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Preparation and Identification of Furosemide Nanoparticles

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ABSTRACT

Nanoparticles are of great scientific interest as they are effectively a bridge between bulk materials and atomic or molecular structures. Furosemide is a potent loop diuretic used in the treatment of edematous states associated with cardiac, renal and hepatic failure and the treatment of hypertension. Furosemide, in the form of nano sized particles, is prepared by ultrasonic method in tetrachloride carbon solvent. The produced furosemide nanoparticles were characterized by X-ray Diffraction (XRD), Infrared Spectroscopy (IR), Scanning Electron Microscope (SEM), and other techniques.
KEYWORDS: Sonochemical, Furosemide, Nanoparticles, Characterization.

1. INTRODUCTION

Up to 40% of currently available drug substances and up to 70% of those under investigation by the pharmaceutical industry exhibit poor water solubility, leading to reduced bioavailability and increased potential of adverse effects. The problem is even more complex for drugs like itraconazole, simvastatin, and carbamazepine which are poorly soluble in both aqueous and nonaqueous media, belonging to BCS class II as classified by biopharmaceutical classification system. Furthermore, fears of problems with future launch preclude many otherwise promising water-insoluble compounds from being taken beyond early R&D stages. Particle size reduction down to the nano-scale (nanocrystallization) has been shown to increase the bioavailability and reduce the required dose frequency, thereby improving patient compliance and decreasing drug side-effects [1]. Nanotechnology can be used to solve the problems associated with various approaches described earlier. Nanotechnology is defined as the science and engineering carried out in the nanoscale that is 10^{-9} m. The drug microparticles/micronized drug powder is transferred to drug nanoparticles by techniques like Bottom-Up Technology and Top-Down Technology [2]. Nanosuspensions are submicron colloidal dispersions of nanosized drug particles stabilized by surfactants [3]. Nanosuspensions consist of the poorly water-soluble drug without any matrix material suspended in dispersion [4]. These can be used to enhance the solubility of drugs that are poorly soluble in water as well as lipid media. As a result of increased solubility, the rate of flooding of the active compound increases and the maximum plasma level is reached faster. This approach is useful for molecules with poor solubility, poor permeability, or both, which poses a significant challenge for the formulators. The reduced particle size renders the possibility of intravenous administration of poorly soluble drugs without any blockade of the blood capillaries. The suspensions can also be lyophilized and into a solid matrix. Apart from these advantages, it also has the advantages of liquid formulations over others [5]. Currently, the utilization of ultrasound for materials synthesis has been extensively examined over many years. The process of ultrasonic top-down nanocrystallization requires extremely high ultrasonic amplitudes to be applied to particle suspensions producing extreme shear forces. The shear forces are the result of intense ultrasonic cavitation, which creates violently and asymmetrically imploding vacuum bubbles and causes micro-jets that break up the original drug particles down to the nano-size range. However, prior to the introduction of BHUT, none of the existing ultrasonic liquid processors could generate the required high amplitudes on the industrial scale. The usefulness of sonochemical synthesis as a synthetic tool resides in its versatility. With a simple modification in reaction conditions, various forms of nanostructured materials can be synthesized, including metals [6, 7], carbides [8] and sulfides [9] nanostructured supported catalysts. Furosemide is 5-(aminosulfonyl)-4-chloro-2-[(2-fuanyl-methyl) amino] benzoic acid (Fig. 1.). Furosemide has narrow absorption window. It is potent high ceiling (loop) diuretic, mainly used in the treatment of edema of hepatic, cardiac, pulmonary and renal failure and in chronic hypertension [10, 11]. This drug has been classified as a class IV drug as per the Biopharmaceutical Classification System (BCS) [12]. The poor bioavailability has been hypothesized to be due to the poor solubility of the compound, site-specific absorption, presystemic metabolism and/or other unknown mechanisms. Furosemide is highly bound to plasma proteins, almost exclusively to albumin. Although the drug is insoluble in water and favours partitioning into fatty tissue, the high degree of plasma protein binding restricts the apparent volume of distribution at steady-state to values within a multiple of 2 to 5 times the plasma volume. Furosemide has two documented metabolites-furosemide glucuronide and saluamine (CSA). In this paper, we have developed a simple sonochemical to prepare nano furosemide and studied some parameters, such as effects of concentration, sonicating time in growth and morphology of the furosemide nanoparticles. The results show that with change of reaction conditions, such as above parameters, nanoparticle structures changed to uniform.

