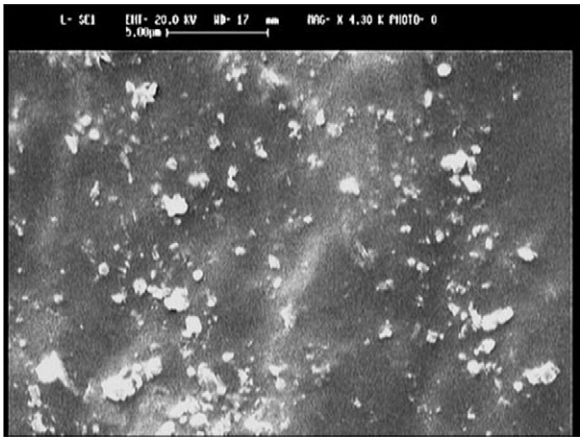

Fig. 7. The SEM image of deferasirox at 170 bar, 313 K, 1200 μm with acetone.

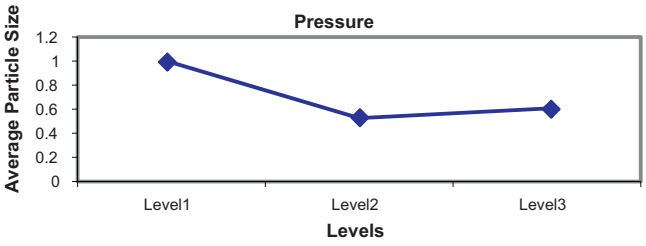

Fig. 8. The average particles size versus pressure levels.

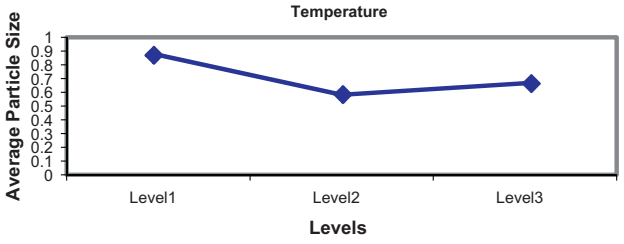

Fig. 9. The average particles size versus temperature levels.

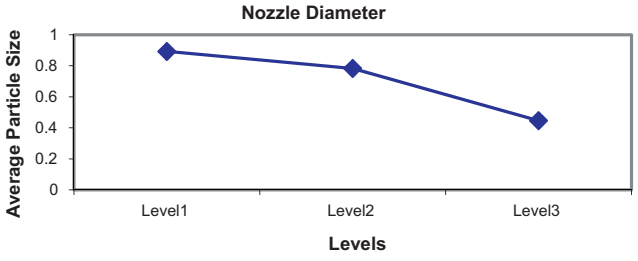

Fig. 10. The average particles size versus nozzle diameter levels.

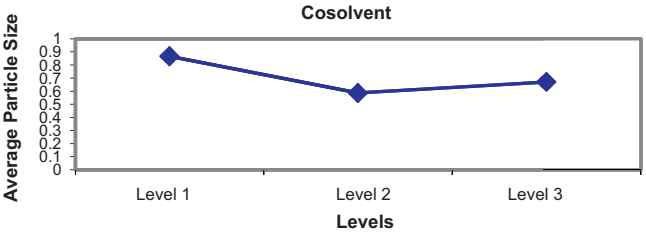

Fig. 11. The average particles size versus cosolvent levels.

