Powder Technology 278 (2015) 204–210

Contents lists available at ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

Enhanced hypotensive effect of nimodipine solid dispersions produced by supercritical CO_2 drying

Manoela Klüppel Riekes [a], Thiago Caon [a], José da Silva Jr. [b], Regina Sordi [c], Gislaine Kuminek [a], Larissa Sakis Bernardi [d], Carlos Renato Rambo [b], Carlos Eduardo Maduro de Campos [e], Daniel Fernandes [f], Hellen Karine Stulzer [a,*]

[a] Programa de Pós-Graduação em Farmácia, Universidade Federal de Santa Catarina, Florianópolis 88040-970, Brazil
[b] Programa de Pós-Graduação em Engenharia Elétrica, Universidade Federal de Santa Catarina, Florianópolis 88040-970, Brazil
[c] Programa de Pós-Graduação em Farmacologia, Universidade Federal de Santa Catarina, Florianópolis 88040-970, Brazil
[d] Departamento de Ciências Farmacêuticas, Universidade Estadual do Centro-Oeste, Guarapuava 85040-080, Brazil
[e] Programa de Pós-Graduação em Física, Universidade Federal de Santa Catarina, Florianópolis 88040-970, Brazil
[f] Programa de Pós-Graduação em Ciências Farmacêuticas, Universidade Estadual de Ponta Grossa, Ponta Grossa 84030-900, Brazil

ARTICLE INFO

Article history:
Received 4 December 2014
Received in revised form 4 March 2015
Accepted 20 March 2015
Available online 28 March 2015

Keywords:
Nimodipine
PVP K-30
Solid dispersions
Supercritical fluid technology

ABSTRACT

Solid dispersions of nimodipine and PVP K-30 were prepared by supercritical fluid technology at three drug:carrier ratios (1:9, 2:8, 3:7, w/w). The samples were characterized by X-ray powder diffraction, infrared spectroscopy and scanning electron microscopy, and evaluated by means of their solubility, dissolution rate and hypotensive effect. The solid dispersion with the highest amount of PVP K-30 (SD 1:9) presented an amorphous state, a porous surface and hydrogen bonds between nimodipine and the carrier. On the other hand, the other solid dispersions were semicrystalline. All formulations enhanced the solubility and dissolution rate of nimodipine and the best results were found for SD 1:9. This formulation promoted an increase of more than 1300% in the solubility of nimodipine, besides releasing 100% of the drug within 5 min. When submitted to in vivo studies SD 1:9 decreased significantly the mean arterial pressure and also reduced its phenylephrine-induced increase.

1. Introduction

As a consequence of the synthesis tools employed, the number of new drug candidates with poor aqueous solubility and dissolution rate has grown constantly over the past two decades [1]. Since the poor solubility of active pharmaceutical ingredients (APIs) is considered a limiting step for their oral bioavailability [2], this fact demonstrates an urgent need for new approaches regarding poorly water-soluble APIs.

Amongst the available technological tools which have been developed to increase the solubility of poorly water-soluble compounds, converting a crystalline API into their amorphous counterpart is one of the most promising strategies [1–3]. As a result of their high internal energy, amorphous materials usually exhibit greater molecular mobility and enhanced thermodynamic properties compared to the crystalline structures, which generally lead to increased apparent solubility and dissolution rate [3–5]. In this regard, solid dispersions (SDs) have been widely explored [2,6,7] and can be defined as glass solutions of poorly soluble compounds with hydrophilic carriers [1]. However, the high internal energy of amorphous materials is also responsible for their thermodynamic instability leading to relaxation, nucleation and crystal growth phenomena during storage, processing or dissolution in the gastrointestinal tract [1]. In this context, SDs can also be considered an efficient strategy, since the carrier can inhibit crystallization through the raise of the overall glass transition temperature of the dispersion, which reduces API molecular mobility, or through the interaction with the API via hydrogen bonding [6].

