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Research Article

STUDY OF CONTROLLED LIQUID ANTISOLVENT PRECIPITATION PROPERTY OF POORLY WATER SOLUBLE DRUGS

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ABSTRACT

The production of pharmaceutical nanoparticles has been performed using rapid mixing devices. The particles with controllable size distribution were precipitated and characterized using SEM. Preliminary, studies have been focused on Fenofibrate and Griseofulvin. Efforts are being made to understand mixing conditions to obtain narrow size particle distribution,stabilization of nanoparticles and the ostwaldripening phenomenon. This study will help to understand how the poorly soluble drug can be developmore soluble with the control of size of particles. It will also help to provide the scientific methodology of particle formation mechanism to predict size distribution with given mixing, chemical and physical parameters.

Keywords: Nanoparticles, Rapid Mixing, SEM, Griseoflavin.

INTRODUCTION

Griseofulvin is used as antifungal drug to treat skin infections such as athlete's foot, jock itch and ringworm; and fungal infections of the scalp, fingernails, and toenails. Whereas as fenobirate act as cardiovascular drugs used to treat high triglycerides level and high cholesterol. Both drugs have poor water solubility, hence, it hinder their bioavailability and thus efficiency. There are several studies has been performed to increase the bioavailability and solubility of these drugs. In determining the solubility of drug, particle size and size distribution are the most important characteristics. The in vivo distribution of small particles determine drug bioavailability, dissolution rate, drug loading, drug release and stability of particles. Smaller particles have larger surface area, therefore, most of the drug associated would be mostly at or very nearr the particle surface, leading to fast drug release and this can improve the bioavailability of the drug. However, the suspension and particle size increases as a function of time. In recent years, processes such as emulsification and antisolvent precipitation methods which is considered as bottom-up process have emerged as methods for the synthesis of micro or nano size particles from the liquids. In today's world, approximately 40% of drugs in the industry fall in the category of low solubility–high permeability (Class II), and low solubility–low permeability (Class IV). These drugs have the limited bioavailability due to their low solubility and dissolution rate .The bioavailability is defined as the percentage of the quantity of the drug absorbed compared to its initial quantity of dosage, which can be improved by a decrease in their particle size. Increased in surface area of the particle with the decrease in size of the active pharmaceutical ingredients as described by the Noyes–Whitney equation and, in addition, by an increasing the solubility of nanosized drug particles is also expected to enhance the dissolution rate as described by the Ostwald–Freundlich equation. The objective of this study is to determine particle size diameter and particle size distribution as a function of time for the drugs Fenofibrate and Griseofulvin.

EXPERIMENTAL SECTION

The T-shaped Micro-mixer (L) and Impinging Jets (R) has been used in the production of stable particles of for film Formation. Figure 1

represent the scheme of production of nanoparticles. The APIs utilized were fenofibrate (FNB; Sigma-Aldrich), griseofulvin(GF; Sigma-Aldrich), ascorbylpalmitate (ASC; Spectrum) Sodium dodecyl sulfate (PDS; Delhi), sodium alginate (Sigma-Chem, Mumbai), polyethylene glycol (PEG) 4000, and polysorbate 80 (Tween-80;Sunpharmaceuticals , Delhi) were used as stabilizers. Theorganic solvents used were dimethyl sulfoxide (DMSO; Sigma-Chem, Mumbai), acetone (Sigma-Chem, Mumbai), ethanol (EtOH; Quali-Chem, Mumbai), and tetrahydrofuran (THF; Sigma-Chem, Mumbai) and purchased or acquired from the indicated sources. All these materials were used without further processing. The antisolvent was prepared using deionized water with PEG (4000). The solvent solution was prepared by mixing various concentrations of the drug (1–10 mg mL1). The antisolvent was maintained at 1 1C before processing and post-processing temperatures were recorded by inserting a 4000 traceable digital thermometer.

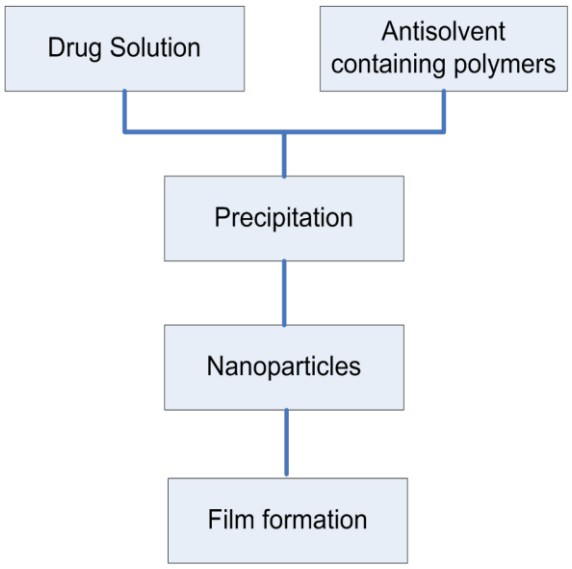

Fig. 1: **Schematics of production of nanoparticles**

Compositional analysis was obtained by SEM S-3400N. Magnetic properties of samples were obtained by using Lake Shore's Vibrating Sample Magnetometer (model 7410). The UV-VIS Spectrophotometer (Perkin Elmer) was used to obtain optical properties of nanoparticles and to determine drug concentration in the solutions. The JEOL JEM-2100 was used for preparation of Transmission Electron Microscopy (SEM) images. Digital pH meter (model 2001) was used for pH measurements. The mean particle size as a power of sonication power is depicted in figure 2.

