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Original Research Paper

Preparation of drug nanocrystals embedded in mannitol microcrystals via liquid antisolvent precipitation followed by immediate (on-line) spray drying

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ABSTRACT

The aim of this study is to investigate the feasibility of producing pharmaceutical nanoformulations for enhanced oral or pulmonary delivery of poorly water-soluble drugs *via* liquid antisolvent precipitation followed by immediate (on-line) spray drying. A poorly water-soluble corticosteroid, budesonide, was chosen as the model drug. Budesonide nanoparticles were prepared through liquid antisolvent precipitation, and then processed into a powdered nanoformulation which consists of budesonide nanoparticles embedded in mannitol microcrystals by immediate (on-line) spray drying. The size of the freshly precipitated and the reconstituted budesonide particles was analyzed by dynamic light scattering (DLS). The spray-dried nanoformulation, together with budesonide and mannitol raw materials, their physical mixture and the spray-dried mannitol, were characterized by field emission scanning electron microscopy (FESEM), differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD). *In vitro* dissolution test and aerosol deposition study were conducted on the spray-dried nanoformulation and the physical mixture of budesonide and mannitol raw materials. It was found that the spray-dried nanoformulation, consisting of mannitol microcrystals comprising budesonide nanocrystals with z-average mean size of 520 ± 11.4 nm, exhibited enhanced drug dissolution rate and higher fine particle fraction (FPF). The results of this study indicated the potential of the combined process of liquid antisolvent precipitation followed by immediate (on-line) spray drying to be used as a direct and continuous formulation process to produce powdered nanoformulations to achieve enhanced oral or pulmonary delivery of poorly water-soluble drugs.

1. Introduction

Pharmaceutical scientists have encountered tremendous problems in formulation of poorly water-soluble drugs. It has been reported that approximately 40% of new chemical entities failed to reach commercialization due to low solubility/permeability and thus poor oral bioavailability [1–3]. In the last two decades, nanoformulation technologies have emerged to overcome the formulation hurdles related to poorly water-soluble drugs by reducing drug particle size to nanosized range (with concomitant increase in surface area and thus improved dissolution rate and enhanced bioavailability) [4,5]. With an enormous increase in surface area, the newly formed nanoparticles need to be stabilized to prevent subsequent agglomeration induced by interparticulate interactions [6]. One approach is to embed the nanoparticles in another matrix material to prevent agglomeration of nanoparticles and maintain them as individual nanoentities in the final solid dosage forms. In order to maintain the fast-dissolution advantage of drug nanocrystals in solid dosage forms, the matrix needs to be made by highly water-soluble excipients, such as lactose and mannitol.

Currently, the industrial-scale production of drug nanoformulation products falls mainly into the category of "top-down" approaches which are essentially high energy processes and rely on mechanical attrition to render large crystalline particles into nanoparticles, such as wet media milling and high pressure

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homogenization [5–11]. Although the top-down process is more universal and industrially more feasible than the other approaches, it also has its own limitations in terms of particle size reduction efficiency and other issues related to the solid-state changes of the nanosized product, chemical degradation and residual metal content [9,12,13]. Unlike the top-down approaches where particle size is reduced by physical attrition or grinding, the bottom-up approaches involve the formation of the solid nanoparticles from solution either by precipitation or by removal of solvent, where particles are built up from molecular state, such as precipitation by liquid solvent-antisolvent addition, precipitation in supercritical fluid, spray freeze drying and nano spray drying [12,14,15]. Some of these approaches have been used in pharmaceutical research for many years and possess the potential to produce drug nanoparticles in a continuous manufacturing process [15]. Among the various bottom-up approaches, precipitation by liquid solvent-antisolvent addition has been considered as the simplest and most cost effective method to prepare fine particles [12,14]. Basically, a compound may be dissolved in a solvent, and then poured into a nonsolvent, resulting in the precipitation of fine particles of this compound. This approach has been used to produce drug particles in micron size range for a long time, and the same approach can also be tailored to produce smaller particles in nanosized range [12]. As a matter of fact, the liquid antisolvent precipitation process can be a simple method to prepare drug nanoparticles using only simple mixers. However, the drug nanoparticles produced by liquid antisolvent precipitation are normally not stable in the resultant mixture of solvent and antisolvent, and the precipitated nanoparticles are inclined to grow in size due to the recrystallization and the "Ostwald ripening" effect, which is a phenomenon whereby coarse particles grow at the expense of fine particles redissolving in the liquid system [16]. "Top-down" techniques are not notably affected by this phenomenon, as the drug nanoparticles produced are typically not soluble in the working medium and remain comparatively stable in particle size. Therefore, retaining the precipitated drug particles in nanosized range after the liquid antisolvent precipitation process is a key challenge, which limits the application and commercialization of this approach in pharmaceutical industry. Although some excipients (e.g. hydroxypropyl methyl cellulose) can be used as short-term stabilizers to retard the growing process of freshly precipitated drug nanoparticles, prolonged stabilization can only be achieved by immediate drying for rapid and complete removal of the resultant mixture of solvent and antisolvent [17,18]. Therefore, liquid antisolvent precipitation followed by immediate (on-line) spray drying has the potential to be developed as a continuous and scalable process for producing drug nanoformulation products, to overcome the challenge rendered by the "Ostwald ripening" effect after precipitation [18].

