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Microfluidic fabrication of silybin nanodispersion with high dissolution rate and tunable sizes

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HIGHLIGHTS

- Water-insoluble drug silybin nanoparticles were prepared by microfluidics.
- Silybin powder containing hydrophilic stabilizers was obtained by spray-drying.
- The transparent nanodispersion was formed when silybin powder was added in water.
- Silybin nanodispersion had a high dissolution rate and tunable sizes.
- Drug concentration and microfluid flow rate had a great effect on particle size.

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ABSTRACT

Silybin is widely used as a therapeutic agent for a variety of acute and chronic liver diseases. However, its application is limited by its extremely poor aqueous solubility, which results in poor oral absorption and bioavailability. In this work, silybin nanodispersion with high dissolution rate was prepared by using T-shaped microchannel antisolvent precipitation combined with spray-drying. The effects of the key operation parameters, including (1) silybin concentration, (2) solvent flow rate, (3) antisolvent flow rate, and (4) overall flow rate, were investigated on the particle size and size distribution. The experimental results indicated that the average particle size decreased from 101 nm to 26 nm with the reduction in the flow rate of silybin solution from 40 to 2 mL/min. However, with increasing overall flow rate at a fixed flow ratio of five, the average particle size decreased from 62 nm (at 6 mL/min) to 39 nm (at 18 mL/min), and then increased to 77 nm (at 96 mL/min). Moreover, the average particle size initially decreased, and then increased, with increasing silybin concentration and antisolvent flow rate. The as-prepared silybin nanodispersion with an average particle size of 26 nm exhibited a faster dissolution rate of 10 times than that of raw drug. This work showed that the continuous preparation in a T-shaped microchannel was a simple and economic way to prepare water-insoluble drug nanodispersion with tunable sizes.

1. Introduction

The formulation of poorly water-soluble drugs has always been a challenging problem faced by pharmaceutical scientists and it is expected to increase because a surprisingly large proportion (about 40% or more) of new lead compounds emerging from drug discovery efforts are compounds with low aqueous solubility and poor bioavailability, and therefore leading to abandoned development efforts [1,2]. Reducing drug particle size, which provides significant increases in surface area, not only increases saturation solubility (Ostwald–Freundlich equation) but also accelerates dissolution kinetics (Noyes–Whitney equation) [3], consequently improving the oral bioavailability [4]. Drug nanoparticles exist in the final drug products either in dry powder or nanosuspension form [5]. A pharmaceutical nanosuspension is defined as aqueous dispersion of nanosized solid drug particles that are produced by a suitable method and stabilized by a suitable stabilizer [1]. Nanosuspension of poorly water-soluble drugs is an emerging and rapidly growing field that has drawn increasing attention due to its amazing stability by adding surfactants, which may prevent the aggregation and growth of drug nanoparticles [6–11]. Moreover, nanosuspensions with better particle dispersion close to monodispersion, which have properties similar to solutions or can be visualized by the bluish opalescence (the Tyndall effect), are usually regarded as nanodispersions [12–14]. Generally, there are three ways for nanosuspension preparation: precipitation produced by Sucker et al. in 1980s [15], pearl milling developed by Liversidge et al. in 1990 [16], high-pressure homogenization developed by Müller

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et al. in 1994 [17], with the liquid antisolvent (LAS) precipitation being the most attractive approach due to the higher level of control offered.

Two steps involved in the precipitation process are nucleation due to supersaturation attained by mixing and simultaneous growth of nuclei by coagulation and condensation [18,19]. Higher nucleation rate, which depends more strongly on supersaturation, results in low or negligible growth and, hence, can potentially produce submicrometer particles [18]. The influence of mixing on phase separation may be characterized by the Damkohler number (D_a) or the ratio of mixing time (τ_{mix}) to overall precipitation time (τ_{precip}), $D_a = \tau_{mix}/\tau_{precip}$. τ_{precip} is composed of τ_{cond} and τ_{coag}. Under conditions such that $D_a > 1$, attainment of supersaturation is slow and low in magnitude due to poor mixing, and subsequent nucleation rate may be slow relative to growth, resulting in large particles. Whereas values of $D_a < 1$, generation of supersaturation can be high, and subsequent nucleation rates may be faster relative to growth, leading to the precipitation of ultrafine particles. Thus, it is necessary to decrease τ_{mix} and/or increase τ_{precip} in order to keep $D_a < 1$ [18,19–21]. Application of microfluidics can be used to reduce the mixing equilibration time (τ_{mix}) by enhancing micromixing.