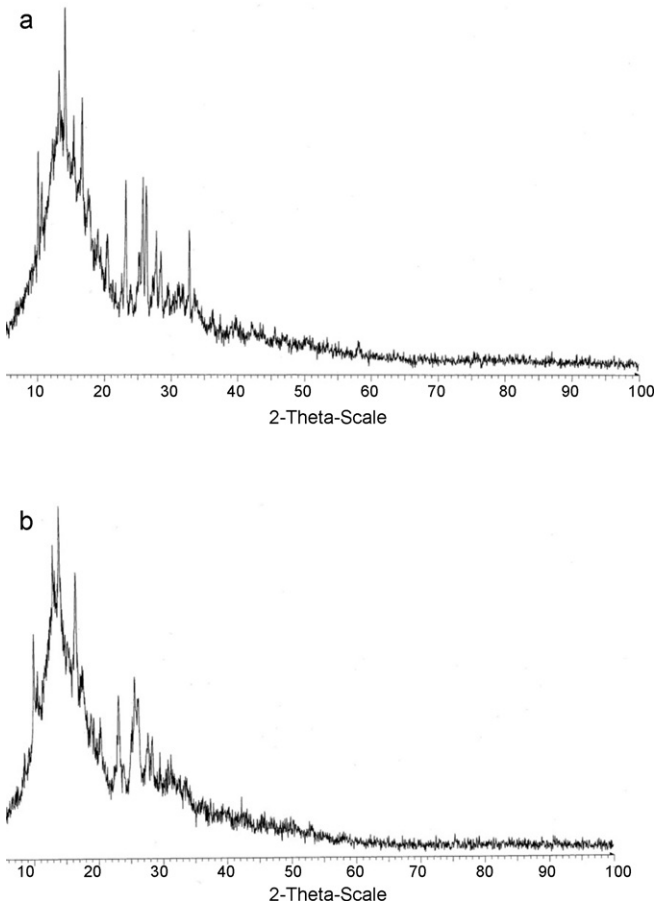

Fig. 12. XRD diagram of (a) unprocessed deferasirox and (b) processed deferasirox by RESS.

4. Conclusions

The rapid expansion of supercritical solutions (RESS) was successfully used to produce deferasirox submicron particles. Deferasirox was micronized and a great size reduction of deferasirox particles in comparison with the original one was observed. The precipitated particles of deferasirox were in the range of 50 nm–5 μm while the size of unprocessed defererasirox particles was between (5–500 μm). The obtained results indicate the influential role of extraction pressure and nozzle diameter in forming finer particles of deferasirox. In addition, the optimum pressure, temperature, effective nozzle diameter and cosolvent for micronization of deferasirox particles are 170 bar, 313 K, 1200 μm and using acetone as cosolvent, respectively which leads to precipitation of deferasirox particles by the size of 0.175 μm.

Acknowledgements

The authors are grateful to the Shiraz University for supporting this research. The authors would like to thank Arasto Pharmaceutical Chemicals Inc. for their cooperation. The authors would also like to thank Dr Seyyed Mohammad Mousavi from Biotechnology Group, Chemical Engineering department of Tarbiat Modares University from Tehran, Iran, Dr. Seyyed Shahabodin Ayatollahi and Dr. Mahmood Hoormand for their collaboration.

References

Cox, D.R., Reid, N., 2000. The Theory of the Design of Experiments. Chapman & Hall/CRC.