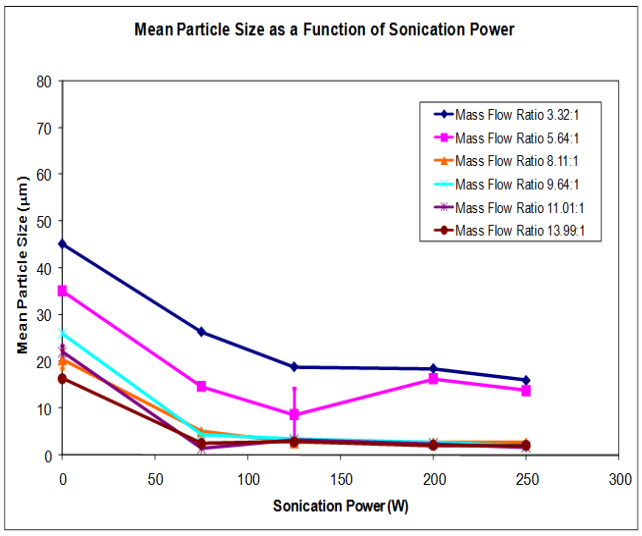

Fig. 2: Mean particle as a function of sonication power

The obtained sizes of nanoparticles from SEM analysis are around 21 nm, 24 nm, and 27 nm respectively at 200 °C, 300 °C, and 400 °C. SEM image of synthesized at 300 °C is presented in Fig.3. According to Fig.3, the nanoparticles have a semi spherical shape with homogenous particles size distribution.

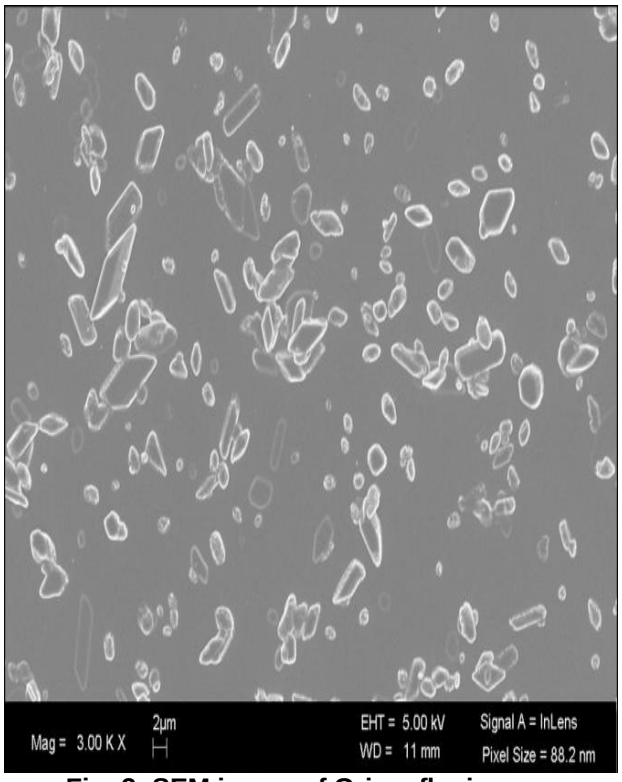

Fig. 3: SEM image of Griseofluvin

RESULT AND DISCUSSION

Particle size becomes larger as time proceeds and that depends on degree of super saturation, crystal growth and ostwald ripening. It was observed that the solubility of drugs increases with time in the organic-water mixture. Therefore super saturation decreased with time. The lower super saturation lowers the nucleation rate. As a result smaller number of nuclei may be expected to produce larger particles. This can be observed when ethanol was used as solvent. There are various techniques available for production of ultra-fine particles, but, liquid antisolvent (LAS) precipitation offers flexibility to control the particle size and distribution which allow you to manipulate both physicochemical properties of solution and antisolvent phases using different additives. It involves two steps, namely the mixing of solution-antisolvent streams to generate supersaturation and the precipitation. In this work, we demonstrate the use of an ultrasonically driven T-shaped mixing device to precipitate particles with nano diameter. This enable greater control over particle size and its distribution. has been The methodology developed has been illustrated for precipitation of particles of in the size range of 240 - 89 size nm as a function of material and process parameters.

CONCLUSIONS

In this study the nanoparticles of fenofibrate and griseofulvinwere synthesized by enhanced micro-mixing using T-mixer/impinging jets. This technique enables narrow particle size distribution and in turn improve the solubility of the poor water soluble drugs. It also suggest that combination of HPMC and SDS is most effective stabilizer combination.

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