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Preparation of fenofibrate nanoparticles by combined stirred media milling and ultrasonication method

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ABSTRACT

The production of fenofibrate nanoparticles combining stirred media milling and ultrasonication method was investigated in the current work. The fenofibrate drug sample was first wet milled in stirred media mill for different times and subsequently processed by ultrasonication. The effects of ultrasonication time, power on final product particle sizes were studied. The pre milling by stirred media milling was resulted into reduction of comminution resistance of material. Subsequent treatment by ultrasonication produced smaller particles than obtained by stirred media milling alone. The resulting nanoparticles were found to exhibit excellent stability as investigated by particle size, zeta potential, and multiple light scattering measurement techniques. Further, qualities of nanoparticles obtained by combined approach were characterized by TEM and XRD analysis.

1. Introduction

The nanomaterials have recently received great attention on account of their promising properties and their use in advanced applications. Different methods were reported for production of nanomaterials. They are basically classified as a bottom-up and top-down methods and can produce nanoparticles in solid, liquid and gas phase [1]. Bottom-up methods are chemically driven and are limited by requirements of suitable precursors and specific reaction conditions which are difficult to realize many times [2]. On the contrary, top-down methods can produce nanoparticles from easily available macroscopic materials [3]. Amongst reported top-down methods, stirred media milling is very efficient technique for the production of nanoparticles and many top-down methods cannot compete with stirred media milling processes for large scale production of nanoparticles. However, like other top-down methods stirred media milling method also has certain limitations. Stirred media milling is a highly energy and time intensive process to produce nanoparticles. Additionally product contamination by grinding media wear and mill surfaces also constraint the use of stirred media milling methods for many applications where very high purity is demanded [3]. Problems of stabilisation of the dispersion have to be addressed for successful preparation of nanomaterials by wet milling process. To overcome these issues many strategies were proposed in literature to improve grinding performance in stirred media mill. Wang and Forssberg [4] suggested the use of grinding aids/chemical additives, microwave assisted grinding, and ultrasound assisted grinding strategies for effective size reduction. The effects of many other processing strategies on grinding performance were reported [5–7]. Ultrasound assisted methods for preparation nanomaterials were widely reported. The preparation of fenofibrate nanosuspension using probe sonication method was reported [8]. The effects of ultrasonic treatment for production and dispersion of nanomaterials were widely reported in the literature. Nguyen et al. [9] studied the influence of process parameters, such as time, power and irradiation modes, on the ultrasonic deagglomeration of aluminium oxide nanoparticles. Nanomaterials production by hybrid top-down methods was also studied to enhance the nanoparticles productivity by taking advantages of individual method. For instances, the α-Fe_2O_3 nanoparticles were fabricated with controlled dispersion by a mixed type of mechanical and ultrasonic milling [10]. Radzuan et al. [11] reported that pre-sonication of drug samples prior to nanomilling resulted into easy breakup of the drug agglomerates. Nanohydroxyapatite was prepared using an ultrasound assisted hydrothermal chemical precipitation method [12]. Wagener et al. [3] studied the process of milling followed by laser fragmentation to fabricate zinc oxide nanoparticles and reported improvement in laser fragmentation efficiency and nanoparticles productivity. Preparation of magnesium ferrite nanoparticles by ultrasonic wave-assisted aqueous solution ball milling was reported [13]. Eggshell nanoparticles were prepared by ultrasound assisted techniques [14,15]. Ige et al. [8] reported fenofibrate particles of size 420 nm after 17 min, however they observed that further ultrasonication for 13 min could not reduce the particle size further. It is clear that ultrasonication alone cannot produce

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smaller particles, whereas in the case of stirred media milling product contamination is major issue for materials like pharmaceutical drugs. The focus of present work is to take advantage of both stirred media milling and ultrasonication methods.

In the present work drug nanoparticles were prepared by effectively combining stirred media milling and ultrasonication method. A fenofibrate is a poorly water soluble drug and used in this study. Fenofibrate drug sample was first wet milled in stirred media mill for different times, and subsequently processed by high power ultrasonication. The stability of prepared nanoparticles was investigated over the period of 15 days. Further, characterization of drug nanoparticles were carried out using TEM and XRD analysis.

2. Experimental

2.1. Materials

Fenofibrate sample was kindly donated by M/s. Almbic Ltd., Vadodara, India. The mean size of feed fenofibrate was 10 μm as given by supplier. Hydroxypropyl methyl cellulose (HPMC) of average molecular weight of 50,000 and viscosity of 12–18 cP (2 wt.% in H_2O) was obtained from Kemphasol, Mumbai, India. The HPMC contains 28–30% methoxy- and 7–12% hydroxypropoxy. Sodium dodecyl sulphate (SDS) was purchased from Finar Chemicals Ltd., Ahmadabad, India. All the suspensions were prepared in the Millipore water (Millipore, Elix, Bangalore, India). High density (6000 kg/m^3) yttria stabilized zirconia (ZrO_2) grinding media (chemical composition: 93% ZrO_2, 5% Y_2O_3 and 2% others) purchased from M/s. Saint Gobain ZirPro, France, were used for the nanogrinding experiments.

