Preparation and Solidification of Redispersible Nanosuspensions

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ABSTRACT: To test the feasibility of preparing redispersible powders from nanosuspensions without further addition of drying protectants, Lovastatin was processed into nanosuspensions and subsequently converted into a powder form using a spray-drying process. The effects of spray-drying process parameters and stabilizers on the properties of the spray-dried powders were evaluated. The inlet air temperature was found to have the most pronounced impact; a low-inlet air temperature consistently yielded dried powders with improved redispersibility. This was attributed to the low Peclet number associated with a low-inlet air temperature, making nanoparticles less prone to aggregation and coalescence during spray drying, as evidenced by the well-defined boundary shown between nanoparticles in the SEM photomicrographs of the spray-dried microparticles. The influence of atomization pressure is significant particularly at a low-inlet air temperature. The redispersibility index value of the powder is dependent on the type of stabilizers used in the nanosuspension formulation. Spray-dried powders with acceptable redispersibility were prepared with drug concentration as high as 3%. In conclusion, with optimized process parameters and selected stabilizers, spray drying is a feasible process in the solidification of nanosuspensions with high drug loading and acceptable redispersibility. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:2166–2176, 2014
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INTRODUCTION

An increasing number of poorly water-soluble drug candidates have been generated in recent years as the outcome of more productive drug discovery efforts by the pharmaceutical industry.[1,2] However, it has been a challenge in solving the poor bioavailability of these drugs for preclinical investigations using conventional solubility enhancement methods.[3] Nanolization, the process of forming a nanosuspension of a solid drug has evolved as a promising strategy in formulating a poorly water-soluble drug for preclinical research and clinical development. The superior *in vivo* performance via oral delivery of a drug in the form of nanoparticles is generally attributed to bioavailability enhancement and elimination of food effects, which have been shown to be the results of fast dissolution because of the vast surface area and increased solubility associated with nanoparticles.[4–7] The preparation of nanosuspensions can be achieved by a top-down method, a bottom-up method, or a combination of both.[3] Because of the more streamlined process-flow pattern and the solvent-free feature, top-down methods have been developed for the production of a few commercially successful nanoparticle-based products. A top-down method commonly involves the use of either high-pressure homogenization or media milling. The particle size reduction by high-pressure homogenization is mainly achieved by the cavitation force generated when particles are passing through a gap at an extremely high velocity. The key limitation of this method is that the solid content/drug concentration of the suspension being homogenized cannot to be very high to ensure effective particle size reduction. Therefore, it is imperative to remove excessive water from the nanosuspension during manufacturing or convert the nanosuspension into a dry powder form that can be further processed into a solid finished product.

Many methods have been developed to directly incorporate a nanosuspension into the manufacturing of a solid dosage form. Coating of a drug nanosuspension onto a substrate material (core tablets or granules/pellets) by either pan film coating or fluidized bed coating exhibits many advantages, such as enhanced drug release, improved stability, and bioavailability, and has been successfully utilized for commercial production.[8,9] However, the coating method is not suitable for a high-dosed drug because of the large quantity of nanosuspension required. In this case, it becomes more feasible to convert a fluid nanosuspension into a dry powder form via drying, which can be subsequently used in the manufacturing of the solid dosage form. Freeze-drying and spray drying are the two processes that have been evaluated for converting a nanosuspension into a powder form.[10–12] When considering the relatively high-energy consumption and long-processing time of the freeze-drying process and the lack of desirable processing characteristics (i.e., flowability) of a freeze-dried product, spray drying has been the method of choice in transforming a nanosuspension into a powder in particular for solid dosage form manufacturing.[13,14] Prior to spray drying, a high concentration of protectants is usually added to the nanosuspension at a protectant to drug ratio ranging from 0.7 to 3.[15,16] Protectants are water-soluble sugars such as mannitol, lactose, and trehalose, which are added to prevent nanoparticles from aggregating during the drying process.[17] The addition of protectants will greatly reduce the drug content of the spray-dried powder and this is particularly undesirable for formulations with a high drug loading; hence, it is advantageous to prepare dry powder of a nanosuspension

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without further addition of drying protectants. It has been reported that appropriate stabilizer could play a critical role in preventing nanoparticle aggregation during a drying process.[18] Yue et al.[19] studied the influence of drug properties and type of stabilizers on the preparation and solidification of nanosuspensions, and the results showed that polymeric stabilizers present a better potential to stabilize nanosuspensions during drying process compared with that of surfactant stabilizers. Also, drying protectant-free powders of nanosuspensions with high dispersibility can be obtained at a high voltage using the electrospray-drying method.[20] Therefore, it is the aim of this study to investigate the feasibility of preparing redispersible spray-dried nanosuspensions through screening of stabilizers and optimizing spray-drying process parameters. Nanosuspensions of lovastatin, a BCS class II drug, were prepared using high-pressure homogenization. The nanosuspensions were subsequently spray dried with no protectant added. The effects of spray-drying process parameters, type and concentration of stabilizers, and drug concentration on the redispersibility of the dried nanosuspension powders were investigated. The results were further analyzed and explained with proposed mechanisms.