As a more recent approach to obtain SDs, the supercritical fluid technology is based on a compound existing as a single fluid phase above its critical temperature and critical pressure [8]. In pharmaceutical applications, carbon dioxide (CO_2) is the most widely used supercritical fluid because it has a low critical point and is non-toxic [9]. The most typical methodology based on supercritical fluid extraction involves the use of CO_2 as a solvent and is called as 'rapid expansion of a supercritical solution' (RESS). This procedure is characterized by firstly solubilizing the solute in a supercritical fluid, which is then rapidly expanded by sudden decompression, typically by passing through an orifice at low pressure [10]. As an advantage of RESS when compared to other supercritical fluid methodologies, it does not require the use of organic solvents, which generates particles of high purity and with reduced particle diameter [11]. Moreover, RESS is a very attractive process as it is simple and relatively easy to implement [12].

* Corresponding author. Tel.: +55 48 3721 4585; fax: +55 48 3721 9542.
E-mail address: hellen.stulzer@gmail.com (H.K. Stulzer).

http://dx.doi.org/10.1016/j.powtec.2015.03.029
0032-5910/

In addition, the selection of an ideal carrier is also crucial for successful SDs [1]. Polyvinylpyrrolidone (PVP) (Fig. 1A) is a hydrophilic polymer generated by polymerization of vinylpyrrolidone [2]. Due to its good aqueous solubility, biocompatibility, lack of toxicity, temperature-resistance and stability under different pH values [13], this second generation carrier has been often used to produce SDs of poorly water APIs [1,2,14]. More recently, PVP has been employed on the obtainment of several API solid solutions through supercritical fluid approaches [13,15,16].

Nimodipine (NMP) (Fig. 1B), a classical BCS II drug, is a dihydropyridine calcium channel blocker originally developed for the treatment of hypertension, although nowadays it has also been used to prevent subarachnoid hemorrhage complications [17–19]. Moreover, this compound presents limited bioavailability (only 13%), low aqueous solubility [20] and an extensive first-pass metabolism, which typically requires frequent doses (60 mg each 4 h) during the therapeutic treatment. For the patient, lower drug dosage administration intervals imply an inconvenient and non-compliant treatment [17–19].

Some SDs of NMP have been reported in literature during the past years. However, these reports are related to SDs obtained via conventional methods, such as solvent evaporation under vacuum, hot melt extrusion, melting and more recently, ball milling [21–37]. In addition, few studies have considered the in vivo impact of these preparations. In this context, the evaluation of a novel technique to obtain SDs of an API model is extremely relevant in order to optimize its characteristics and comprehend its in vivo behavior.

Considering the limited biopharmaceutical properties of NMP and the need to explore novel manufacturing techniques, this study reported the production and physicochemical characterization of SDs composed of NMP and PVP K-30 through supercritical fluid drying technique. The formulation with the most promising results, regarding the enhancement of the solubility and dissolution rate of the API was also submitted to in vivo studies, in order to evaluate its hypotensive effect.

2. Material and methods

2.1. Materials

NMP was purchased from Chang Zhow ComWin Fine Chemicals (batch 20110305; Jiangsu, China) and PVP K-30 was derived from Via Farma LTDA (batch 10713659/1; São Paulo, Brazil). High-performance liquid chromatography (HPLC)-grade acetonitrile and methanol were obtained from J.T. Baker® (Phillipsburg, NJ). Phenylephrine chloride was purchased from Sigma Chemical Co. (St Louis, MO, USA). All other chemicals used were of pharmaceutical grade.

