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Research paper

Spray-dried nanocrystals for a highly hydrophobic drug: Increased drug loading, enhanced redispersity, and improved oral bioavailability

Yanxian Hou, Jingbo Shao, Qiang Fu*, Jingru Li, Jin Sun*, Zhonggui He

School of Pharmacy and School of Wuya, Shenyang Pharmaceutical University, No. 103, Wenhua Road, Shenyang 110016, China

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ABSTRACT

For a highly hydrophobic and drug, it is difficult to formulate and solidify its nanocrystals with high drug loading and good redispersity. In this study, Allisartan Isoproxil was used as a model drug, and SDS was tested in combination with sugar alcohols to improve the drug loading and redispersity for its spray-dried nanocrystals, simultaneously. These spray-dried nanocrystals had high drug loading of 61.7% and good redispersity, which was mainly attributed to the addition of SDS. In addition, the nanocrystals were characterized by scanning electron microscopy, differential scanning calorimetry, X-ray power diffraction analysis, Fourier transform infrared spectroscopy and Raman spectroscopy. The results showed that Allisartan Isoproxil was unchanged in chemical structure, but was partially amorphous. Regarding the *in vitro* dissolution, the optimism formulation shown an increased dissolution compared with the bulk drug and aggregated nanocrystals. Importantly, the optimum formulation increased the oral bioavailability of crude ALS-3 for 4.73 times. In conclusion, we developed a method to solidify aqueous nanocrystals with increased drug loading, good redispersity and improved bioavailability for high hydrophobic drugs.

1. Introduction

Over the last decade, new drug candidates have become more hydrophobic and less water-soluble, which was one of the key challenges in their dosage form development. Accordingly, formulation scientists have to consider more complicated drug delivery platforms including micronization (Rasenack and Muller, 2004), self-emulsification (Miao et al., 2016), salt formation (Serajuddin, 2007), the use of co-crystals (Kuminek et al., 2016), cyclodextrin inclusions (Brewster and Loftsson, 2007), solid dispersions (Srinarong et al., 2011) and solid lipid nanoparticles (Bunjes, 2010) for this class of compounds. Although some of these approaches have been successfully utilized, due to the large amount of excipients used, most strategies have low drug loading and they were only suitable for delivering the drugs with low dose requirements. Hence, there is a growing need for a formulation with high drug loading for delivering that class of drugs with high daily dose.

Unlike other formulation strategies, drug nanocrystals can have a high loading for these drugs because the nanocrystals are composed of almost 100% drug particles and only a minimum amount of suitable surfactants and/or polymers as stabilizers. Drug nanocrystals (Singh et al., 2011), a submicron colloidal dispersion system with sizes ranging from 100 to 1000 nm, and the nanosized particles can enhance dissolution velocity and saturation solubility as predicted by the Noyes–Whitney and Ostwald–Freundlich principles (Dolenc et al., 2009; Shen et al., 2015). Therefore, it is reasonable to use the nanocrystals strategy to develop high drug loaded formulations for drugs with a high hydrophobicity. However, the nanocrystals in aqueous phase are usually physically (*e.g.* Ostwald ripening and agglomeration) and chemically (*e.g.* hydrolysis) unstable, thus, transformation of liquid state nanocrystals into solid state is necessary. Technically, it can be achieved using established unit-operations such as freeze-drying, spray-drying, pelletization and granulation. However, drying of nanoparticles may cause aggregation on their redispersion, leading to the decrease in dissolution and, thus, the variability of oral bioavailability (Ma et al., 2013). Accordingly, supporting agents were usually added prior to drying, in order to achieve adequate redispersion. Nevertheless, it has been shown that drugs with high hydrophobicity resulted in hard aggregates and were difficult to be redispersed compared to drugs with low hydrophobicity (Van Eerdenbrugh et al., 2008). For extremely

* Corresponding authors at: Mailbox 59#, Department of Pharmaceutics, School of Pharmacy, Shenyang Pharmaceutical University, No. 103, Wenhua Road, Shenyang, 110016, China.
E-mail addresses: graham_pharm@aliyun.com (Q. Fu), sunjin0529@aliyun.com (J. Sun).

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hydrophobic drugs nanocrystals, more supporting agents were necessary during solidification, in other words, it is scarcely possible to obtain the high drug loading and good redispersity simultaneously. What is more, in the case of the strongly hydrophobic active ingredients, it is extremely hard to be dispersed uniformly in water (Hu et al., 2014), which may lead to a poor batch to batch reproducibility of the nanocrystals. Thus, formulation of drug nanocrystals with high drug loading, good redispersity and improved oral bioavailability, simultaneously, for extremely hydrophobic drugs were needed.

Allisartan Isoproxil (ALS-3), a newly developed sartan-type antihypertensive drug with a novel chemical structure is a prodrug to produce an active carboxylic acid metabolite (EXP-3174) in vivo.Unlike Losartan, ALS-3 was completely converted to EXP-3174 after oral absorption, which blocks angiotensin II receptors to produce an antihypertensive effect (Liu et al., 2013; Wu et al., 2009). Hence, ALS-3 is an effective antihypertensive drug with a lower toxicity than Losartan (Li et al., 2015; Wu et al., 2009), which would possess a bright and wide clinical application for the treatment of hypertension in the future. Thus, in this study, the ALS-3 was used as a model. The purpose of this article was to provide a method for the solidification of ALS-3 nanocrystals with high drug loading, easy redispersity and improved oral bioavailability. The nanocrystals were prepared by bead milling followed by spray drying. Then, the supporting agents were optimized based on the drug loading and redispersed hydrodynamic diameters, and the optimism formulation possesses the drug loading of 61.7% and high redispersity, which was mainly attributed to the addition of SDS prior to spray drying. The nanocrystals were characterized by dynamic light scattering, scanning electron microscopy (SEM), differential scanning calorimetry (DSC), X-ray power diffraction analysis (XRPD), Fourier transform infrared spectroscopy (FT-IR), and Raman spectroscopy. Then, a dissolution test was carried out to evaluate the *in vitro* behavior. Finally, nanocrystal formulations and the crude drug were compared for their *in vivo* pharmacokinetic performance after oral administration to Sprague-Dawley rats, and an LC–MS method was used to measure the drug plasma concentrations.

