Powder Technology 323 (2018) 219–229

Contents lists available at ScienceDirect

Powder Technology

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

Design and evaluation of nanocomposite microparticles to enhance dissolution and oral bioavailability of andrographolide

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ARTICLE INFO

Article history:
Received 28 May 2017
Received in revised form 29 September 2017
Accepted 3 October 2017
Available online 05 October 2017

Keywords:
Nanocomposite microparticles
Nanocrystals
Glycyrrhizin
Andrographolide
Bioavailability

ABSTRACT

To enhance dissolution and improve oral bioavailability of the poorly water-soluble drug (andrographolide, ADP), using a natural triterpenoid glucoside (glycyrrhizin, GLC) as stabilizer, the ADP nanocrystals (ADP-NC) were prepared in water by homogenization method and converted into ADP nanocrystals-agglomerated particles (nanocomposite microparticles, ADP-NP) using spray-drying. Different types of matrix formers from glucoside (GLC), polyol (mannitol), disaccharide (lactose), polysaccharide (maltodextrin), and polymer (PVPK30) were systematically investigated their effects on particles properties of ADP-NP. And the acceptable ADP-NP was further characterized for oral bioavailability. The results demonstrated that ADP–NC with particles size of 476 ± 22 nm and span of 2.134 ± 0.016 were successfully prepared. The ADP-NP containing 100% ratio of GLC possessed a higher yield (60.47%), more excellent redispersibility (1.06) and flowability (HR 1.16), compared to those containing mannitol, lactose, PVPK30 and maltodextrin as matrix formers. These were related with the glass transition property of mannitol, lactose, PVPK30 and maltodextrin. The DSC and XRD analysis demonstrated that the mannitol, lactose, PVPK30 and maltodextrin were amorphous state presented in ADP-NP, but the crystal state of ADP and GLC remained unchanged during the preparation. The ADP-NP containing GLC showed the fast dissolution rate and significantly improved the bioavailability (794.338 ± 229.259 μg/L·h) of ADP. This study demonstrated the feasibility of nanocomposite microparticles strategy to improve the oral bioavailability of poorly soluble ADP, and GLC can be an alternative matrix former of ADP-NP, which could prevent from irreversible agglomerates of ADP-NC during spray-drying.

1. Introduction

Andrographolide (ADP, Fig. 1A) is a major diterpenoid lactone isolated from *Andrographis paniculata Nees* (Acanthaceae), an herb found in Asian countries such as Thailand, India and China. ADP exhibits a wide range of biological activities including anti-bacterial [1], anti-inflammatory [2], anti anti-cancer [3], which is approved by the China Food and Drug Administration (CFDA) for treatment of influenza, viral respiratory infection and bacillary dysentery. According to the Biopharmaceutical classification system (BCS), ADP belongs to BCS class II, which is characterized by low solubility (3.29 μg/mL) and high permeability (log P = 2.63) [4,5]. The poor dissolution of ADP is the rate-limiting step for absorption, which results in its poor bioavailability (0.98%) [6].

Nanocrystals are promising formulation approach for drugs belong to BCS class II [7]. Nanocrystals are typically produced in the form of nanosuspensions, which are submicron, colloidal dispersions of nanosized drug particles, stabilized by surfactants, polymers, or a mixture of both [8,9]. The drug is maintained in the required crystalline state with particle size reduction which leads to an increase in surface area and creation of high energy surface due to the disruption of drug microcrystals to nanocrystals (NC) [10]. Therefore, the stability issue (such as sedimentation, aggregation and crystals growth) can occur during either the preparation process or storage, which limits usage of nanocrystals in pharmaceutical industry. To overcome nanosuspensions stability problem, it is an increasingly popular formulation strategy that, the nanocrystals suspensions is transformed into nanocomposite microparticles (also named nanocrystals-aggregated particles, NP), which combined the advantages of liquid nanosuspensions with the benefits of solid formulations [11,12].

Spray-drying is a fundamental particle engineering technique and also a popular method to transform nanosuspensions into NP [13,14]. Moreover, the NP may be subjected to irreversible aggregation of nanocrystals due to thermal stresses of spray-drying [15]. Among variables affecting the quality of spray-drying process, addition of a proper excipient is critical to ensure the redispersibility of NP [16,17]. Selection of the right excipients for formulation of the NP is very important. Sugars are common excipients playing a significant role in preventing NP from aggregation, which could form a matrix around nanocrystals

