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Clay as a matrix former for spray drying of drug nanosuspensions

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ABSTRACT

Utilization of sugars (e.g. lactose, sucrose) as matrix formers for spray drying of drug nanosuspensions is associated with two drawbacks: (1) sugars are incapable of preventing agglomeration of drug nanoparticles (NPs) in the suspension state; and (2) the spray-dried sugars are usually amorphous and hygroscopic. This work aimed to apply a clay, montmorillonite (MMT) as an alternative matrix former for spray drying of drug nanosuspensions with fenofibrate (feno) as a model compound. Drug nanosuspensions were synthesized by liquid antisolvent precipitation with different amount of MMT followed by spray drying. It is found that MMT is able to reduce the agglomeration of drug nanoparticles in the suspension state, as observed from the gradual alleviation of the clogging with the increased clay during the spray drying. The spray-dried feno NPs/MMT powders exhibited a much lower moisture sorption than spray-dried feno NPs/lactose powders as evidenced by the dynamic vapor sorption (DVS) analysis. The dissolution within 5 min for the spray-dried feno NPs/MMT powders at drug:MMT weight ratio of 1:3 was 81.4 ± 1.8% and the total dissolution within 60 min was 93.4 ± 0.9%. Our results demonstrate that MMT is a useful matrix former for preservation of the high dissolution rate of nanosized drug particles after drying.

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1. Introduction

Nanosizing, leading to the creation of an extremely enhanced surface area and increased saturation solubility, is an effective approach to expedite the dissolution rate of the poorly water-soluble drugs and result in an improved bioavailability (Rabinow, 2004; Kesisoglou et al., 2007; Shegokar and Müller, 2010; Möschwitzer, 2013). Size diminution to the submicron range can be realized by either "top-down" approach from the large coarse drug particles (milling and high pressure homogenization) or "bottom-up" means from the drug solution (e.g. liquid antisolvent precipitation, supercritical fluid technology, etc.) (Sinha et al., 2013). Whichever the approach used, suspensions of the nanoparticles (NPs), i.e. nanosuspensions, are generally the initial product form achieved, as the water and/or solvent have to be used in most of the nanosizing processes. Drug nanoparticles in the suspension state, however, are not stable, as they tend to grow and agglomerate, especially the nanosuspensions of poorly water-soluble drugs (Liu et al., 2007; Verma et al., 2011). Therefore, in terms of the stability as well as the convenience for the patient, drug nanosuspensions are required to be processed into the dried powders, which can be achieved by spray drying, freeze drying, pelletization or granulation (Chaubal and Popescu, 2008; Van Eerdenbrugh et al., 2008a; Cerdeira et al., 2013). Agglomeration of the individual nanoparticles, however, would occur upon drying leading to a reduced effective surface area and slower dissolution rate. To preserve the high dissolution rate of the nanosized drug particles, some water-soluble sugar-based matrix formers are frequently used in the drying process to prevent agglomeration, e.g. lactose, sucrose, etc. After drying, the individual nanoparticles are embedded inside or layered onto the sugar particles. Upon redispersion, sugars are immediately dissolved releasing the individual nanoparticles to the medium and resulting in a high dissolution rate. However, two inherent drawbacks are associated with the sugar matrix formers: first, sugars are incapable of preventing agglomeration of drug nanoparticles in the suspension state (Chaubal and Popescu, 2008), as the dissolved sugar molecules cannot form a permanent solid barrier against particle–particle interaction (Fig. 1(a)). Previously, our group has synthesized drug nanosuspensions using liquid antisolvent precipitation followed by spray drying to achieve the redispersible powders (Hu et al., 2011). It was observed that clogging in the pumping tubing frequently occurred during the spray-drying process due to the formation of the large agglomerated lumps. Once clogging arose,

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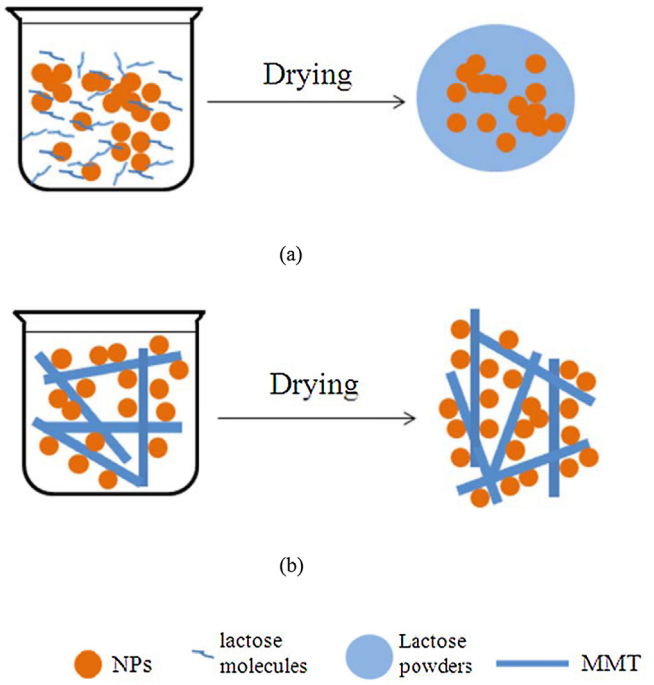

Fig. 1. Schematic description of suspension and dried state of NPs with (a) lactose and (b) MMT as a matrix former.

pumping of the drug nanosuspensions to the spray drier failed to proceed. Second, sugars, after the spray drying process, are generally amorphous and hygroscopic. More strict conditions for storage or further processing (tableting or capsule-filling) are thus required. Therefore, an alternative matrix former is demanded to circumvent the problems encountered using the sugars. In literature, some insoluble alternative matrix formers, e.g. microcrystalline cellulose, S_iO_2, etc., have been reported to exhibit excellent performance for preservation of high dissolution rate of drug nanoparticles after drying (Van Eerdenbrugh et al., 2008b,c,d, 2009).

