International Journal of Pharmaceutics 423 (2012) 435–439

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

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

Pharmaceutical Nanotechnology

Nano-sized flake carboxymethyl cassava starch as excipient for solid dispersions

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ARTICLE INFO

Article history:
Received 9 October 2011
Received in revised form
21 November 2011
Accepted 9 December 2011
Available online 17 December 2011

Keywords:
Solid dispersion
Nano-size
Carboxymethyl cassava starch (CMCS)

ABSTRACT

Nano-sized excipients were used in solid dispersions (SD) to enhance the dissolution rate of poorly water-soluble drug in this study. Nano-sized flake carboxymethyl cassava starch (CMCS) was firstly synthesized under ultrasonic irradiation. Then acetylsalicylic acid (ASA) was selected as water insoluble drug model to prepare solid dispersions using three different kinds of excipients. SD1 was prepared using native cassava starch as carrier. SD2 and SD3 were prepared using nano-sized CMCS (degree substitution, DS = 1.15, 100–400 nm) and micro-sized CMCS (DS = 0.36, 8–28 μm), respectively. These solid dispersions were characterized by powder X-ray diffractometry, scanning electron micrographs and dissolution. The results suggested that the SD2 prepared by nano-sized CMCS had much better dispersion capability for the drug than the other two solid dispersions. And the dissolution rate of SD2 was considerably higher than that of pure drug. These results indicated that the nanoscale CMCS was a kind of good carrier for solid dispersion to improve the solubility of poorly water-soluble drugs.

1. Introduction

Successful formulation of poorly water-soluble drugs was one of the major problems in pharmaceuticals manufacture. It was important for the development of drug preparation to improve the dissolution rate and solubility, because water-insoluble drugs often showed low absorption and weak bioavailability (El-Badry et al., 2009; Mellaerts et al., 2008). Solid dispersion (SD) technique has been widely used to improve the dissolution rate, solubility and oral absorption of poorly water-soluble drugs. The drug dissolution was improved because the wettability and the dispersibility were enhanced with the reducing of particle size in SD (Douroumis et al., 2007; Okonogi et al., 1997).

Excipients were important constituents of solid dispersions for the choice of excipients could determine the quality of products, such as bioavailability, therapeutic activity and so on. Many kinds of materials were involved in solid dispersion as excipients, such as PEG, PVP, EC, HPMCP, CMEC and so on (Bley et al., 2010; Fini et al., 2008; Miyazaki et al., 2011). What is more, characteristics of excipient also played an important role in the stability of solid dispersion. Since the solid dispersion was an unstable system and the structure of SD would change during the storage period. In this paper, nano-sized carboxymethyl cassava starch as excipient for solid dispersants was investigated to reduce particle size of drug and to increase surface area and close contact between the carrier and the drug, therefore the stability of SD was increased.

2. Experimental

2.1. Materials

Cassava Starch was provided by Guangxi Maple Leaf Starch Co. Ltd. Monochloroacetic acid (MAC) was purchased from Sinopharm Chemical Reagent. Acetylsalicylic acid (ASA) was obtained from Sigma–Aldrich. All other reagents were of analytical grade without further treatment.

2.2. Measurements

FTIR spectra were recorded on a Bruker EQUINOX 55 spectrometer with the KBr-technique. Powder X-ray diffraction measurements (XRD) were performed on a Bruker D8 Advance diffractometer using pressed pellets as samples with Cu Kα radiation (λ = 1.5418 Å) at a voltage of 40 kV and current of 200 mA. Scanning electronic microscopy (SEM) images were taken on a Nova NanoSEM 200 scanning electron microscope.

2.3. Preparation of nano-sized flake carboxymethyl cassava starch (CMCS)

Nano-sized flake carboxymethyl cassava starch was prepared according to the method presented in our early study (Gao et al., 2011). 0.1 mol cassava starch in 70 mL anhydrous ethanol was placed in a glass reactor. 0.25 mol sodium hydroxide

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doi:10.1016/j.ijpharm.2011.12.014

(in 20 mL distilled water) was added dropwise to the starch–solvent mixture under stirring. The mixture was allowed to react at 40 °C for 1 h. Then, 0.075 mol MAC was added to the mixture under ultrasonic irradiation (400 W, 20 min). Then the temperature was kept at 48 °C for 80 min. CMCS with different substitution degree (DS = 0.36, 1.15) were used for solid dispersants.

2.4. Preparation of solid dispersants

Solid dispersants were prepared using evaporation and mechanical abrading. To a solution of 0.1 g ASA in 2.0 mL anhydrous alcohol, 0.5 g carrier was added. This suspension was grinded until dryness. Another 1.0 mL anhydrous alcohol was added and grinded again to collect the solid dispersant. Three kinds of solid dispersions were prepared in this paper. SD1 was prepared using native cassava starch as carrier. SD2 and SD3 were prepared using CMCS (DS = 1.15) and CMCS (DS = 0.36) individually.

2.5. Solubility determination

Dissolution experiments were performed in triplicate according to the Ch.P 2010 (paddle method). The dissolution media was 900 mL phosphate buffer (pH 7.4). A sample equivalent to 10 mg ASA of the solid dispersion was spread on the surface of the dissolution medium. The stirring speed was 50 rpm, and the temperature was maintained at 37 ± 0.5 °C. At selected time intervals for a period of 120 min, 5 mL solution was withdrawn from the dissolution medium through a 0.22 μm membrane filter and assayed spectrophotometrically at 227 nm.

