Journal of Drug Delivery Science and Technology 33 (2016) 51–57

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

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

Research paper

Novel tablet formulation of amorphous indomethacin using wet granulation with a high-speed mixer granulator combined with porous calcium silicate

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ARTICLE INFO

Article history:
Received 12 December 2015
Received in revised form
22 February 2016
Accepted 1 March 2016
Available online 8 March 2016

Keywords:
Porous calcium silicate
Solid dispersion
Tablet
Wet granulation
Indomethacin

ABSTRACT

Solid dispersion techniques are useful for improving the dissolution of poorly water-soluble drugs. This study aimed to produce and evaluate solid dispersion tablets improving the solubility and oral bioavailability of a poorly water-soluble indomethacin (IND) by wet granulation method with a high-speed mixer granulator combined with porous calcium silicate (PCS). A low density of PCS is a major disadvantage which is a bulky volume and scattering. So, it is necessary to prepare a high density PCS granule. Our system is very simple. At first, IND ethanol solution was added to PCS in a high-speed mixer granulator. After mixing, the granulation started the addition of the binder water solution to the PCS/IND mixture. The solid dispersion granules were obtained after drying the mixture. The dissolution rates of IND from PCS tablets were markedly enhanced compared with the dissolution rate of the pure drug. IND did not recrystallize in granules prepared using water and this formulation provided superior bioavailability in rats. Our amorphous solid dispersions have been successfully employed to enhance both solubility and oral bioavailability of IND. Though the use of PCS, it may be possible to maximize the bioavailability benefit of amorphous solid dispersions administered as tablet dosage forms.

1. Introduction

Currently, most new candidate drugs show poor solubility in aqueous media [1–4]. The increase in the number of poorly soluble candidate compounds is frequently attributed to improvements in synthesis technology that has enabled the design of highly complicated compounds and to the change in discovery strategy from the so-called phenotypic approach to the target-based approach [4,5]. Poorly water-soluble drug compounds exhibit low systemic absorption and bioavailability; therefore, the development of oral formulations for increased solubility remains an important issue for pharmaceutical scientists.

Solid dispersion techniques, where the active pharmaceutical ingredient is dispersed in an inert matrix [4], are useful for improving the dissolution of poorly water-soluble drugs [6–14]. For example, a polymeric excipient has been used as an inert carrier for obtaining solid dispersion formulations [6–10]. While polymeric excipients are now most commonly used as inert carriers, many attempts have also been made to use porous materials as carriers because they offer a large area for drug adsorption [11–17]. Solid dispersions with porous materials are referred to as surface solid dispersions [17] because the drug is present on the surface of the carrier, unlike the conventional solid dispersions where the drug is trapped within the polymer network. The interactions between the carrier and the drug also play an important role in the release of the drug from the carrier.

Porous calcium silicate (PCS) exhibits a highly porous structure and a large individual pore volume, and it has been used as a liquid absorber and a compressive adjuvant of powder for tableting [18]. While PCS-based solid dispersions have been shown to be effective for improving the dissolution of poorly water-soluble drugs [11–13], PCS, owing to its low density, can easily become airborne during manufacturing. Additionally, low-density materials may not mix uniformly with other materials because of differences in density [19] and may affect the filling of rotary tableting machines [19,20]. Development of high-density PCS granules is therefore essential. Nevertheless, little research on increasing the density of

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http://dx.doi.org/10.1016/j.jddst.2016.03.001
1773-2247/

PCS granules has been reported so far.

Wet granulation is currently the most widely used granulation technique [21,22] because of its favorable characteristics such as increased particle size, improved flow and compression properties, and improved content uniformity of low-dose (<20 mg) tablets [19]. Three main types of granulators are used in the pharmaceutical industry for wet granulation: tumbling granulators, fluidized-bed granulators, and mixer granulators [23]. In particular, high-speed mixer granulators are used extensively because they can produce small (typically less than 1 mm) and dense granules that are ideal for blending and tableting [23]. The granules formed by mixing the powder with an agitator while adding a liquid binder (mainly water) are smaller, denser, and often more spherical than those obtained using tumbling or fluidized-bed granulators [24]. It is likely that the wet granulation method will be useful for producing dense granules of low-density materials such as PCS.

Because of their high entropy, enthalpy, and free energy, amorphous drug particles in a solid dispersion generally recrystallize easily and thus are inherently unstable [4,25–27]. Recrystallization is especially likely in the presence of water [7–10] and solid dispersions are therefore generally prepared without using water, leading to a paucity of reports on solid dispersion granules prepared using water. The aim of the present study was to produce and evaluate PCS-based solid dispersion tablets that improve the solubility and oral bioavailability of poorly-water-soluble indomethacin (IND) (PubChem CID: 3715) using wet granulation with a high-speed mixer granulator.

