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Preparation of Deferasirox in nano-scale by ultrasonic irradiation and optimization the amount and reaction time parameters

ABSTRACT

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This work reports a facile sonochemical route in the synthesis of nano particle of deferasirox for the first time. One application of nanotechnology is in improvement of available treatments for various diseases. Deferasirox (ICL670 or Exjade) is a tridentate chelating agent for removing transfusion overload iron in thalassemia patients. In the present work, deferasirox was prepared in nano size by using of ultrasound waves. The effects of amount and reaction time on the size of deferasirox were investigated. These parameters were optimized at various amounts and different reaction times. Fourier transform infrared spectroscopy (FT-IR) and X-ray diffraction (XRD) studies show that the deferasirox in nature structure does not change during the reaction. The results show that the finest particle is related to the following conditions: 45min, time reaction and 0.1g, amount of deferasirox. Therefore, the ultrasonic bath method has a fundamental role in the preparation of deferasirox in nano scale. This method is simple, relatively fast and low cost.

Keywords: *Nano drug; Deferasirox; Iron chelators; Bath ultrasound; Fast synthesis; High absorption.*

INTRODUCTION

In recent years, a great deal of attention has been paid to the drug formulation and delivery systems for issues such as targeting and controlled release. In fact, the poor water solubility of many drugs is a serious limitation in drug development. Poorly water-soluble drugs can lead to limited dissolution rate as a result, decreasing of absorption of orally administered drugs. The poorly water-soluble therapeutic drug concentration range would be enhanced until to reach the blood drug concentration. This dose escalation causes toxicity in the gastrointestinal tract upon oral administration. The manufacturing cost increases because a large amount of active pharmaceutical ingredient might be consumed to manufacture the drug product.

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One of the effective and broadly applicable approaches of poorly water-soluble drugs is particle size reduction to nano-meter range. The nanosizing of poorly water-soluble drugs could lead to an increase of the surface area which could provide an enhanced dissolution rate, easier absorption for drugs and the reduction of unwanted side effects [1, 2].

Nanomaterial have a complex relationship between a physicochemical properties (e.g., size, charge and surface properties), and its interaction within a biological system. Small changes in size can lead to radically different interactions with living systems. These interactions then determine the biocompatibility, stability, biological performance and side effects of the nanomaterial [3].

Researchers have proposed several synthesis approaches for preparation of nanomaterials. Sonochemistry is one of the simple ways for the synthesis of nanoparticles in low temperatures. Materials synthesized by sonochemistry are highly active due to their particles size and high surface area [4-7].

Deferasirox, 4-[3, 5-Bis (2-hydroxyphenyl)-1H-1, 2, 4-triazol-1-yl]-benzoic acid or ICL670 (Figure 1) is a new drug to remove toxic metal ions from biological systems [8-10]. Deferasirox is used to remove chronic iron overload in the people who have received a large number of blood transfusions such as β -thalassemia and other chronic anemias [11, 12]. The half-life of deferasirox is between 8 to 16 hours allowing once a day dosing. Deferasirox is a white to slightly yellow powder. Its molecular formula is $C_{21}H_{15}N_3O_4$ and its molecular weight is 373.4 g/mol. Deferasirox has low molecular weight and high lipophilicity allows the drug to be absorbed through the mouth, and bond strongly to the serum proteins. It is a tridentate chelator and binds to iron in a 2:1 ratio. Deferasirox makes stable complex with Fe (III) ion and two distinct atoms donation (Nitrogen and Oxygen) arises from one triazole nitrogen and two phenolate oxygen donors [13-16].

The aim of this research was to prepare the nano particles of deferasirox and to investigate the effect of deferasirox quantity and reaction time on the size of precipitated deferasirox particles.

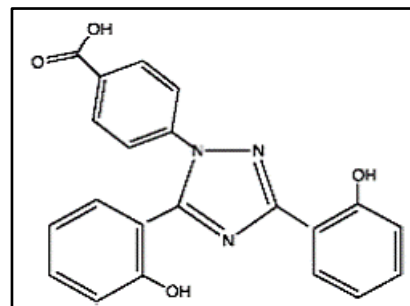


Fig.1. Molecular structure of deferasirox

EXPERIMENTAL

Materials

Deferasirox was purchased from Novartis Co. (Basel, Switzerland). Dimethyl Sulfoxide (DMSO) was prepared from Merck Co (Germany). Double distilled water was used in all parts of experiments.