3. Results and discussion

3.1. Characteristics of solid dispersion with native cassava starch (SD1)

3.1.1. XRD analysis of solid dispersion (SD1)

The XRD spectra of native cassava starch, ASA and SD1 were shown in Fig. 1. The diffraction pattern of pure acetylsalicylic acid was highly crystalline in nature as indicated by numerous peaks. Three peaks at 15.6°, 23.1° and 27.0° were noticeable and the main peak at 15.6° was particularly distinctive. The starch showed peaks at approximately 15.0°, 17.8° and 23.0°, while the characteristic peaks of SD1 appeared at 2θ equal to 15.5°, 22.7° and 27.0°. The major peaks remained at the same position as those of acetylsalicylic acid crystals but the intensity decreased a lot in the distinctive diffraction peak of 15.6°. At the same time the intensity of the diffraction peaks at 23.1° and 27.0° increased. These results

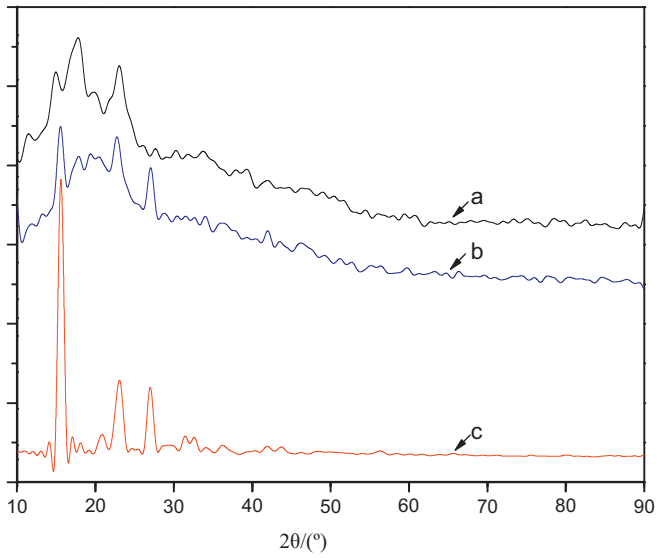

Fig. 1. XRD spectra of native cassava starch (a), SD1 (b) and acetylsalicylic acid (ASA) (c).

suggested the mutual influence of starch and acetylsalicylic acid crystals. Since the ASA molecules were adsorbed to the surface of starch or the molecular ASA inserted into the starch molecules, the crystallite structure of ASA and starch were destroyed, therefore the diffraction peaks were changed. But the damage was relatively minor. These results could be further confirmed by the scanning electron microscopy of SD1 (García-Rodriguez et al., 2011; Maulvi et al., 2011).

3.1.2. SEM analysis of solid dispersion (SD1)

Scanning electron micrographs of the native cassava starch and SD1 were presented in Fig. 2. Native cassava starch granules were round or oval in shape with smooth surface and wide distribution of size ranging from 2 μm to 20 μm, as shown in Fig. 2(a). After preparation of solid dispersion, the particles appeared minor change in shape compared to native starch. On the surface of SD1 particles, it appeared to be relatively rough, which looked like surface corrosion. The interaction between starch particles was reduced with the involvement of ASA molecules, and the internal adhesive force of particles was destroyed, which led to good dispersion of starch particles. However, the crystallite structure of starch and ASA had not been completely destroyed by the mutual interaction. Therefore, the diffraction peaks of ASA crystals in solid dispersion showed no significant attenuation, just as shown in Fig. 1.

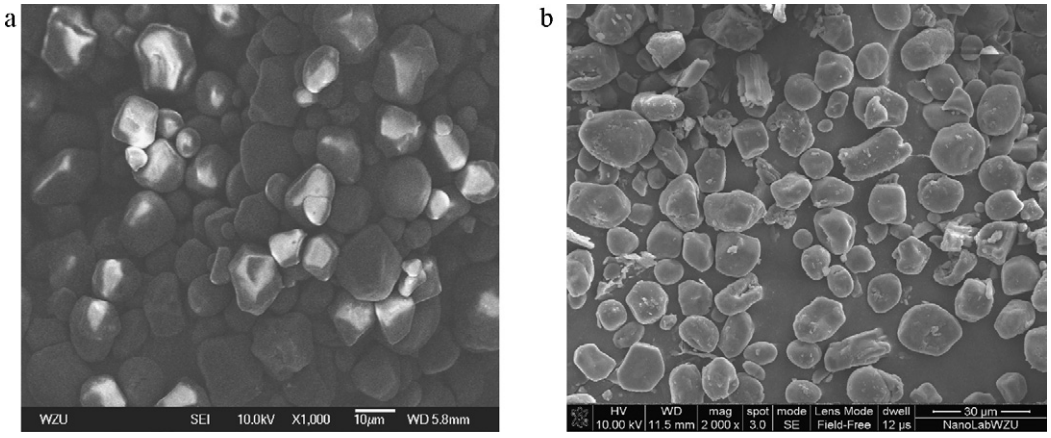

Fig. 2. SEM images of starch (a) and SD1 (b).