As indicated by the name, the term microfluidics manipulates fluid streams in microscale channels (micro) devices [22]. Microfluidics can be defined as the science and engineering of systems in which fluid behavior differs from conventional flow theory primarily due to the small length scale of the system [23,24]. The ability of microfluidics to rapidly mix reagents, provide homogeneous reaction environments, continuously vary reaction conditions, and add reagents at precise time intervals during reaction progression has made it an attractive technology for a myriad of applications [25–27]. Since the products produced by microfluidics offer a variety of advantages over conventional methods with respect to distributions and reproducibility of particle size, it has shown considerable promise allowing for the preparation of various inorganic nanoparticles including metal, semiconductor, oxide, etc. [28–33]. However, relatively little has been done to harness the benefits of microfluidics for the synthesis of a few organic nanoparticles such as PLGA, solid lipid and drug [34–36], especially transparent drug nanosuspensions or nanodispersions. It would be desirable to produce aqueous nanodispersions for oral, parenteral, pulmonary, and transdermal applications [37,38], and tackle the formulation-related problems associated with the delivery of poorly water-soluble drugs.

Silybin is a main biologically active component in silymarin, which is an antihepatotoxic polyphenolic substance isolated from the milk thistle plant named silybum marianum, and it has been widely used as a therapeutic agent for a variety of acute and chronic liver diseases. However, the therapeutic effects of silybin are discounted by its extremely poor aqueous solubility, which results in poor oral absorption and bioavailability.

In this paper, we reported the preparation of silybin nanodispension with tunable sizes and greatly enhanced dissolution rate by combining liquid antisolvent (LAS) precipitation in the presence of stabilizers in a T-shaped microchannel and spray-drying process. Silybin solid dispersion that drug nanoparticles are fully dispersed within other hydrophilic carriers/surfactants was firstly generated by a spray-drying process. The stable transparent aqueous silybin nanodispersion could be easily formed upon the exposure of silybin solid dispersion to aqueous media. Acetone and water were used as solvent and antisolvent of silybin, respectively. The effects of concentration of silybin acetone solution, the flow rate of silybin acetone solution, the antisolvent flow rate, the overall flow rate, and injection phase on particle size and distribution of drug nanosuspension were investigated. The dissolution rate was also evaluated.

2. Experimental

2.1. Materials and experimental setup

The raw drug of silybin (purity: 98.6%) was purchased from Panjin Huacheng Pharmaceutical Co., Ltd. (Liaoning, China). Polyvinyl pyrrolidone K30 (PVP) was obtained from Beijing Yili Fine Chemicals Co. Ltd. (Beijing, China). Sodium dodecyl sulphate (SDS) was supplied by Tianjin Bodi Chemical Reagent Company (Tianjin, China). Tween-80 and acetone were of analytical grade and provided commercially by Beijing Chemical Works. Deionized water was purified by Hitech-K Flow Water Purification System (Hitech instruments Co., Ltd., Shanghai, China).

Fig. 1a is a picture of the T-shaped microchannel (TMC) used in this work and Fig. 1b schematically illustrates the whole experimental system. The system consists of a T-junction microchannel module (1), two continuous nonpulsatile pumps (Cole Parmer 74900) (2) for supplying the antisolvent and the drug solution stored in both tanks (3), and a stirred collection unit (4) with a slurry container (5) for collecting the drug suspension. The TMC system was made of stainless steel, and its structure is schematically illustrated in Fig. 1c. The width and the depth of the TMC are 400 and 500 μm, respectively. The lengths of inlet channel (6) and mixing channel (7) are both 20 mm, and the two channels merge at a right angle. According to these TMC structure dimensions, the mixing volume of TMC is calculated as about 4 mL. So the residence time of fluid in the mixing channel of the TMC can be obtained based on both the flow rates.

2.2. Preparation of silybin nanoparticles and nanodispersion

This experiment was performed at a temperature of 25 °C. 1.0 g raw silybin was dissolved in 50 mL acetone, and the formed solution was then filtrated through a nylon membrane with a pore size of 0.22 μm to remove the possible particulate impurities. 5.0 g PVP and 0.03 g SDS were dissolved in 500 mL deionized water, which was used as antisolvent. Subsequently, the drug acetone solution and the antisolvent streams, which was selected as the injection phase, were pumped into the two inlet channels (8), respectively, met at the crossing, and the precipitation occurred in the mixing channel. When a steady state was established, the suspension containing the precipitated silybin nanoparticles was collected at the outlet (9). Afterward, the collected nanosuspension was processed by spray drying to generate silybin nanocomposite powder (silybin solid dispersion). Spray drying was carried out using laboratory scale spray dryer (SD-Basic, Labplant, UK) under the conditions of feed rate of 10 mL/min, atomization air pressure of 0.60 MPa, and inlet and outlet temperatures of 140 °C and 80 °C. Upon the exposure of silybin solid dispersion to aqueous media, the stable transparent aqueous silybin nanodispersion containing the water-redispersible silybin nanoparticles could be formed.

2.3. Characterization

2.3.1. Particle size and distribution

The particle size was analyzed by laser diffractometer (Malvern, ZETASIZER-3000HS), 3 measures/sample, 3 runs/measure at 25 °C, after adequate dilution of a suspension aliquot in deionized water. The mean particle size and size distribution indicated as polydispersity index (PDI) are the typical measured parameters.

2.3.2. Sem

SEM images were obtained through a scanning electron microscopy (SEM) (JEOL, JSM-6701) at 10 kV. The sample, an appropriate amount of powder or a glass slide with a small drop of the suspen-