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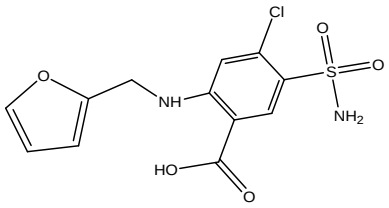


Fig. 1: Furosemide

2. EXPERIMENTAL

2.1 Synthesis of nanoparticles

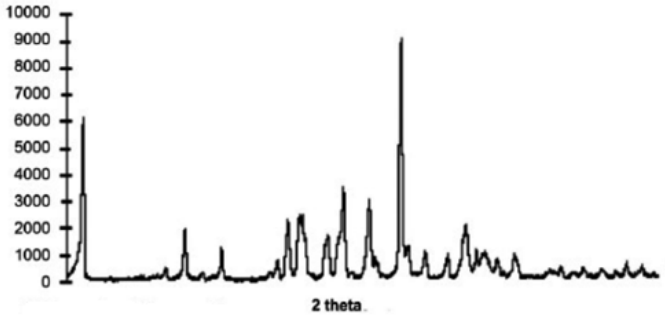
The furosemide sample was obtained from Alborz Darou pharmaceutical company. Different amounts (Table 1) of furosemide were dispersed in CCl_4. This dispersion was sonicated with different powers for 20, 40, 60 and 80 min with a high density ultrasonic probe immersed directly into the dispersion (Table 1). The obtained powders were characterized by XRD, IR spectroscopy, SEM. At all conditions the consequences of changing the sonochemical parameters were marginal. However, different particle sizes were obtained. A multiwave ultrasonic generator (Sonicator_3000; Misonix, Inc., Farmingdale, NY, USA), equipped with a converter/transducer and titanium oscillator (horn), 12.5 mm in diameter, operating at 20 kHz with a maximum power output of 600 W, was used for the ultrasonic irradiation. X-ray powder diffraction (XRD) measurements were performed with an X'pert diffractometer of Philips Company with monochromated Cuk_{α} radiation. The IR spectra were recorded using Bruker spectrometer, with KBr pellets in the range from 400-4000 cm^{-1}. The morphology of synthesized sample was studied using Transmission Electron Microscope (TEM) [Zeiss CEM 902 A] and Scanning Electron Microscopy (KYKY-EM3200) and (Philips XL 30), by a sputtering technique, with gold as covering contrast material.

3. RESULTS AND DISCUSSION

Fig. 2 shows the powder XRD patterns of furosemide nanoparticles prepared by the sonochemical process (bottom) and bulk furosemide (top). The SEM images of the bulk furosemide and of the nanoparticles of the sample 2 (Table 1) are shown in Fig. 3. The particle size histogram of the nanoparticles (Fig. 3, c) showed that the particle size ranged from 7 to 44 nm. The best particles were obtained for sample 2 (Table 1). The TEM (Fig. 4) showed that the particles were amorphous and were dispersed in CCl_4.

Table 1: Experimental conditions for the preparation of furosemide nanoparticles.

Sample	Time (min)	Solvent (mL)	Furosemide (g)
1	20	20	0.2
2	40	20	0.2
3	60	20	0.2
4	80	20	0.2
5	40	20	0.08
6	40	20	0.1
7	40	20	0.15



