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Investigations on solid dispersions of valsartan with alkalizing agents: Preparation, characterization and physicochemical properties

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ABSTRACT

Valsartan has been used for the treatment of hypertension disease. However, the oral bioavailability of valsartan has been reported to be only ~23%, accompanied with high permeability and poor aqueous solubility. The object of this research was to prepare solid dispersions of valsartan with an inorganic ($CaCO_3$) and organic base (*N*-methyl-D-glucamine) in an effort to increase the aqueous solubility and dissolution rate of the drug. The as-prepared solid dispersions of valsartan were prepared in an environmentally friendly manner using $CaCO_3$ and MG and a roll mill. The physicochemical properties were studied in the solid state using DSC, PXRD and IR. Furthermore, the solubility of valsartan increased 46-fold in solid dispersion with $CaCO_3$ and 9-fold in solid dispersion with MG. More than 95% of valsartan in solid dispersions was found to be released in simulated intestinal fluid, whereas only 35% was found to be released using pure valsartan within the same time interval. Storage tests showed that the as-prepared solid dispersions were equally stable compared to pure valsartan at 40 °C. Potentially, the synthesized solid dispersions of valsartan with enhanced solubility and dissolution rates may represent promising formulations for improving the overall oral bioavailability of the drug in clinical applications.

1. Introduction

Valsartan represents a highly selective angiotensin II (type I-receptor subtype) antagonist [1]. The compound is mainly used in the treatment of hypertension disease with reduced adverse side effects compared to other drugs used against hypertension [2]. However, the clinical applicability of valsartan is generally limited by its low oral bioavailability (~23%), primarily caused by the poor aqueous solubility of valsartan (0.180 g/L, 25 °C) [3,4]. To improve the oral bioavailability of valsartan, extensive formulation approaches have been reported, including self-emulsifying drug-delivery systems, nanosuspensions, inclusion complexation with cyclodextrin and solid dispersion with hydroxypropyl methylcellulose, sodium lauryl sulphate, poloxamer and sodium starch glycollate [5–10]. Although some progress has been made in previous research studies, various critical aspects still remain to be addressed. In particular, the preparation process is often accompanied with the use of toxic organic solvents. Furthermore, a partial decomposition of the drug is frequently observed and the overall production process is reported to be rather complex [5–11,35].

For several decades, mechanochemistry has been known to be a relatively simple and environmentally friendly technology [12]. The term describes the processes of mixing, pressing and crushing materials manually with a mortar and pestle or mechanically using a mill. Carrying out above actions, mechanical energy is transferred to the surface of the materials in the solid state, resulting in local energy accumulation in submicroscopic areas. This in turn creates a metastable structure that releases part of the accumulated energy to reach a more stable thermodynamic stage. After the redistribution of energy, the starting materials experience some modifications including solid particle aggregations, propagation of dislocations, phase transformation and molecular interactions [13,14]. Based on these observations, mechanochemistry can be used to synthesize “pharmaceutical solid dispersions” in an effort to optimize the physicochemical properties of drugs without changing their chemical structures [15–17]. By comparison with traditional methods used for the preparation of drug solid dispersions, the mechanochemical synthesis represents a one-stage process with no strict requirements on the use of solvents, often requiring a difficult and expensive solvent removal process. Furthermore,

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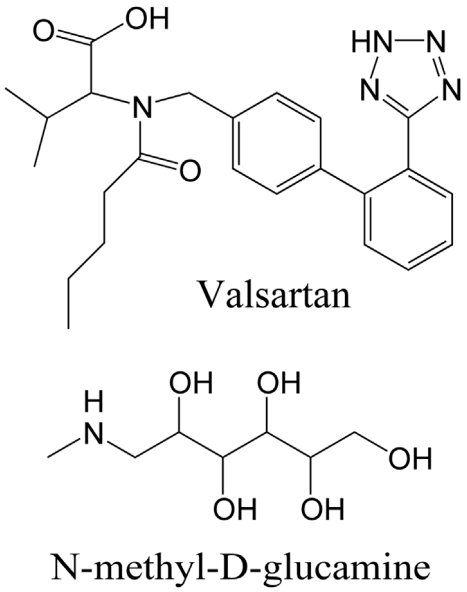

Fig. 1. Molecular structures of valsartan and MG.

no sophisticated equipment is required [18,19].

The present study was designed to increase the aqueous solubility and the dissolution rate of valsartan to improve the oral bioavailability of the drug. Because of the free acid form of valsartan, $CaCO_3$ and *N*-methyl-D-glucamine (MG) were selected as alkalizing additives. Binary solid dispersions of valsartan were prepared using planetary and roll mills. The obtained solid dispersions were characterized in the solid state by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), X-ray powder diffraction and Fourier transform infrared spectroscopy (FT-IR). Moreover, the solubility and dissolution rates of valsartan in solid dispersions as well as the stability characteristics during storage were studied.