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https://doi.org/10.1016/j.powtec.2017.10.010
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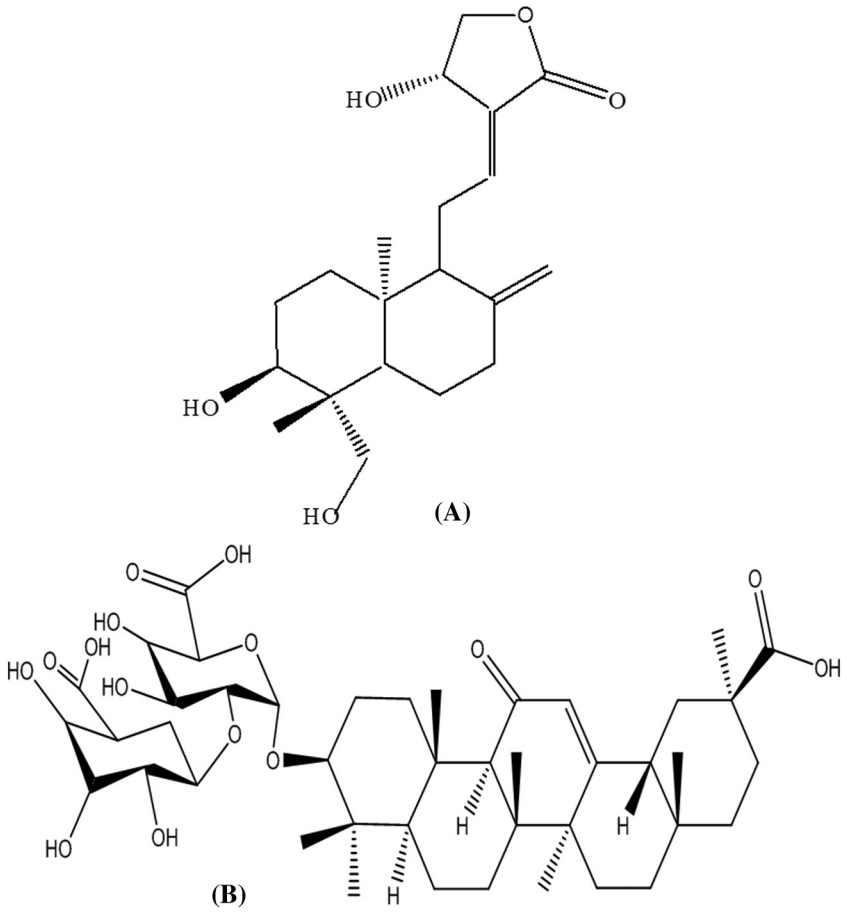

Fig. 1. The chemical structure of ADP (A) and GLC (B).

and help NP to reconstitute into the original nanosuspensions. Recently, interest in use of novel triterpenoid glucoside as the matrix carrier in the NP system has been studied [18,19]. Glycyrrhizin (GLC, Fig. 1B), a triterpenoid glucoside with two glucuronic acids, present in the root of licorice belonging to the genus Glycyrrhiza, is used as a natural sweetener with a low calorific value, because it exhibits sweetness 50 times more than that of sucrose [20,21,22]. Due to its amphiphilic property, it can be used as a natural matrix former for NP and an active solubilizer with the ability to enhance solubility of poorly water-soluble drugs.

The objective of the present study was to convert ADP nanocrystals suspensions (ADP-NC) into the stable ADP nanocomposite microparticles (ADP-NP). Different types of matrix formers from natural glucoside (GLC), polyol (mannitol), disaccharide (lactose), polysaccharide (maltodextrin), and polymer (PVPK30) in 3 ratios of ADP-NC/matrix formers (0.5, 1 and 2 (w/w)), were systematically investigated their effects on particles properties of ADP-NP. Physicochemical properties of the obtained ADP-NP were assessed in terms of particle size, redispersibility, morphology, thermal behavior, flowability and dissolution profile. And the acceptable ADP-NP was further characterized for oral bioavailability.

2. Materials and methods

2.1. Materials

ADP and GLC (purity > 95%) were purchased from Zelang Co. (Nanjing, China). Maltodextrin was commercially obtained from Fengli Jingqiu Pharmaceutical Co., Ltd. (Beijing, China). Mannitol and lactose were obtained from Damao Chemical Co., Ltd. (Tianjin, China). Polyvinylpyrrolidone (Kollidon®30, PVPK30) was commercially obtained from BASF (Beijing, China).

2.2. Methods

2.2.1. Production of ADP-NC

ADP-NC was prepared according to our previous report [19]. In briefly, ADP (1%, w/v) was dispersed in 100 ml GLC solutions (0.1%, w/v) using a high shear homogenizer (FLUKO® FA25, Essen, Germany) for 2 min at 19,000 rpm. The obtained ADP coarse suspensions were firstly passed through a high-pressure homogenizer (AH-1000D, ATS Engineering Inc., Seeker, Canada) at four different pressures (100 bar, 300 bar, 500 bar and 800 bar) with 20 cycles per each pressure. The resultant suspension was subsequently homogenized at a final pressure of 1200 bars for 30 cycles.

2.2.2. Particle size measurements of ADP-NC

The diameters of freshly and redispersed ADP-NC were measured by a Mastersizer Micro Plus (Malvern Instruments Limited, Worcestershire, UK) by wet method. Analysis of the diffraction patterns was done using the Mie model ("standard" presentation: dispersant refractive index = 1.55, real particle refractive index = 1.670, imaginary particle refractive index = 0.01). All measurements were performed in triplicate. And span was determined as span = $(D_{90} - D_{10})$ / D50.

2.2.3. TEM

The morphology of ADP-NC were observed using TEM (JEM-1200EX, Japan). One drop of ADP-NC suspensions was placed on a copper grid.