Sample characterization

The nano particles were prepared by using ultrasonic irradiation (operating frequency 35 kHz, 560 W, Sonorex Digitec, Bandelin). Characterizations of the particles were analyzed by scanning electron microscopy (SEM) (S4160-Hitachi Japan). FT-IR spectrum was recorded as KBr pellets on a Bruker tensor 27 spectrometer and X-ray diffraction (XRD) technique using Cu radiation at 40 kV and 30 mA and data were collected in the range of $2\theta = 10-100^\circ$ (Advance Bruker D8).

Methods

Various amounts of pure deferasirox (0.1, 0.05 and 0.025g) were weighed and dissolved in DMSO. Hot DMSO was used as a solvent in the lowest volume. The round- bottom flask contain the sample was placed on ultrasonic bath and deionized water was added to the solution drop wise. A white precipitate in colloid form was obtained, filtrated and dried at room temperature.

The above procedure was repeated in three different times (15, 30 and 45 min). Then, precipitated deferasirox particles for 0.1g amounts of deferasirox and 45 min reaction time (Figure 2c) were analyzed by fourier transform infrared spectroscopy (FT-IR) and X-ray diffraction (XRD).

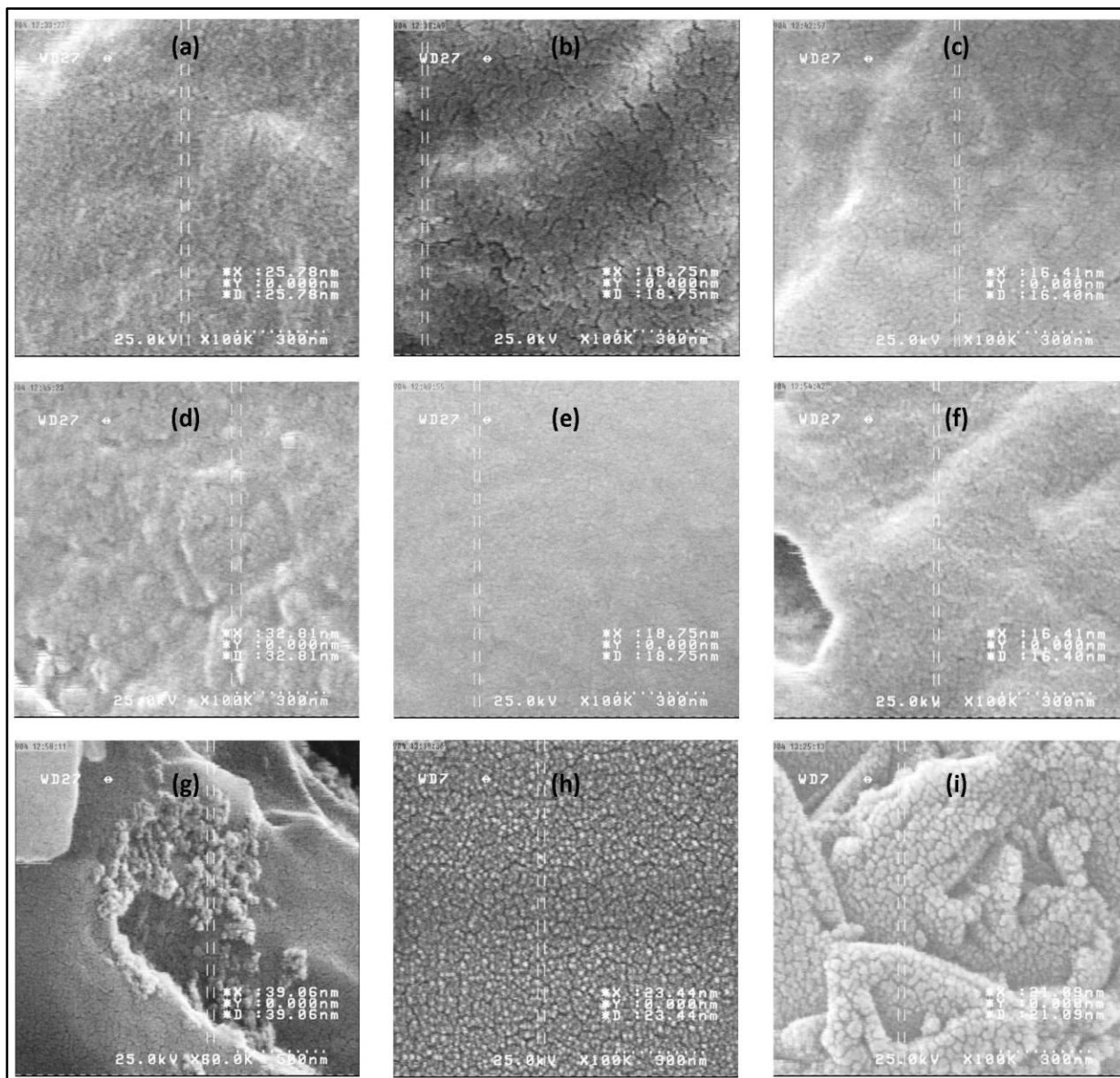


Fig. 2. SEM images of nano-particles prepared at various amounts of deferasirox and different reaction times: (a) 0.1 g, 15min, (b) 0.1g, 30min, (c) 0.1g, 45min, (d) 0.05g, 15min, (e) 0.05g, 30min, (f) 0.05g, 45min, (g) 0.025g, 15min, (h) 0.025g, 30min and (i) 0.025g, 45 min

RESULTS AND DISCUSSION

Deferasirox in different amount dissolved in DMSO. Then the solution was placed on ultrasonic bath and water was added as anti-solvent until substrate precipitated and filtrated, completely. This procedure was repeated in three different times. SEM images of nano-particles have been shown in [Figure 2 \(a, b, c\)](#) for 0.1g amounts of deferasirox with (15, 30, 45 min) reaction time,