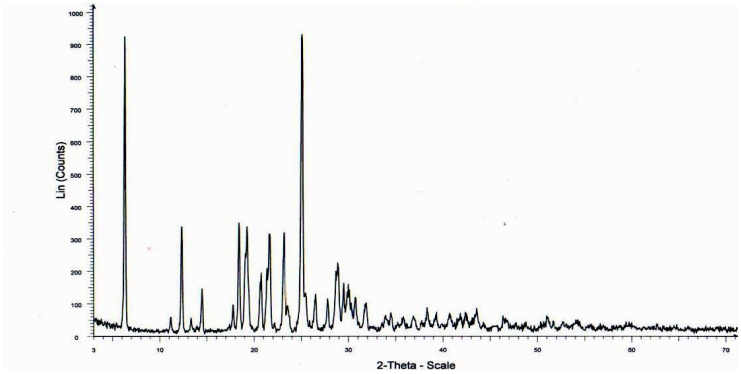


Fig. 2: The XRD pattern of furosemide (top) and furosemide nanoparticles (bottom).

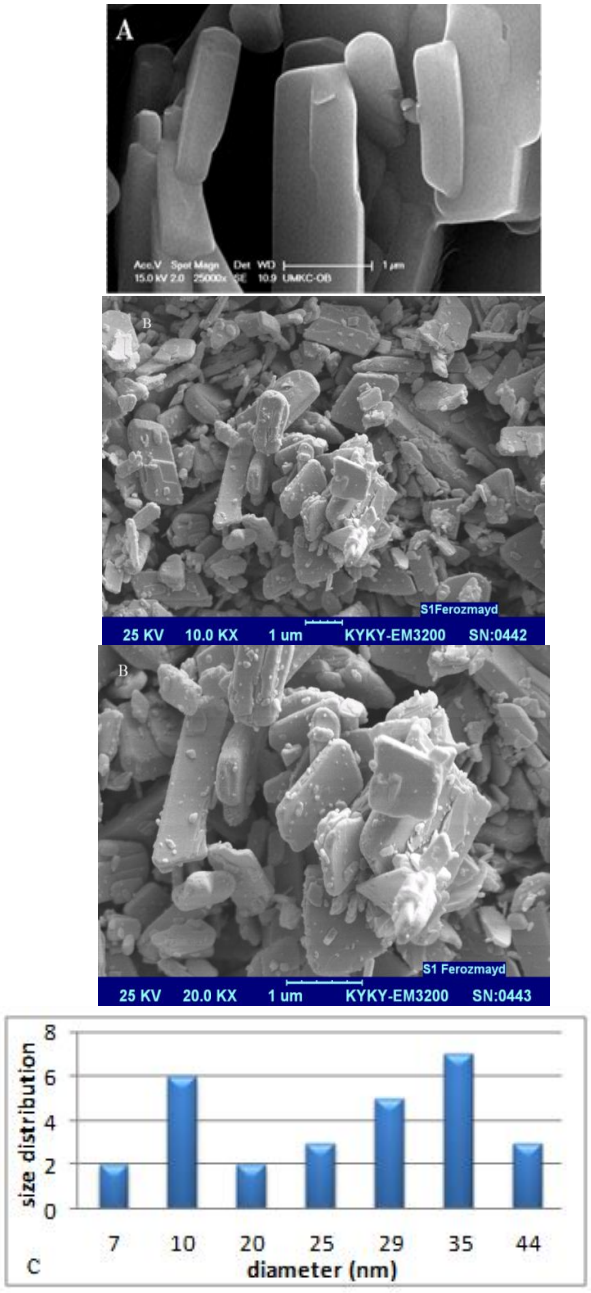


Fig. 3: SEM photographs of a) furosemide, b) furosemide nanoparticles (sample 2) and c) the particle size histogram of the nanoparticles.

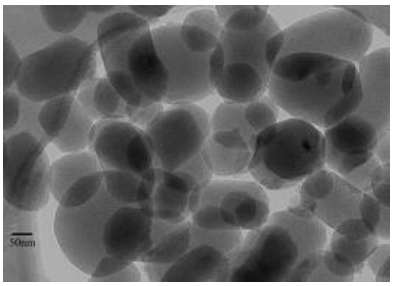


Fig. 4: **TEM image of furosemide nanoparticles (sample 2).**

The study of IR spectra of furosemide (Fig. 5) demonstrated that the characteristics absorption bands for N-H stretching vibration of secondary amine, C = O stretching vibration and S = O stretching vibration of sulfonamide group and C-Cl stretching vibration appeared at 3400.26, 1672.18, 1564.21, 1323.81 and 580.29 cm^{-1}, respectively.