2.2. Preparation of SDs

SDs were composed of three different drug:carrier (w/w) ratios (1:9, 2:8 and 3:7) and denoted as SD 1:9, SD 2:8 and SD 3:7, respectively. These compositions were chosen based on previous reports of SDs of NMP and PVP K-30 [30]. An E3100 Critical Point Dryer equipment (Quorum Technologies®,West Sussex, United Kingdom) was employed and the RESS methodology applied was adapted according to the experimental procedures described by Guan and coworkers [11]. Within this context, amounts corresponding to 2.5 g of each sample were sealed in a porous cellulose pouch (22 μm pore size) and kept inside the vessel. The liquefied CO_2 filled the vessel and was maintained in contact with the sample during 3 days, at room temperature and pressure. After this period, the CO_2 was compressed and heated until achieving the controlled operating conditions of 100 bar and 40 °C. Under these conditions, the system was allowed to equilibrate for 3 days. In the end of the sixth day, the vessel was depressurized and the samples were collected from the cellulose pouch. The obtained SDs were passed through a 60 mesh sieve and stored under vacuum, at room temperature.

Physical mixtures were prepared through simple spatulation of drug and carrier, accurately weighed at different proportions. No processing with supercritical CO_2 drying was performed in these samples. The physical mixtures were named as PM 1:9, PM 2:8 and PM 3:7, corresponding to proportions of NMP:PVP K-30 (w/w) of 1:9, 2:8 and 3:7, respectively.

2.3. HPLC analysis

The HPLC analyses were carried out through a stability-indicating method already described [38]. A Shimadzu® LC-10A system (Kyoto, Japan) equipped with an LC-10AD pump, DGU-14A degasser, SPD-10AV variable-wavelength detector (set at 235 nm) and an SCL-10AVP system controller unit was used. The experiments were performed with a reversed-phase Phenomenex® (Torrance, CA) Luna C18 column (250 × 4.6 mm i.d., 5 μm), including a security guard holder (C18, 4.0 × 3.0 μm i.d.). The mobile phase consisted of an isocratic system composed of acetonitrile:methanol:water (55:11:34 v/v/v), with a flow rate of 0.5 mL min^{-1}, at 40 °C. After the filtration in 45 μm membranes, 20 μL of sample (at theoretical concentration of 20 μg mL^{-1}) was injected. Data acquisition was performed using the CLASS-VP software. This method was revalidated according to ICH Guidelines [39] and it was considered specific, linear ($r > 0.999$), sensible (limits of quantification and detection of 1.22 μg mL^{-1} and 0.40 μg mL^{-1}, respectively), precise (intra- and interday relative standard deviations of 0.9 and 1.2%, respectively) and accurate (recoveries ranged from 98.2 to 100.8%), for measurements with SDs.

2.4. Measurement of solubility

In order to determine the NMP solubility, an excess of drug in SDs was weighed and added to 30 mL of acetate buffer (pH 4.5) containing 0.3% of sodium lauryl sulfate (SLS), giving a final concentration of 2.0 mg mL^{-1}. Samples were kept under stirring at 150 rpm in a thermostatically controlled water bath (37 ± 2 °C) (Dist®, model DI-06) until a constant concentration of NMP was reached. At pre-determined intervals, aliquots were withdrawn (with immediate replacement of fresh solution) and filtered through 22 μm filters before taking the readings on a UV/VIS spectrophotometer (Cary 50 BIO, Varian®) at 340 nm.

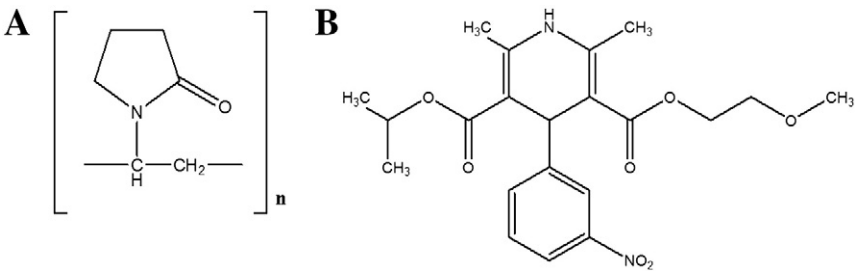

Fig. 1. (A) Monomeric unit of PVP K-30 and (B) chemical structure of NMP.