In this study, budesonide, a widely used corticosteroid with poor aqueous solubility, was selected as the model drug. Budesonide is an anti-inflammatory drug used for the treatment of asthma, inflammatory bowel disease and allergic rhinitis [19]. It is available as an inhaler, pill, nasal spray, and rectal foam. In this work, the powdered nanoformulation of budesonide was prepared by a procedure of repeated small-quantity batchwise liquid antisolvent precipitation followed by immediate spray drying. As described in our previous work, this procedure can be used as a proof-of-concept at lab scale with a common magnetic stirrer and a mini spray dryer to mimic a process of continuous liquid antisolvent precipitation followed by on-line spray drying [18,20]. Mannitol was dissolved in the antisolvent (water) phase and used as a highly water-soluble matrix excipient for embedding, separation and thus immobilization of the precipitated budesonide nanoparticles. As reported, both mannitol and lactose are commonly used water-soluble excipients in the formulations for oral or pulmonary drug delivery [21–24]. Unlike lactose which is in amorphous state after spray drying from an aqueous solution, the spray-dried mannitol remains in crystalline state [25]. Therefore, mannitol is a more suitable water-soluble matrix material than lactose to form microcrystals by spray drying. Through this process, the spray-dried nanoformualtion consisting of budesonide nanoparticles embedded in mannitol microcrystals was produced. After preparation, the physicochemical characteristics of the spray-dried nanoformulation, together with the *in vitro* dissolution profile and aerosol deposition behavior, were investigated and compared with the raw materials and their physical mixture.

2. Materials and methods

2.1. Materials

Budesonide (99.5%) was purchased from Wuhan Fortuna Chemical Corporation. Methanol was supplied from Fisher Scientific. Mannitol and other chemicals used in this study were purchased from Sigma-Aldrich.

2.2. Experimental procedure

2.2.1. Preparation of drug nanoparticles embedded in mannitol microcrystals

Fig. 1 shows the procedure of repeated small-quantity batchwise precipitation, which was employed to mimic a continuous liquid antisolvent precipitation process to produce budesonide nanoparticles at lab-scale, followed by immediate (on-line) spray drying. In this process, methanol was used as the solvent to dissolve the drug substance, budesonide, and an aqueous solution of mannitol was used as the antisolvent to precipitate budesonide particles from its methanol solution. Briefly, 0.9 g of budesonide was dissolved in 30 ml of methanol to make a drug solution with the concentration of 30 mg/ml, and 2.25 g of mannitol were dissolved in 900 ml of ultrapure water to make an aqueous solution of mannitol. The mannitol solution was cooled down and maintained at 5 °C before the precipitation process. As shown in Fig. 1, in the first batch of precipitation, 1 ml of drug solution was rapidly injected into a 50 ml-beaker containing 30 ml of mannitol solution using an Eppendorf Pipette at the stirring rate of 1000 rpm (IKA magnetic stirrer, Germany), to produce a milky suspension. Upon precipitation, the freshly prepared milky suspension was immediately and continuously fed into a Büchi B-290 mini spray dryer via a peristaltic pump, and spray dried using a standard 2-fluid nozzle with a set of 0.7-mm tip and 1.5-mm cap according to the spray-drying parameters shown as follows: inlet temperature of 170 °C, spray gas flow rate of 473 Nl/h (based on nitrogen, 40 mm on the gas rotameter indicator), feed rate of 10 ml/min (30% on the pump setting indicator), and aspirator flow rate of 100%. Shortly before the spray-drying process of the first-batch precipitated suspension ended, batch precipitation was repeated and followed by spray drying in the same manner. By repeating the same procedure, all the freshly precipitated suspensions were able to be completely spray dried within minutes after precipitation.

2.2.2. Preparation of the spray-dried mannitol and the physical mixture of budesonide and mannitol raw materials

Spray-dried mannitol was obtained from spray drying of an aqueous solution of 2.5 mg/ml mannitol according to the same spray drying parameters as described in Section 2.2.1. The physical mixture of budesonide and mannitol raw materials was prepared by the physical mixing of 1.2 g of budesonide and 3.0 g of mannitol raw materials using a mortar and pestle. The physical mixture has the same composition as the spray-dried nanoformulation.