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Mitigating the adverse effect of spray drying on the supersaturation generation capability of amorphous nanopharmaceutical powders

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ABSTRACT

Amorphous nanopharmaceuticals (NP) have emerged as a highly effective bioavailability enhancement formulation strategy of poorly soluble drugs owed to their supersaturation generation capability. Spray drying, which is regularly employed in solid dosage form preparation of amorphous NP, adversely affects the supersaturation generation. The adverse effect is caused by the high crystallization propensity of the spray-dried products resulted from poor disassociation of the spray-dried nanoparticle aggregates. Herein, we developed adjuvant formulations to mitigate the adverse effect of spray drying on the supersaturation generation capability of amorphous NP. Two types of water-soluble adjuvants were investigated, i.e., (1) fast-dissolving mannitol and trehalose and (2) crystallization inhibiting hydroxypropylmethylcellulose (HPMC). The supersaturation generation was evaluated in terms of the area under the curve (AUC) of the supersaturation versus time plot. The results showed that co-spray drying of amorphous NP with two adjuvant types were mandatory to have a prolonged supersaturation profile, which significantly improved the AUC (≈70% larger) compared to spray drying without adjuvants. Using only one adjuvant type resulted in either stagnant or high yet short-lived supersaturation profiles manifested in less than 20% improvement in the AUC. Furthermore, physically mixing the two adjuvant types (instead of co-spray drying) led to inferior supersaturation generation. Thus, adjuvant formulations targeted only at effective disassociation of the nanoparticle aggregates were ineffective if the improved supersaturation generation rate was not accompanied by crystallization inhibition of both the supersaturated solution and the remaining solid phase.

1. Introduction

A large majority (≈80%) of the recently marketed drugs and new drugs currently in the pharmaceutical pipeline possess poor aqueous solubility due to their increasingly intricate chemistry, resulting in their low systemic bioavailability upon administration [1]. Amorphous nanoparticle formulations of such pharmaceuticals have been widely demonstrated to be more effective in enhancing the bioavailability of poorly soluble drugs *in vitro* and *in vivo* than their crystalline nanopharmaceutical counterparts [2–5]. The enhanced bioavailability afforded by the amorphous nanopharmaceuticals (or amorphous NP in short) can be attributed to two factors. First, the metastable state of the amorphous form produces a highly supersaturated drug solution upon dissolution, resulting in an apparent increase in the drug solubility that is significantly higher than the thermodynamic saturation solubility [6]. Second, the fast dissolution velocity of the drug nanoparticles (owed to their small size) minimizes the solution-mediated crystallization tendency of the remaining solid phase (caused by Ostwald ripening), thus ensuring the generation of highly supersaturated drug solutions [7,8].

The enhanced drug bioavailability, nevertheless, is only realized when the high supersaturation level generated by the amorphous NP is maintained over a time period sufficient for the drug absorption across the gastrointestinal lumen [9,10]. To this end, amorphous NP formulations typically incorporate water-soluble biocompatible polymers having crystallization inhibiting properties, such as polyvinylpyrrolidone (PVP) and hydroxypropylmethylcellulose (HPMC) [11]. In the presence of these polymer stabilizers, the supersaturation generation capability of amorphous NP in their aqueous suspension form has been well established [3,4]. Typically, the drug release from the amorphous NP suspension follows a "spring and parachute" profile, where the dissolution initially produces a peak in the drug solubility denoting the maximum achievable supersaturation level of the amorphous form ("spring"). Subsequently, the supersaturation level decreases gradually due to the crystallization of the dissolved drug ("parachute"), before it eventually reaches equilibrium at higher apparent solubility than the solubility of the crystalline form [12].

Abbreviations: AUC, area under the curve; CIP, ciprofloxacin; C_{sat}, drug saturation solubility; C, drug supersaturation solubility; DSC, differential scanning calorimetry; HPMC, hydroxypropylmethylcellulose; NP, nanopharmaceuticals; PBS, phosphate buffer saline; Phys. Mix, physical mixture; PVP, polyvinylpyrrolidone; PXRD, powder x-ray diffraction; SD, spray dry; SEM, scanning electron microscope; TGA, thermogravimetric analysis.

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The supersaturation generation capability of the amorphous NP, however, has been demonstrated in several studies to be greatly diminished upon drying [13–15], which is a mandatory step in the oral solid dosage form preparation of any pharmaceuticals. The amorphous NP powders, which were made up of microscale aggregated nanoparticles, were found to be unable to generate the "spring and parachute" supersaturation profile. This was believed due to poor disassociation of the nanoparticle aggregates upon dissolution [13–15], which resulted in reduced surface areas available for dissolution, hence a slow dissolution velocity. The slow dissolution velocity in turn increased the crystallization propensity of the remaining solid phase undergoing dissolution, thus significantly lower supersaturation levels were generated after drying.

Among the drying techniques, spray drying has been widely established as the most suitable drying technique for nanoparticles as it enables direct transformation of the aqueous nanoparticle suspension to powders having controlled morphology and good flowability [16–19]. For this reason, the present work aimed to develop spray-drying adjuvant formulations to mitigate the adverse effect of spray drying on the supersaturation generation capability of amorphous NP. Two types of water-soluble adjuvants were investigated, i.e., (1) fast-dissolving adjuvant (i.e., trehalose, mannitol), whose role was to act as "interstitial bridges" to prevent the formation of irreversible aggregates of the NP upon drying [18], and (2) slowly dissolving HPMC, whose functions were to suppress (i) crystallization of the amorphous solid phase undergoing dissolution, as well as (ii) crystallization of the dissolved drug from the supersaturated solution.