2.2. Experimental set-up and procedure

For a production of fenofibrate nanoparticles, the premix solution was prepared by dispersing 12.5 wt.% hydroxypropyl methyl cellulose (HPMC) and 0.1 wt.% sodium dodecyl sulphate (SDS) in 125 mL of water (all the concentrations are expressed with respect to the amount of drug). The solution was homogenized by Ultra-turrax homogenizer (IKA, Germany) for 5 min. Then 5 g of fenofibrate was added to premix solution and homogenized further for 5 min by Ultra-turrax homogenizer. The milling experiments were carried out in a research laboratory mill (WAB, Switzerland) in recirculation mode. The mill consists of a silicon carbide chamber of 80 mL capacity, DYNO®-Accelerator made up of hardened chrome alloy, and cooling jacket to dissipate heat generated during milling. The grinding media were first charged into the mill and then as prepared drug premix suspension was introduced into the mill chamber via feed hopper using the conveyor screw. The DYNO®-Accelerator transfers the energy of the main drive to the grinding beads causing beads to start moving. The particles are captured and broken between the colliding grinding beads, between beads and mill chamber, and between beads and mill stirrer. The schematic representation of stirred media mill used in the present work can be found in Ref. [16]. The samples were collected regularly at desired time intervals for particle size measurement. For a combined stirred media milling and ultrasonication method; fenofibrate suspension was ground for different times and then suspension was processed further by ultrasonication. The ultrasonication experiments were conducted using Vibra-Cell (Model VCX 750) ultrasonic processor (Sonics & Materials Inc., USA) as shown in Fig. 1. The ultrasound is produced by a piezoelectric lead zirconate titanate crystal transducer of 63.5 mm diameter and 183 mm length. The ultrasound is delivered from the titanium alloy probe with tip of 13 mm diameter. The ultrasonic probe can be operated with maximum power input of 750 W and a frequency of 20 kHz. The ultrasonication experiments were conducted at ultrasonic intensity of 10, 19, and 30 W/cm^2, which corresponds to different vibration amplitudes of 20%, 35%, and 50% of maximum power delivered by ultrasonicator, respectively. For ultrasonication samples were diluted to contain 0.5 wt.% fenofibrate in 50 mL water. The ultrasonication was performed in 100 mL glass jar. The probe tip was immersed 15 mm in solution. The ultrasonication was carried out in pulsed mode with pulse ratio on/off 50/10 (s/s) by maintaining constant temperature of 20 °C by circulating cooling water system, Accel 250 LC (Thermo Scientific, India) through jacketed jar.

2.3. Characterization

The particle size measurements of the ground sample were carried out by a dynamic light scattering (DLS) technique (Malvern Zetasizer Nano ZS90, UK). The size measurement range of the instrument is between 3 nm and 6.5 μm as claimed by instrument supplier. All the measurements were performed at 25 °C temperature with a measurement angle of 90°. A disposable polystyrene cuvette with 4 optical sides was used for the size measurement. The intensity-weighted average particle diameter d_{DLS} (Z-Average size) can be calculated using the Stokes–Einstein equation defined

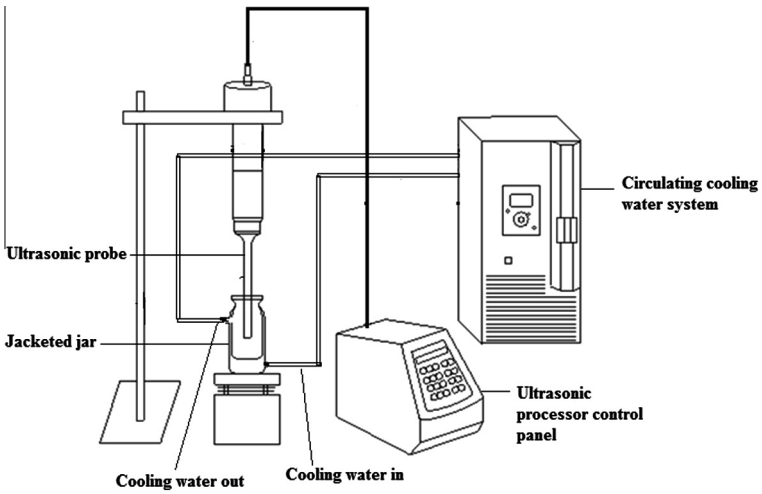

Fig. 1. Schematic diagram of experimental set up used for the ultrasonication.