respectively. [Figure 2 \(d, e, f\)](#) shows the particle size for 0.05g amounts of deferasirox with (15, 30, 45min) reaction time, respectively. Also, [Figure 2 \(g, h, i\)](#) shows the particle size for 0.025g amounts of deferasirox with above times.

The effects of different reaction times (15, 30 and 45 min) were investigated. The results of SEM images indicate that as the reaction time increases, the size of particles is reduced. The

average particle sizes of precipitated deferasirox versus reaction time are shown in Figure 3.

The effect of sample amount was investigated by changing the amount of deferasirox (0.1, 0.05 and 0.025g). The SEM images show that by increasing the sample amount, the size of nano particles would be smaller (Table 1). The average particle sizes of precipitated deferasirox versus the amount of deferasirox are illustrated in Figure 4.

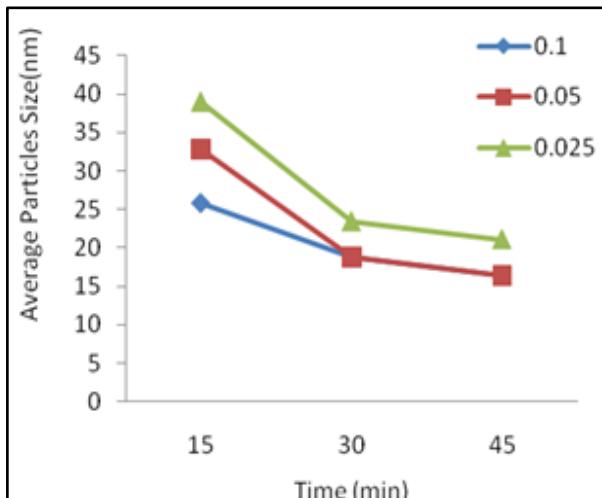


Fig. 3. The average size versus time for different amounts of deferasirox

Table 1. The particle size at different amounts of deferasirox and various reaction times

	15 min	30 min	45 min
0.1 gr	25.78 nm	18.75 nm	16.41 nm
0.05 gr	32.81 nm	18.75 nm	16.41 nm
0.025 gr	39.06 nm	23.44 nm	21.09 nm

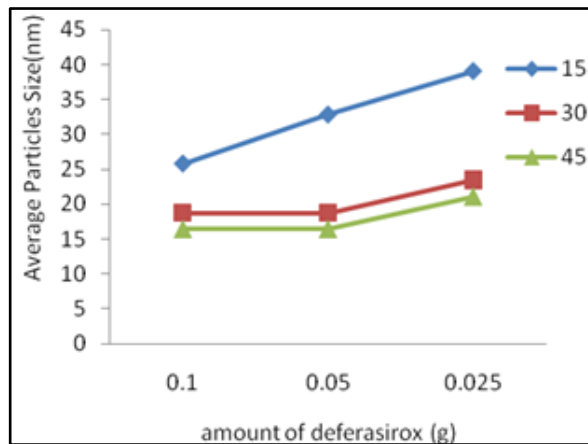


Fig. 4. The average size versus amount of deferasirox at various reaction times

The nano particles that prepared with this approach were the smallest size compared with the other researches [1]. The obtained particles of deferasirox (in presence of ultrasonic waves) were in the range of (40-16nm) while the size of unexposed deferasirox particles was in the range of (5-500 μ m). In addition the optimum reaction time and amount of sample are 45 min and 0.1g respectively. In these conditions deferasirox particles have an average size about 16.41nm. Also, some analysis (FTIR and XRD) has been done by using of this particle size precipitate.