2. Materials and methods

2.1. Materials

Crude ALS-3 was a gift from Shenzhen Salubris Pharmaceutical Co., Ltd. (Shenzhen, China). Gelatin capsule shells (size 00) were a gift from Capsugel (Suzhou, China). Irbesartan was obtained from Hubei Prosperity Galaxy Chemical Co., Ltd. (Wuhan, China). Polyvinylpyrrolidone K30 (PVP K30) and Pluronic F127 was obtained from BASF Co., Ltd. (Shanghai, China). Glucose, sucrose, maltose, sorbitol were obtained from Tianjin Bodi Chemical Holding Co., Ltd. (Tianjin, China). Tween 80 was obtained from Tianjin Hengxing Chemical Preparation Co., Ltd. Mannitol and Pluronic F68 were provided by Beijing Fengli Jingqiu Pharmaceutical Co., Ltd. (Beijing, China). Sodium dodecyl sulfate (SDS), hydroxypropyl methyl cellulose E5 (HPMC E5), hydroxypropyl methyl cellulose E50 (HPMC E50) and hydroxypropyl methyl cellulose (HPC) were obtained from Anhui Sunhere Pharmaceutical Excipients Co., Ltd. (Huainan, China). Acetonitrile and methanol were HPLC grade and obtained from Thermo Fisher Scientific (Shanghai, China). Formic acid was obtained from Dikma Technology Inc. (Beijing, China). Polyethylene glycol 4000 (PEG 4000), polyethylene glycol 6000 (PEG 6000), methanol and all other organic reagents were obtained from Tianjin Kermel Chemical Reagent Co., Ltd. (Tianjin, China).

2.2. Preparation

2.2.1. Preparation of nanocrystals

A PM4L planetary ball mill (Nanjing Chishun Science & Technology Co., Ltd., China) was used to prepare ALS-3 nanocrystals. Firstly, in order to obtain uniform coarse suspensions, crude ALS-3 (5%, *w/v*) was dispersed in a stabilizer solution using a DF-101S magnetic stirrer (Yuhua Instrument, China) for 10 min at the maximum speed. Then coarse suspensions were transferred to 100 mL milling bowls and beads (Φ=0.3 mm) were added to break up the crude drug at 35.0 HZ for 30 min. The formulations were optimized based on the hydrodynamic diameters and PDIs by using a variety of stabilizers (HPC, HPMC E5, HPMC E50, PVP K30 and Pluronic F68) and concentrations (0.05, 0.075, 0.1, 0.125, and 0.15%, *w/v*).

For physical characterization and physical stability improvement, ALS-3 nanocrystals were spray-dried using a B290 mini spray dryer (Buchi Labortechnik AG, Switzerland). Six types of hydrophilic excipients (sucrose, maltose, mannitol, sorbitol, PEG 4000 and PEG 6000) in combination with three types of surfactants (SDS, Tween 80, Pluronic F127) were used as supporting agents. The types of hydrophilic excipients, the concentration of mannitol, the types of surfactants and the concentration of SDS were investigated, respectively, based on drug loading and redispersed size. In order to maintain homogeneous suspensions, the liquid nanocrystals were stirred slowly using a magnetic stirrer during the spray drying process. The spray drying conditions were as follows: inlet temperature, 120 °C; outlet temperature, 60 °C; feeding rate, 3.5 mL/min; and air flow, 50 mL/min.

2.2.2. Preparation of blank excipients and physical mixtures

The blank excipients and physical mixtures were prepared by spray drying the composition of the corresponding formulations, and no drug was added in the blank excipients. The spray drying conditions were as the same as those described in Section 2.2.1. These samples were used as references for the characterization.

2.3. Characterization

2.3.1. Hydrodynamic diameters and PDIs

The average hydrodynamic diameters (z-ave) and PDIs of fresh and redispersed nanocrystals were measured using a Zetasizer Nano ZS90 instrument (Malvern Co., UK). The spray-dried nanocrystals were re-dispersed in pure water at a drug concentration of 2.5% (*w/v*), which was the same as that for fresh nanocrystals. Each sample was diluted 900-fold with pure water then measured in triplicate with 5 cycles at a fixed angle of 90° at 25 °C.

2.3.2. SEM

The surface morphology and the degree of redispersion of nanocrystals were observed using an ultra plus SEM (Zeiss, Germany). The liquid nanocrystals were diluted to 1 mg/mL. For the spray-dried powders, they were pretreated to eliminate the supporting agents. Firstly, the spray-dried nanocrystals (equivalent to 10 mg ALS-3) were redispersed in 1 mL followed by centrifuging at 13000 rpm for 1 min. Then, the supernatant was abandoned and 10 mL pure water was added to resuspended the residue by vortexing for 3 min. Then, the nanocrystals were dropped onto the surface of a conducting resin and dried in air. Finally, the samples were sputtered with gold for 90 s under vacuum for observation.

2.3.3. DSC

A Discovery 2500 (TA Instruments, USA) instrument was used to investigate the crystallinity of raw ALS-3, blank excipients, a physical mixture, and nanocrystal powders.ith an empty