Dasu, V.V., Panda, T., Chidambaram, M., 2003. Determination of significant parameters for improved griseofulvin production in a batch bioreactor by Taguchi's method. Process Biochem. 38, 877–880.
Dobbs, J.M., Wong, J.M., Lahiere, R.J., Johnston, K.P., 1987. Modification of supercritical fluid phase behavior using polar cosolvents. Ind. Eng. Chem. Res. 26, 56–65.
Dobbs, J.M., Johnston, K.P., 1987. Selectivities in pure and mixed supercritical fluid solvents. Ind. Eng. Chem. Res. 26, 1476–1482.
Del Valle, E.M.M., Galan, M.A., 2005. Supercritical fluid technique for particle engineering: drug delivery applications. Rev. Chem. Eng. 21, 33–69.
Lipinski, C.A., 2002. Poor aqueous solubility—an industry wide problem in drug discovery. Am. Pharm. Rev. 5, 82–85.
Fages, J., Lochard, H., Letourneau, J.J., Sauceau, M., Rodier, E., 2004. Particle generation for pharmaceutical applications using supercritical fluid technology. Powder Technol. 141, 219–226.
Hezave, A.Z., Esmaeilzadeh, F., 2010. Micronization of drug particles via RESS process. J. Supercrit. Fluids 52, 84–98.
Huang, Z., Sun, G.B., Chiew, Y.C., Kawi, S., 2005. Formation of ultra fine aspirin particles through rapid expansion of supercritical solutions (RESS). Powder Technol. 160, 127–134.
Huang, Z., Lu, W.D., Kawi, S., Chiew, Y.C., 2004. J. Chem. Eng. Data 49, 1323–1327.
Hirunsit, P., Huang, Z., Srinophakun, T., Charoenchaitrakool, M., Kawi, S., 2005. Particle formation of ibuprofen supercritical CO_2 system from rapid expansion of supercritical solutions (RESS): a mathematical model. Powder Technol. 154, 83–94.
Hershko, C., Konijn, A.M., Nick, H.P., Breuer, W., Cabantchik, Z.I., Link, G., 2001. ICL670A: a new synthetic oral chelator: evaluation in hypertransfused rats with selective radioiron probes of hepatocellular and reticuloendothelial iron stores and in iron-loaded rat heart cells in culture. Blood 97, 1115–1122.
Jung, J., Perrut, M., 2001. Particle design using supercritical fluids: literature and patent survey. J Supercrit. Fluids 20, 179–219.
Kayser, O., Lemke, A., Hernandez-Trejo, N., 2005. The impact of nanobiotechnology on the development of new drug delivery systems. Curr. Pharm. Biotechnol. 6, 3–5.
Kayrak, D., Akman, U., Hortac su, O., 2003a. Micronization of ibuprofen by RESS. J. Supercrit. Fluids 26, 17–31.
Kayrak, D., Akman, U., Hortacsu, O., 2003b. J. Supercrit. Fluids 26, 17.
Kröber, H., Teipel, U., Krause, H., 2000. The formation of small organic particles using supercritical fluids. In: Proceedings of the 5th International Symposium on Supercritical Fluids, 8–12 April, Atlanta, USA.
Leuner, C., Dressman, J., 2000. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 50, 47–60.
Muller, R.H., Jacobs, C., Kayser, O., 2001. Nanosuspensions as particulate drug formulations in therapy rationale for development and what we can expect for the future. Adv. Drug Deliv. Rev. 47, 3–19.
Mainardes, R.M., Silva, L.P., 2004. Drug delivery systems: past, present and future. Curr. Drug Targets 5, 449–455.
Nick, H., Acklin, P., Lattmann, R., Buehlmayer, P., Hauffe, S., Schupp, J., Alberti, D., 2003. Development of tridentates iron chelators: from desferrithiocin to ICL670. Curr. Med. Chem. 10, 1065–1076.
Noyes, A., Whitney, W., 1897. The rate of solution of solid substances in their own solutions. J. Am. Chem. Soc. 19, 930–934.
Nagahama, K., Liu, G.T., 1997. Supercritical fluid crystallization of solid solution. In: The 4th International Symposium on Supercritical Fluids, 11–14 May, Sendai, Japan, pp. 43–46.
Peace, G.S., 1993. Taguchi Methods: A Hands-on Approach. Addison-Wesley Publishing Company, Inc., Massachusetts.
Piga, A., Gaglioti, C., Fogliacco, E., Tricta, F., 2003. Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis. Haematologica 88, 489–496.
Rabinow, B.E., 2004. Nanosuspensions in drug delivery. Nat. Rev. Drug Discov. 3, 785–796.
Rehman, M., Shekunov, B.Y., York, P., Colthorpe, P., 2001. J. Pharm. Sci. 90, 1570.
Ross, R.J., 1989. Taguchi Techniques for Quality Engineering. McGraw-Hill, New York.
Ryan, N.E., 1988. Taguchi Methods and QFD: Hows and Whys for Management. ASI, Press, Michigan.
Stanton, L.A., Dehghani, F., Foster, N.R., 2002. Improving drug delivery using polymers and supercritical fluid technology. Aust. J. Chem. 55, 443–447.
Thakur, R., Gupta, R.B., 2006a. Rapid expansion of supercritical solution with solid cosolvent (RESS-SC) process: formation of 2-aminobenzoic acid nanoparticle. J. Supercrit. Fluids 37, 307–315.
Thakur, R., Gupta, R.B., 2006b. Formation of phenytoin nanoparticles using rapid expansion of supercritical solution with solid cosolvent (RESS-SC) process. Int. J. Pharm. 308, 190–199.
Tom, J.W., Debenedetti, P.G., Jerome, R.J., 1994. J. Supercrit. Fluids 7, 9.
Turk, M., Hils, P., Helfgen, B., Schaber, K., Martin, H.J., Wahl, M.A., 2002. J. Supercrit. Fluids 22, 75–84.
Yildiz, N., Tuna, S., Doker, O., Calimli, A., 2007. Micronization of salicylic acid and taxol (paclitaxel) by rapid expansion of supercritical fluids (RESS). J. Supercrit. Fluids 41, 440–451.