2. Materials and methods

2.1. Materials

Valsartan represents a tetrazole derivative that contains acidic (pK_a = 4.00) and carboxylic functional groups (pK_a = 4.61) [22] (cf. Fig. 1). Alkalizing agents used throughout this study were *N*-methyl-D-glucamine (cf. Fig. 1), an amino sugar derived from glucose (pK_a = 9.5) [20], and $CaCO_3$ (pK_a = 9.0) [22].

Valsartan (Huahai Pharmaceutical Co. Ltd., Taizhou, China) of pharmaceutical grade was used without further purification. *N*-methyl-D-glucamine (MG, purity ~99.5%) was purchased from Aladdin Industrial Co. Ltd., Shanghai, China. Calcium carbonate ($CaCO_3$, PC-000658, 2013-07-30, purity > 99%) was purchased from Shanghai Nuochen Pharmaceutical Co. Ltd., China.

2.2. Preparation of samples

2.2.1. Treatment in planetary mill: "a stress-test"

A planetary mill was used for treatment and to achieve maximum effects on possible phase conversions and chemical interactions. Pure valsartan and its mixtures with MG and $CaCO_3$ at a molar ratio of 1:1 were treated. The selection of this component ratio can be explained by the following factors: valsartan salts with alkalizing agents have not been isolated individually and the stoichiometric ratios of acidic and basic functional groups are unknown. However, valsartan and MG molecules each feature one acidic and basic group. Therefore, it is reasonable to assume the stoichiometry for salt formation as a molar ratio of 1:1. In case of $CaCO_3$, the acidic part of the salt can be both monobasic and dibasic. Type of mill: AGO-2, processing mode: acceleration of grinding media ~40 g, total material weight: ~2.5 g, drum capacity: ~50 mL, grinding media: steel balls (diameter 6 mm, 75.0 g load). The milling time was set to 5 min and 10 min for pure valsartan and 5 min for its mixtures with MG and $CaCO_3$.

2.2.2. Production of valsartan solid dispersions

A so-called "mild mode" was used for processing in a roll mill. The latter allows for obtaining solid dispersion/particle aggregates. Furthermore, the possibility of chemical reactions and/or metal impurities is extremely low using this mode. These factors further influence the purity of the product which proves to be a crucial aspect to be considered when using solid dispersions in future clinical applications. Moreover, this processing mode provides an opportunity to scale up the material production [15,19]. Furthermore, other criteria were considered for the selection of the component ratio and in order to achieve a significant solubility increase and a reduced amount of auxiliary substances. The latter feature benefits formulation creation on the basis of solid dispersions. Thus, a mass ratio of 5:1 was used for processing which corresponds to a molar ratio of 2:1 for MG solid dispersion and a molar ratio of 1:1 M ratio for $CaCO_3$ solid dispersion, where the fraction of auxiliary substance was only 16.7 wt%. This reduced auxiliary substance content lead to solubility decrease.

A roll mill VM-1 was used to synthesize the solid dispersion. The processing mode was as follows: acceleration of grinding media ~1 g, total material weight 20 g, drum capacity ~300 mL, grinding media-steel balls (diameter: 22 mm,load: 675 g). The corresponding milling time ranged from 1 to 4 h.

2.3. Characterization of samples

2.3.1. Scanning electron microscopy (SEM)

Electronic images were acquired using a Hitachi TM-1000 microscope (Tokyo, Japan). The gold coating of samples was performed using a JEOL JFC-1600 auto fine coater (Tokyo, Japan). The coating parameters were as follows: sputtering time of 30 s, amperage of 30 mA, and film thickness of 15 nm.

2.3.2. Fourier transform infrared spectrophotometry (FT-IR)

FT-IR spectra of samples were collected from 500 to 4000 cm^{-1} using the Fourier spectrophotometer "Infralum FT-801" ("Simeks", Novosibirsk, Russia). All samples were taken in thin tablets with KBr.

2.3.3. Powder X-ray diffraction (PXRD)

Powder X-ray diffraction analysis of valsartan and its solid dispersions was carried out on a DRON-4 equipment ("Byrevestnik", St. Petersburg, Russia) using CuKα radiation, a counter speed of 2 deg/min, and a range of intensity measurement of ~1000.

2.3.4. Differential scanning calorimetry (DSC)

Thermal analysis of valsartan and its solid dispersions was carried out on a DSC-550 instrument (Instrument Scientific Specialists Inc., Omaha, NE, USA) in Ar atmosphere. Temperature program: 20–250 °C; Heating rate: 10 °C/min.

2.3.5. HPLC

An Agilent 1200 HPLC (Agilent Technologies, Palo Alto, CA, USA) was used, equipped with a reverse phase column (4.6 × 50 mm, Zorbax Eclipse SB-C18) and a diode-array detector at 30 °C. The mobile phase consisted of a 50:50 (v/v) mixture of acetonitrile and acetate buffer (pH = 3.4), the flow rate was 1.0 mL/min, the detection wavelength was 234 nm, and the injection volume was 5 μL.

2.3.6. Test of valsartan content in solid dispersions

To determine the drug content in synthesized solid dispersions, the prepared compositions were dissolved in 50 mL of ethanol. The