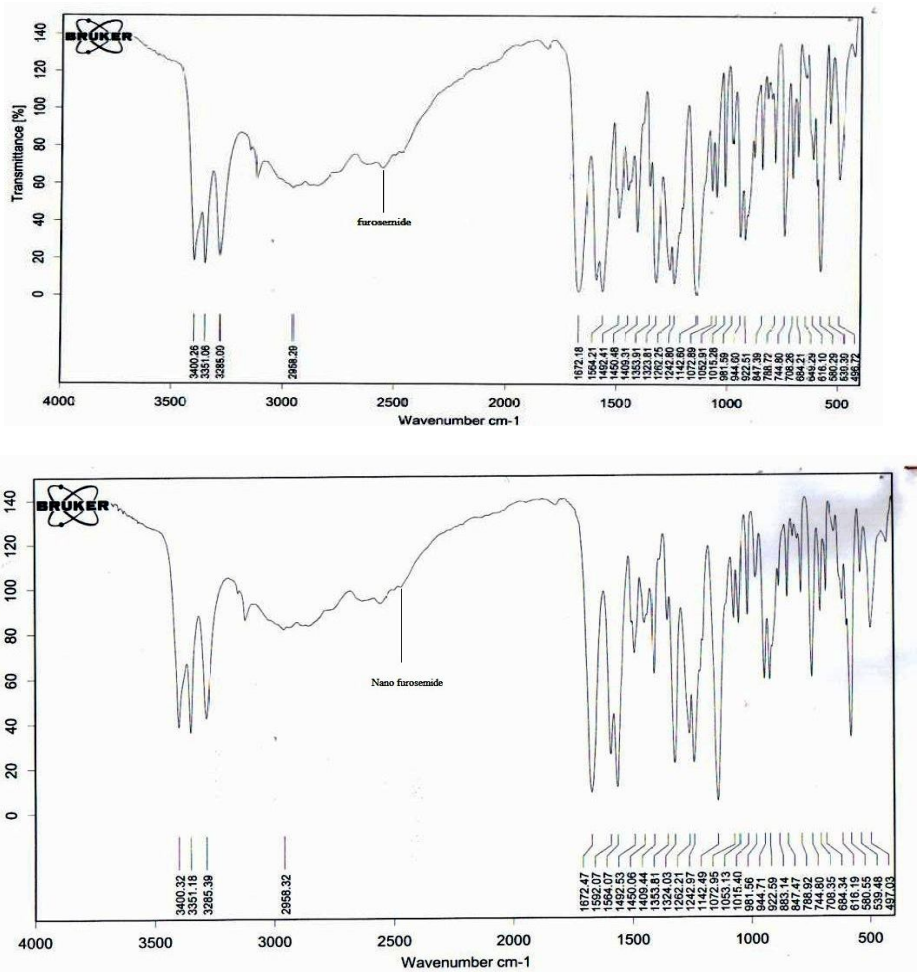


Fig. 4: IR spectrum of a) furosemide, b) furosemide nanoparticles (sample 2)

4. CONCLUSION

Ultrasonic are distinctive and commercially feasible approach to solve the problems of drugs such as poor solubility and poor bioavailability. The described method for preparing furosemide nanoparticles can be used on at industrial scale, because it does not need special conditions, such as high temperature, high pressure, surfactants, long times or temperature and pressure controlling. Solubility increases with decreasing particle size. Since surface area of solids in contact with the medium increases, rapid dissolution is obtained. This increase in solubility ceases when the particle size reaches a particular point. Hence, particle size is critical and beyond a particular value, the solubility of solid decreases. Such a change arises because of the presence of an electrical charge on the particle, which is predominant in small particles. Symmetric molecules may be less soluble than unsymmetrical ones. If crystals are compact, they possess high

lattice energy and therefore, will be lowered. Increased aqueous solubility with the nanoparticle size increases the efficiency, and/or reducing side effects for certain drugs.

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