MATERIALS AND METHODS

Materials

Lovastatin was purchased from Hubei Prosperity Galaxy Chemical Company, Ltd. (Wuhan, China). Poloxamer 188 (F68) and Poloxamer 407 (F127) were generously provided by BASF (Shanghai, China). Povidone K12 (PVP K12), Povidone K17 (PVP K17), and Povidone K29/30 (PVP K30) were kindly donated by ISP. Sodium dodecyl sulfate (SDS) (Amresco, solon, OH), hydroxypropyl methylcellulose 2910 (HPMC 2910) (Shin-Etsu Chemical Company, Ltd., Tokyo, Japan), and polyvinyl alcohol 205 (PVA 205) (Kuraray Company Ltd., Tokyo, Japan) were commercially purchased.

Preparation of Nanosuspension and Particle Size Characterization

Coarse drug powder (0.5%, w/w) was dispersed in distilled water containing specified amount of stabilizers under moderate stirring. Lovastatin nanosuspensions were prepared by high-pressure homogenization as reported previously.[14] The coarse dispersion was first passed through a high-pressure homogenizer AH100D (ATS Engineering Inc., Shanghai, China) at three different pressures (200, 500, and 800 bar) with two cycles per each pressure. The resultant suspension was subsequently passed through the homogenizer at a final pressure of 1300 bars for 20 cycles.

Particle size and polydispersity index (PI) analysis of the nanosuspensions were conducted by photon correlation spectroscopy with a Nano ZS90 (Malvern Instruments, Worcestershire, UK). Samples of nanosuspensions were diluted to an appropriate concentration and were measured at 25°C and at a scattering angle of 90°.

Spray Drying of Nanosuspensions and Determination of Redispersibility

Spray drying of the lovastatin nanosuspensions was carried out by using a laboratory-scale spray dryer SD-1000 (Tokyo Rikakikai Company, Ltd., Tokyo, Japan). Nanosuspensions were atomized through the two-fluid nozzle at different pressures and dried at different inlet air temperatures. Other processing parameters were fixed: drying air flow was 0.6 m^3/min and feed rate was 2.8 mL/min. Spray-dried powders were redispersed in distilled water and shaked gently for 10 s to yield a suspension with the same concentration as the nanosuspension prior to spray drying and particle size measurement was conducted with the resultant suspension.

Redispersibility index (RDI) was used to evaluate the redispersibility of the spray-dried powders and is calculated as:

$$\mathrm{RDI} = \left[\frac{D}{D_0}\right] \times 100\%,$$

where D represents the mean particle size of the redispersed suspension formed by the spray-dried powder and D_0 is the particle size of the nanosuspension prior to spray drying. When the RDI value is close to 100%, the spray-dried powder is said to be completely redispersed, forming nanoparticles with the same size as those in the nanosuspension.[18]

X-ray Powder Diffraction

X-ray powder diffraction (XRPD) patterns were obtained at a wide X-ray scattering angle range ($2\theta = 5°–45°$) with a PW3040/60 X-ray diffractometer (PANalytical B.V., Almelo, The Netherlands). The Cu-Kα radiation at 40 kV and 40 mA was applied.

Differential Scanning Calorimetry

A spray-dried nanosuspension sample was characterized using a differential scanning calorimeter TGA/DSC-1 (Mettler-Toledo Ltd., Schwerzenbach, Switzerland) and the result was compared with that of the coarse drug powder. Prior to measurement, samples were accurately weighed into an aluminum pan and then sealed with a punched cover. Samples were heated from 30°C to 180°C at a rate of 5°C/min in a nitrogen atmosphere.

Scanning Electron Microscopy

The morphology of the samples was examined using a SUPRA 35 Field-Emission Scanning Electron Microscope (Zeiss, Jena, Germany) with an accelerating voltage of 17 kV. Prior to analysis, the mounted samples were coated with gold and dried under vacuum.

Short-Term Physical Stability

The physical stability of lovastatin nanosuspensions was evaluated at 25°C; particle size was determined at predetermined time points over 1 week time period.

In Vitro Dissolution

In vitro dissolution experiments were carried out at 37°C with a paddle speed of 50 rpm. A sample of 60 mg of lovastatin was dispersed in 900 mL of phosphate buffer (pH 7.4) containing 0.1% SDS. Six milliliter samples were collected at predetermined time intervals and filtered through a 0.15-μm millipore filter (cellulose acetate). The concentration of dissolved lovastatin in samples was determined by an UV Spectrophotometer UV-2000 (Unico Instrument Company, Ltd., Shanghai, China) at 238 nm.