Clays, owing to the high specific surface area and ion exchange/adsorption capability, favorable rheological characteristics (swelling, dispersion as well as thixotropic and colloidal properties), nontoxicity and chemical inertness, have been broadly used in the oral and dermal pharmaceutical formulations. As active ingredients, clays have generally been used as gastrointestinal protectors, osmotic oral laxatives, antidiarrhoea agents, antiseptics dermatological protectors, etc.; as excipients, clays have been frequently used as lubricants, disintegrants, drug carriers, emulsifying/thickening/anticaking agents, etc. (Isabel Carretero 2002; Aguzzi et al., 2007; Del Hoyo, 2007; López-Galindo et al., 2007; Isabel Carretero and Pozo, 2009, 2010). Among a wide spectrum of clays, montmorillonite (MMT) is more extensively investigated due to its comparatively higher surface area, higher ion exchange and adsorption capability, and excellent rheological behavior. MMT belongs to the smectite group and is formed by stacking of a number of aluminosilicate layers with 2:1 structure, i.e. one layer is composed of an alumina octahedral sheet sandwiched by two silica tetrahedral sheets. As an active, MMT is used to treat diarrheal and painful symptoms associated with oesophageal-gastric and intestinal diseases (e.g. SMECTA®). As excipients, MMT is capable of controlling the drug release by intercalation of the drug molecules in the interlayers (Park et al., 2008; Joshi et al., 2009) or by forming composites with polymers (Dong and Feng, 2005; Campbell et al., 2009). Moreover, the dissolution rate of the poorly water-soluble drugs could be accelerated by adsorption of the drug molecules onto the MMT surface (McGinity and Harris, 1980).

This work is aimed at seeking an alternative matrix former for spray drying of drug nanosuspensions. The ideal matrix former needs to fulfill the below requirements: (1) it is able to prevent the agglomeration of the drug nanoparticles in the suspension state; (2) it is able to preserve the high dissolution rate of drug nanoparticles after drying; and (3) inclusion of the matrix former has no negative effect on the rheological properties of the nanosuspensions; thus, the spray drying can be operated smoothly without clogging. For this purpose, MMT clay is proposed as an alternative matrix former for spray drying of drug nanosuspensions. The stabilization mechanism of MMT on the nanoparticles is depicted in Fig. 1(b). In the suspension state, the freshly synthesized nanoparticles are instantaneously adsorbed onto the large surfaces of the plate-shaped MMT; therefore, the particle–particle interactions and the subsequent agglomeration are alleviated. After spray drying, the nanoparticles are immobilized and layered onto the MMT surface. Upon redispersion, the individual nanoparticles are desorbed and released to the medium followed by a rapid dissolution. In this work, fenofibrate (feno) was used as a model hydrophobic compound. Drug nanosuspensions in the presence of MMT were synthesized by liquid antisolvent precipitation technique, which was processed into the dried powders by an immediate spray drying. Morphology of the nanoparticles and the dried powders were visualized by field emission scanning electronic microscopy (FESEM). Physical state of the samples was analyzed by X-ray diffraction (XRD) and differential scanning calorimetry (DSC). Moisture sorption behaviors of the spray-dried products were determined by dynamic vapor sorption (DVS). Finally, dissolution was performed to evaluate the success of MMT as a matrix former for drug nanoparticles.

2. Materials and methods

2.1. Materials

Fenofibrate, polyvinylpyrrolidone 10 (PVP10) and sodium dodecyl sulfate (SDS) were purchased from Sigma–Aldrich. MMT (CLOISITE®C_a^{++}) was a gift from Southern Clays Products Inc. HPLC grade ethanol was supplied by Fisher Scientific. D.I water was used throughout the work.

2.2. Synthesis and spray drying fenofibrate nanosuspensions

Fenofibrate nanosuspensions were synthesized by liquid antisolvent precipitation technique. Briefly, 20 mg/ml fenofibrate, 2 mg/ml PVP10 and different amount of MMT were dissolved/suspended in ethanol, 3 ml of which was injected to 9 ml water leading to the formation of fenofibrate nanosuspensions. Spray drying (Büchi B-290) was immediately performed under the below process parameters: the inlet temperature was set as 140 °C; the flow rate of nitrogen was 40 mm; the aspiration and pumping rate was 100% and 20%, respectively. The spray-dried feno NPs/MMT powders with different amount of MMT were denoted as different drug:MMT weight ratios correspondingly, i.e. 1:1, 1:2, 1:3 and 1:4. They were stored in a capped bottle at the ambient conditions for 3 days before physical characterization and dissolution measurement.

2.3. Solubility of fenofibrate in the antisolvent precipitation system

Since the antisolvent precipitation of fenofibrate nanoparticles and the followed spray drying was completed within 3 min, the solubility of fenofibrate in the antisolvent precipitation system was determined in this time range. Briefly, 1 ml 20 mg/ml fenofibrate ethanol solution with 2 mg/ml PVP10 and different amount of MMT was mixed with 3 ml water under stirring. After 3 min, the obtained suspension was filtered through 220 nm syringe filter. The filtrate

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