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Enhanced oral bioavailability and diminished food effect of lurasidone hydrochloride nanosuspensions prepared by facile nanoprecipitation based on dilution

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ABSTRACT

The aim of this study was to improve the oral bioavailability and diminish the food effect of a poorly soluble drug with pH-dependent solubility, lurasidone hydrochloride (LH), by fabricating its nanosuspensions using a facile nanoprecipitation method. Upon dilution with water, LH dissolved in pH 4 solution formed growing cores and aggregated into nanoparticles, due to the maximum solubility of LH at pH 4. Compared with the batches prepared with other stabilizers, the LH nanosuspensions (LH-NS) stabilized by HPMC E50 were found more stable and had a smaller particle size. A Box-Behnken design (BBD) was used to optimize the critical process and formulation parameters. Then the optimized LH-NS were lyophilized with 1% (*w*/*v*) mannitol for long-term stability. According to differential scanning calorimetry and X-ray diffraction analysis, the nanocrystals were still in crystalline state after the preparation procedure. Good physical stability was observed for nanoparticles kept for 6 months at 25 °C and 40 °C/75% RH. The *in vitro* dissolution rate of LH was significantly increased by reducing the particle size. The *in vivo* test demonstrated that the C_{max} and $AUC_{0-24\ h}$ values of nanocrystals in fasted rats were approximately 2.08-fold and 2.39-fold greater than that of raw drug, respectively. Besides, there was no significant difference in the oral bioavailability of nanoparticles between fasting and feeding. This nanoprecipitation technique is a promising method with a facile process and avoidance of toxic organic solvents and undesired byproducts for oral delivery of poorly soluble drugs with pH-dependent solubility.

1. Introduction

Lurasidone hydrochloride (LH) was approved by the United States Food and Drug Administration in 2010 for the treatment of schizophrenia [1]. As a biopharmaceutical classification system (BCS) classification-II drug with pH-dependent solubility, the low dissolution rate of LH is the major reason for its poor oral bioavailability (9%–19% in human) [2]. It is recommended that LH should be administrated along with at least 350 cal of food for absorption enhancement [3]. However, concomitant food intake leads to poor patient compliance. And the presence of food interferes with the dissolution and uniform absorption of poorly soluble drugs [4]. Therefore, it is necessary to improve the solubility and dissolution rate of LH.

Several techniques have been employed to increase the solubility of LH, such as solid dispersions [5], self-emulsions [6] and coamorphous systems [2] which suffer from the drawbacks of complex process, high-cost, poor stability and a large amount of additives. Preparation of nanosuspensions is a promising strategy that can be used to enhance the dissolution rates of poorly soluble drugs [7,8]. Nanosuspensions are colloidal dispersions of nano-sized drug particles stabilized by polymers, surfactants or a mixture of both [9,10] with the advantages of high drug loading [11], food effect reduction [12], bioavailability enhancement [13] and long-term stability [14]. The widely used methods for preparation of nanosuspensions are media milling, high pressure homogenization and antisolvent precipitation [15]. Recently, LH nanosuspensions (LH-NS) have been made by media milling technique [16] which requires high energy input and specialized manufacturing equipment [17]. Antisolvent precipitation generates nanosuspensions generally through dissolving the drug in an organic solvent followed by adding to an aqueous solution [18]. Though it is a simple low energy-consuming process [19], the exclusion of organic solvents would be required and the residue of organic solvents is troublesome in the final products. Lu et al. reported an antisolvent precipitation-ultrasonication method for constructing LH-NS using methanol as the solvent of LH [20]. In order to avoid the use of toxic organic solvents and specialized manufacturing equipment, inorganic acid-base neutralization could be utilized to produce nanosuspensions for hydrophobic drugs with pH-dependent solubility [21–23]. However, the byproducts (e.g. salts) generated by the acid-base reaction reduce the purity of the final products and may bring about instability. Therefore,

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exploring a facile nanonization strategy without generation of undesired byproducts is an attractive focus.

In this work, a facile nanoprecipitation method (Fig. 1) based on dilution was attempted to prepare LH-NS by utilizing the solubility difference of LH in aqueous solutions at various pH values. Owing to the maximum solubility of LH at pH 4, LH molecules could easily reach supersaturation, form growing cores and aggregate into nanoparticles by diluting the drug solution (pH 4) with water. A Box-Behnken design (BBD) was used to optimize the nanosuspensions. Then the optimized LH-NS were lyophilized for long-term stability. Finally, the nanocrystals were characterized with respect to particle size, zeta potential, saturation solubility, *in vitro* dissolution, morphology, crystal form, crystallinity and stability. Besides, pharmacokinetic studies were conducted in fasted and fed rats to determine whether the formulation enhanced the bioavailability and diminished the food effect of LH.