The FTIR analyses were performed for bulk and nano form of deferasirox, the spectra were showed for bulk form of deferasirox in Figure 5a and for nano size of deferasirox in Figure 5b. The IR spectral data for both of the above cases are similar, they revealed an absorptions bonds at 3406 cm^{-1} (OH, stretching), 1680 cm^{-1} (acid, conjugated C=O stretching), 1587 cm^{-1} (aromatic, C=C stretching) and 1608 cm^{-1} (C=N stretching) [17]. These results show that the ultrasonic irradiation does not have any significant effect on the structure of deferasirox.

The XRD patterns of the bulk and nano form of deferasirox are shown in Figure 6a and Figure 6b respectively. These patterns of XRD analysis are showing, the same angle for bulk and nano form of deferasirox. Intensity of the peaks was lower for deferasirox after using sonication. Both compounds showed approximately similar X-ray diffraction patterns.

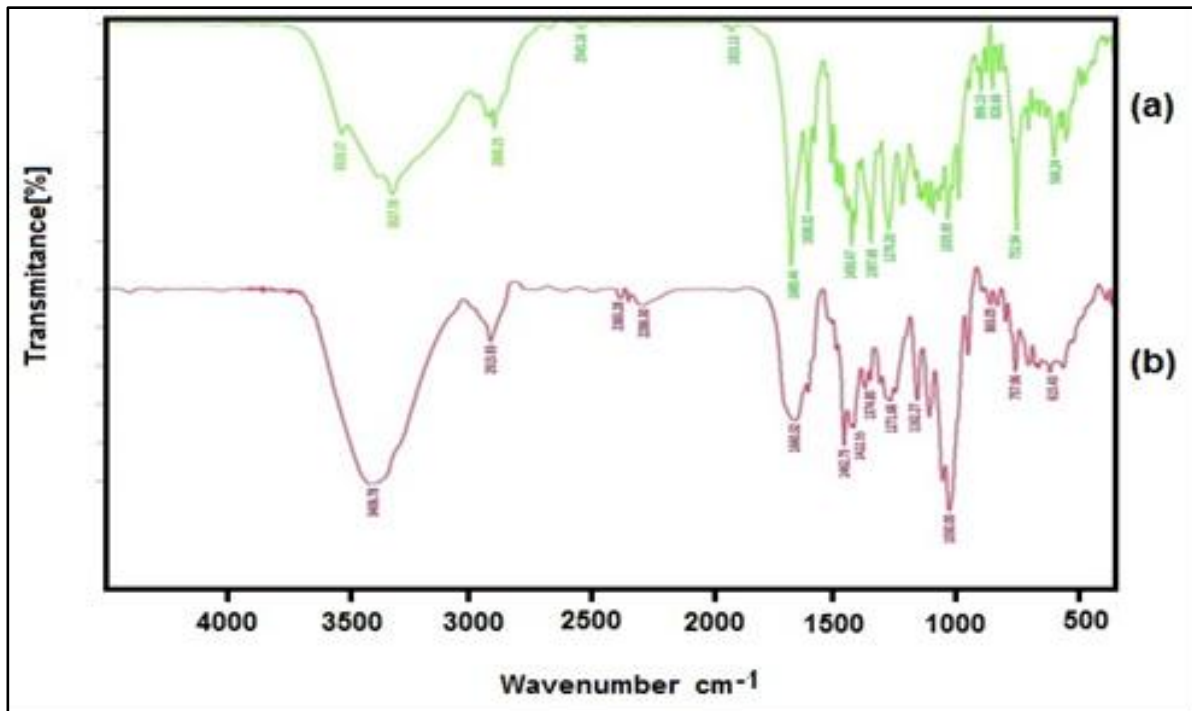


Fig. 5. FTIR spectra of deferasirox in bulk (a) and nano (b) form of deferasirox

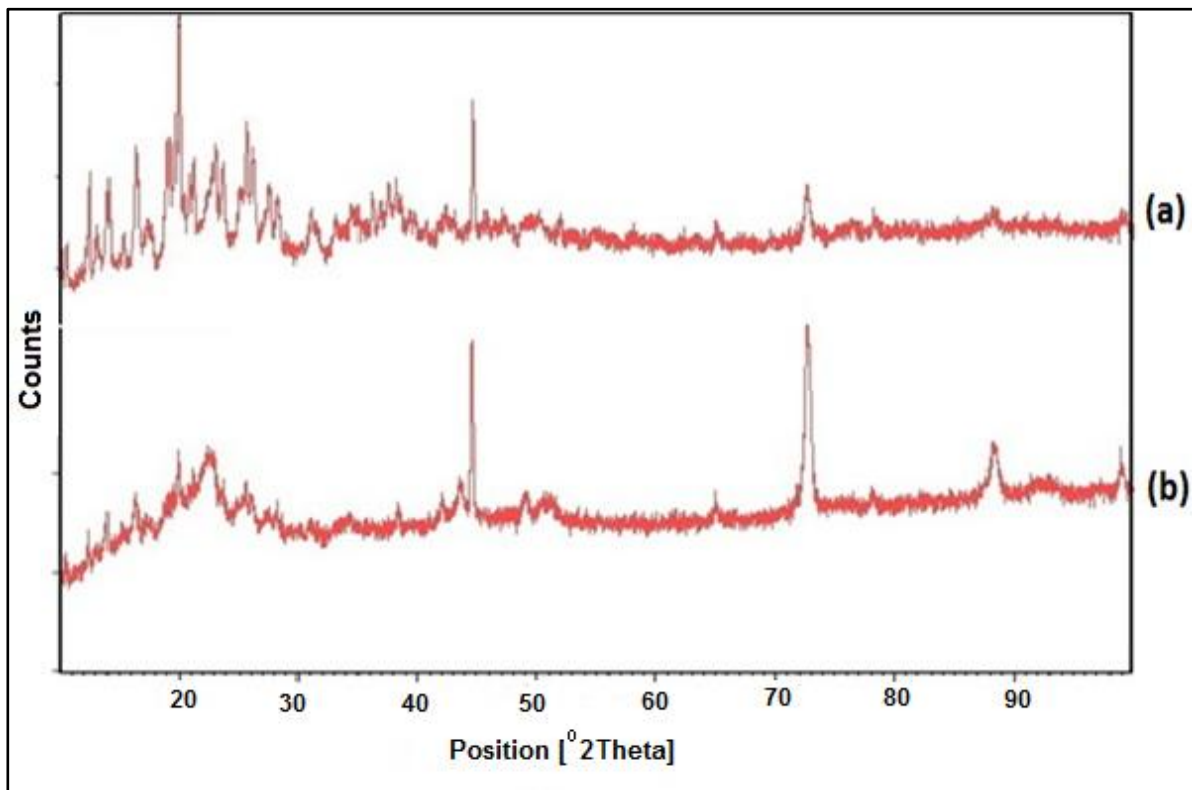


Fig. 6. X-ray diagram of deferasirox in bulk (a) and nano particle size (b)

CONCLUSIONS

Deferasirox in nano particle sizes were successfully prepared in the presence of ultrasound waves by using a bath ultrasonic irradiation. This method is a facile and fast synthesis way for the preparation of nanoparticles. The obtained particle size by this approach has smaller than nano particles that prepared by the other research methods. Different physicochemical parameters such as the reaction time and the amount of sample brought up a signification change in the size of nano particles. The obtained results indicate that the influential role of reaction time and amount of sample in forming finer particles of deferasirox. These showed that by increasing both reaction time and amount of sample, the particle size would become very fine in nano scale. By increasing the exposure time in the ultrasonic bath, the particles encounter more time with ultrasonic waves so the size of nanoparticles becomes smaller. To dissolve greater amount of deferasirox, more solvent is required. Therefore, particle aggregation decreased and the particle size would be small in the least amount of substrate.

The poor water solubility of many drugs such as deferasirox is a challenge in pharmaceutical research. Recently there have been great interests in finding the way to produce fine particles of pharmaceutical products for application in chelation therapy. Many studies have now reported the high absorption, long-term efficacy and safety of deferasirox in removing some toxic metal ions and treating iron overload in patients with β -thalassemia major [18,19]. Therefore nano sizing medicines could change the quality of life and life expectancy of patients because nano drug with enhance surface could increase the bioavailability so the drug recommended in low dose then the toxicity of drug decrease in the body and lead to lower drug cost for patient.

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