2. Materials and method

2.1. Materials

IND was purchased from KONGO CHEMICAL Co., Ltd. (Toyama, Japan; purity over 99.5 w/w%). PCS (Fluorite® RE) was provided by Tomita Pharmaceutical Co., Ltd. (Tokushima, Japan) and xylitol for use as a binder was obtained from B Food Science Co., Ltd. (Tokyo, Japan). Crospovidone (Kollidon® CL) used as a disintegrant was obtained from BASF Co., Ltd. (Ludwigshafen, Germany) and silicified microcrystalline cellulose (Prosolv® SMCC90) and magnesium stearate were obtained from JRS PHARMA GMBH & Co. KG. (Rosenberg, Germany) and Nacalai Tesque Ltd. (Kyoto, Japan), respectively. All other chemicals were of reagent grade and were used without further purification.

2.2. Preparation of the solid dispersion granules (PCS granules), adsorption solid dispersion powder, and physical mixture powder

Fig. 1 shows the preparation method for the PCS-based formulation. PCS granules were prepared using IND, PCS, and xylitol (as binder) in ratios specified in Table 1.

For the preparation of PCS granules, IND was completely dissolved in ethanol by heating at 60 °C. The solution was added to PCS and mixed for 5 min using a high-speed mixer granulator (High-Speed Mixer, EARTHTECHNICA Co., Ltd., Tokyo, Japan) at 250 rpm with an agitator and then at 2500 rpm with a chopper. The binder was then dissolved in distilled water and added to the PCS/IND mixture. If required, distilled water was added to equalize the weight ratio of liquid (ethanol and water) to PCS. After the granulation endpoint was determined visually, PCS granules were dried at 70 °C for 12 h and pulverized in a speed mill (Okada Seiko Co, Ltd., Tokyo, Japan).

The adsorption solid dispersion powder (ASD) was prepared by drying the mixture of IND (6 g) dissolved in ethanol (36 g) and PCS (12 g) without the binder at 70 °C for 12 h. The physical mixture powder (PM) was prepared by direct mixing of IND powder (1 g) and PCS (2 g).

2.3. Preparation and evaluation of solid dispersion tablets (PCS tablet)

PCS tablets were prepared using the mixture of PCS granules, silicified microcrystalline cellulose, crospovidone, and magnesium stearate in ratios specified in Table 1. The total weight of the mixture was 100 g. PCS granules were mixed with silicified microcrystalline cellulose and crospovidone using a V-blender (S-5, Tsutsui Scientific Instruments Co., Ltd., Tokyo, Japan) for 5 min, further mixed with magnesium stearate for 2 min, and then compressed using a rotary tableting machine (PICCOLA, Riva S.A., Buenos Aires, Argentina) with 8 mm diameter bi-convex punches at a rotation speed of 20 rpm. All tablets weighed 300 mg (298.5–303.8 mg) and the target compression load for each batch was 5 kN.

The disintegration times of six individual tablets in water were measured at 37 ± 2 °C using a RIKEN disintegration tester (Miyamoto Riken Ind. Co., Ltd., Osaka, Japan) and the mean values were calculated. Dissolution tests were performed according to the JP16 paddle method using a RIKEN dissolution tester (Miyamoto Riken Ind. Co., Ltd.). One tablet containing 10–40 mg of IND was placed in a dissolution medium (900 ml of purified water) at 37 ± 0.5 °C and the paddle was rotated at 50 rpm. The amount of dissolved IND was analyzed using an ultraviolet spectrophotometer (UV-1200, Shimadzu Corp., Kyoto, Japan) at the wavelength of 320 nm. Three tablets were tested from each batch and the mean values were calculated.

The IND content in the tablets was estimated using an ultraviolet spectrophotometer method. Ten tablets were weighed and

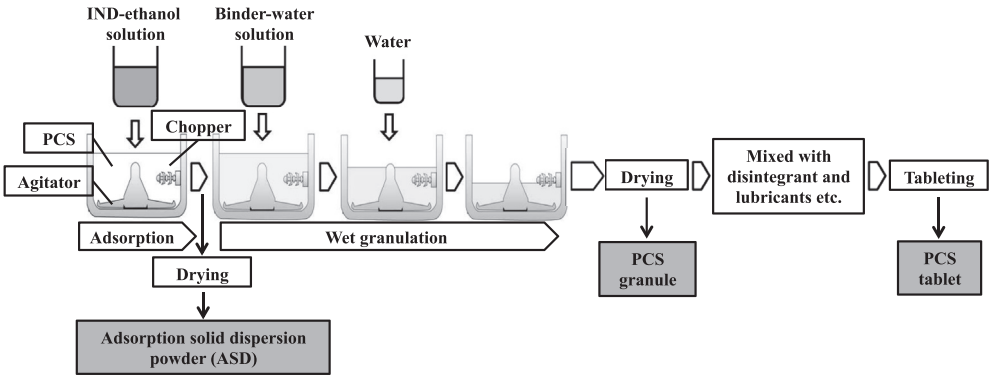

Fig. 1. Preparation method of adsorption solid dispersion powders, granules, and tablets with porous calcium silicate (PCS).