2. Materials and methods

2.1. Materials

Lurasidone hydrochloride (LH) was purchased from Wuhan Humanwell Pharmaceutical Co., Ltd. (Hubei, China). Hydroxyl propyl methyl cellulose E5 Premium LV (HPMC E5), E15 Premium LV (HPMC E15), E50 Premium LV (HPMC E50) and K4M Premium LV (HPMC K4M) were kindly supplied by Shanghai Coloron Co., Ltd. (Shanghai, China). Poloxamer 188 and Poloxamer 407 were procured from BASF (Ludwigshafen, Germany). D-Mannitol was bought from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). Clopidogrel standard was obtained from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Methanol and acetonitrile (HPLC grade) were purchased from Nanjing Chemical Reagent Co., Ltd. (Nanjing, China). All other reagents were of analytical grade.

2.2. Preparation of LH-NS

LH (0.05%, *w*/*v*, relative to distilled water) was solubilized in the mixed solvent (0.4, *v*/*v*, relative to distilled water) of HCl solution at pH 4 and ethanol as a co-solvent. Stabilizer was dissolved in distilled water. Then, both solutions were filtrated through a 0.45 μm filter (Xinya Purification Device Factory, Shanghai, China) to remove possible impurities, respectively. At a certain temperature, the solvent containing LH was moderately injected into the stabilizer solution with stirring at 500 rpm (RCT Basic, IKA, Staufen, Germany) for 60 min.

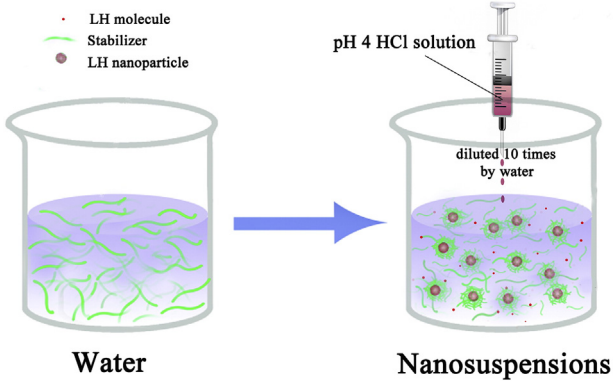

Fig. 1. A sketch of nanoprecipitation based on dilution. (1) The water containing stabilizers. (2) The HCl solution (pH 4) containing LH is diluted 10 times with the water under stirring. LH molecules form growing cores in the mixed solvent (pH 5) upon supersaturation. LH cores grow into nanoparticles surrounded by stabilizers.

2.3. Screening of stabilizer

Different formulations were prepared by changing only the type of stabilizer. The stabilizers investigated included HPMC E5, E15, E50 and K4M, poloxamer 188 and 407. The precipitation temperature, stabilizer/drug ratio and HCl solution/water ratio were kept at 3 °C, 2.5 (*w*/*w*) and 0.2 (*v*/*v*), respectively. The particle size of each formulation was measured before storage and after 2 days of storage at 5 °C. Each experiment was done in triplicate.

2.4. Optimization of LH-NS

Initial screening trials were performed for evaluating the formulation and processing aspects of LH-NS. The results from the initial screening trials indicated that precipitation temperature, stabilizer/drug ratio and HCl solution/water ratio are the main factors which affect the particle size and PDI of nanosuspensions. Based on the number of factors and their levels, a Box-Behnken design (BBD) was used to evaluate the effect of formulation and processing parameters on the physical properties of nanosuspensions. The three independent factors identified for this study were precipitation temperature, stabilizer/drug ratio and HCl solution/water ratio. All these factors were operated at three levels (+1, 0 and −1). The type of stabilizer, HPMC E50, remained unchanged in the experimental trials. Design-Expert® 8.0.7.1 software (Stat-Ease Inc., USA) was used to complete the study. A total of 15 experiments were designed by the software with 3 center points. Table 1 displays the independent factors and their design levels used in this study. Table 2 lists out all the experiments of Box-Behnken experimental design. Each experiment was carried out three times.

2.5. Lyophilization and redispersion

Optimized LH-NS were lyophilized in order to achieve long-term stability. Briefly, 3 ml of freshly prepared nanosuspensions along with 1% (*w*/*v*) of mannitol as a cryoprotectant were placed into a 10 ml Cillin-glass bottle. Each vial was pre-frozen at −20 °C for 48 h and then freeze-dried in a FD-1C-50 lyophilizer (Boyikang Laboratory Instruments Co. Ltd., China) at −55 °C, 0.10 mbar of pressure for 24 h to produce lyophilized powder. Re-dispersed lyophilized LH-NS were developed by re-dispersing the prepared freeze-dried powder with distilled water to an LH concentration of 0.1% (*w*/*v*).

2.6. Characterization of nanosuspensions

2.6.1. Particle size and zeta potential

The particle size, polydispersity index (PDI) and zeta potential of LH-NS were determined by a Nano-Zetasizer (3000HSA, Malvern Instruments Ltd., Malvern, UK). Each sample was suitably diluted with distilled water before analysis. Three observations were recorded for each sample.

Table 1
Critical factors and their levels of Box-Behnken design.

Critical factors		Design levels	
Actual	Coded	Actual	Coded
Precipitation temperature (°C)	A	3	−1
		14	0
		25	+1
Ratio of stabilizer to drug (*w*/*w*)	B	1.5	−1
		2.0	0
		2.5	+1
Ratio of HCl solution to water (*v*/*v*)	C	0.1	−1
		0.2	0
		0.3	+1