Using antibiotic nanoparticles (i.e., ciprofloxacin) as the model amorphous NP, we first investigated the effect of employing only a single-adjuvant (either the fast-dissolving adjuvants or HPMC) on the supersaturation generation. This was followed by studies employing the double-adjuvant formulations in which we also examined the effect of the HPMC incorporation method (i.e., whether it was co-spray dried, or physically mixed with the spray-dried NP and fast-dissolving adjuvant). Lastly, we examined the effects of the adjuvant formulation on the physical characteristics (i.e., morphology, flowability, and amorphous form stability) of the spray-dried amorphous NP.

2. Materials and methods

2.1. Materials

Ciprofloxacin (CIP), mannitol, trehalose, HPMC, glacial acetic acid, Pluronic F68, and phosphate-buffer saline (PBS, pH 7.4) were purchased from Sigma-Aldrich (USA). Dextran sulfate (MW 5000 Da) was purchased from Wako Pure Chemical (Japan).

2.2. Methods

2.2.1. Preparation of amorphous NP suspension

The amorphous CIP nanoparticles were prepared by self-assembly electrostatic complexation between ionized CIP molecules and oppositely charged polysaccharides as described in Cheow, Kiew, and Hadinoto [15]. Briefly, 10 mg CIP was dissolved in 1 mL 0.2% (v/v) aqueous acetic acid solution, while 4.5 mg dextran sulfate was dissolved in 1 mL deionized water containing 2.0 mg Pluronic F68. The CIP solution was added slowly to the dextran sulfate solution under gentle stirring after which the mixture was let sit for 3 h. The amorphous CIP nanoparticles produced was recovered by centrifugation at 13,000×*g* for 5 min, followed by three cycles of washing before they were resuspended in deionized water. Physical characterizations of the amorphous CIP nanoparticles (i.e., size, shape, zeta potential, drug loading) were presented in Cheow, Kiew, and Hadinoto [15]; thus, they were not repeated here.

2.2.2. Spray drying of amorphous NP

The aqueous suspension of the amorphous CIP nanoparticles was mixed with the aqueous solution of the spray-drying adjuvants at the mass ratios prescribed in Table 1. The total solid concentrations were fixed at 1.0% (w/v) for the different adjuvant formulations investigated. The resultant suspension was then spray dried in Büchi B-290 mini spray dryer (Büchi, Switzerland) at 120 °C, 6 mL/min feed rate, and 355 L/h air flow rate. The operating condition of the spray dryer was selected from a prior study aimed at maximizing the production yield. The spray-dried amorphous NP were stored in a humidity cabinet at 25 °C and 55% relative humidity for 48 h prior to characterizations.

2.2.3. Physical characterizations of spray-dried amorphous NP

The morphology of the spray-dried amorphous NP was examined by scanning electron microscope (SEM) model JSM-6700 F (JEOL, USA), where the mean size was determined from the SEM images using ImageJ software (NIH, USA) from a minimum of 200 particle counts. The powder flowability was assessed by the Carr's Index (Eq. (1)) from the bulk and tap densities, where Carr's Index ≥ 33 signified poor flowability and Carr's Index ≤ 21 signified good flowability [20]. In this regard, the bulk density (ρ_{bulk}) was determined by measuring the volume of a known mass of the powders without tapping, whereas the tap density (ρ_{tap}) was determined using tap densitometer (Quantachromme, USA) after 2000 taps.

$$\text{Carr}'\text{s Index} = \left(1 - \frac{\rho_{bulk}}{\rho_{tap}}\right) \times 100\% \quad (1)$$

The amorphous form stability of the spray-dried products was assessed by thermal analysis using differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). In the former, 2 mg of the spray-dried powders were filled into a sealed aluminium crucible and heated from 25 °C to 330 °C at 10 °C/min in DSC 822e (Mettler Toledo, USA), whereas in the latter 5 mg of the powders were filled into an alumina pan and heated from 30 °C to 400 °C at 10 °C/min in SDT Q600 (TA Instruments, USA). To supplement the thermal analysis, powder X-ray diffraction (PXRD) of the spray-dried products was carried out using D8 Advance X-ray diffractometer equipped with Cu Kα radiation (Bruker, Germany) from 10° to 60° (2) with a step size of 0.02°/s.

2.2.4. Supersaturation generation of spray-dried amorphous NP

The supersaturation generation was evaluated by adding excess amount of the spray-dried amorphous NP to 8.5 mL PBS in a shaking incubator at 37 °C. The excess amount was defined as CIP concentration in the feed equal to ≈13× above the CIP saturation solubility (C_{Sat}), which was equal to ≈0.14 mg/mL. Subsequently, 0.2 mL aliquot was withdrawn at specified time intervals over 4 h. The aliquot was filtered immediately in 0.22 μm membranes after which it was diluted tenfold with fresh PBS to prevent drug crystallization from the supersaturated solution. The CIP concentration in the aliquot (i.e., C) was measured in triplicates by UV–vis spectrophotometer (UV Mini-1240, Shimadzu, Singapore) at 324 nm. After taking into account the tenfold dilution, the supersaturation level was determined from the ratio of C to C_{Sat}.

Prior to the above, the supersaturation level generated by the aqueous NP suspension was compared with that generated by the spray-dried amorphous NP without any drying adjuvant. This comparison was used to confirm the adverse effect of spray drying on the supersaturation generation of the amorphous NP. For this comparison, the supersaturation generation was evaluated in 8.5 mL PBS containing 1.8 mg/mL of HPMC solution and at feed concentrations equal to ≈20× above the CIP saturation solubility.

In addition to the supersaturation level, the *in vitro* drug release profile of the spray-dried amorphous NP was characterized under a sink condition with the aim of evaluating the rate of the supersaturation