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

Xiepeng Lin, Wenxia Gao*, Chenen Li, Jiuxi Chen, Chen Yang, Huayue Wu*

College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou 325027, China

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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

* Corresponding author. Tel.: +81 577 86689366; fax: +81 577 86689366.
E-mail addresses: wenxiag@wzu.edu.cn (W. Gao), huayuewu@wzu.edu.cn (H. Wu).

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(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

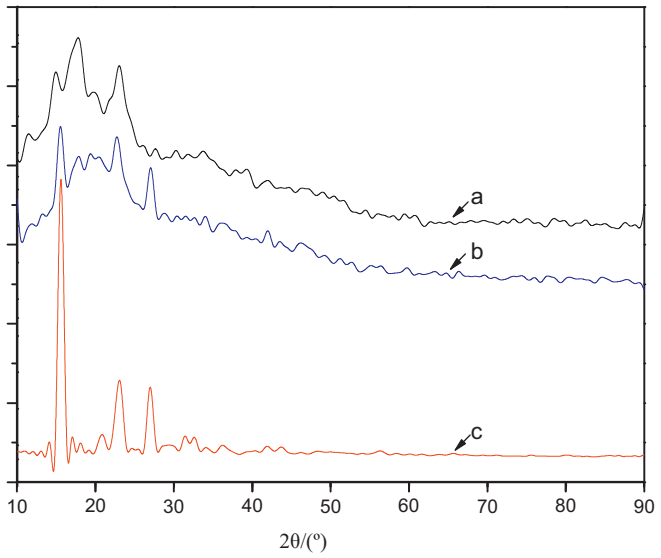

Fig. 1. XRD spectra of native cassava starch (a), SD1 (b) and acetylsalicylic acid (ASA) (c).

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.

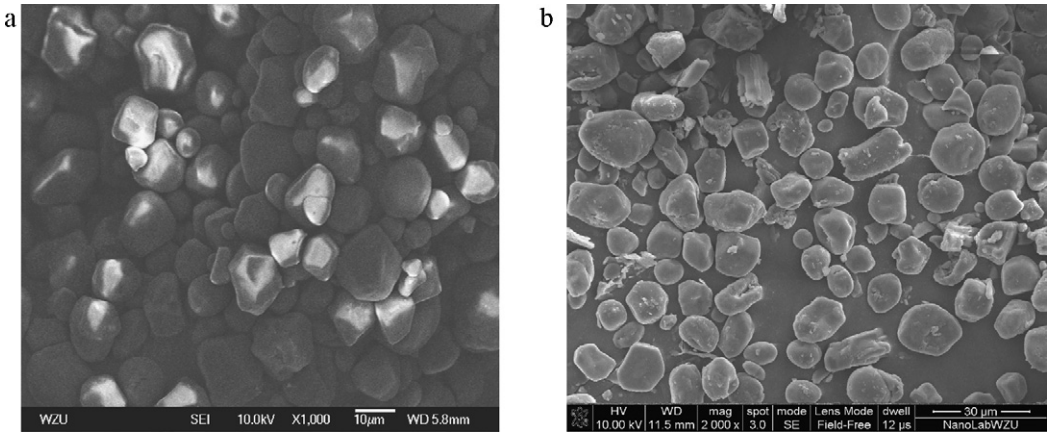

Fig. 2. SEM images of starch (a) and SD1 (b).

This result indicated that ASA molecules in the solid dispersion were mainly attached to the surface of starch particles, with a small quantity of ASA molecules inserting into the starch crystalline area. Its stability of the solid dispersion might be poor for the aggregation of ASA molecules with the storage time going on (Chauhan et al., 2005).

3.2. Characteristics of solid dispersions with CMCS (SD2, SD3)

3.2.1. XRD analysis of solid dispersion (SD2)

The XRD spectra of CMCS, SD2 and acetylsalicylic acid were shown in Fig. 3. The CMCS showed diffraction peaks at approximately 15.2°, 17.2° and 23.0°. It had semi-crystalline structure. While there were no distinctive diffraction peaks of SD2, which showed amorphous structure. This suggested the drug incorporated in the carrier may be molecularly dispersed or may occur as nanocrystals or amorphous nanoparticles. It was reported that the lack of a distinctive peak of a drug in SD systems demonstrated that a high concentration of the drug was dissolved in the solid state, and a large reduction in characteristic peaks indicated an amorphous state (Hu et al., 2003; Sheen et al., 1995; Tran et al., 2008). This formation of an insertion-type solid dispersion where drug molecules found place inside the structure of the carrier could improve the dissolution rate of drug (Srinarong et al., 2009). SD2 had much better dispersion of acetylsalicylic acid molecules in the excipient of

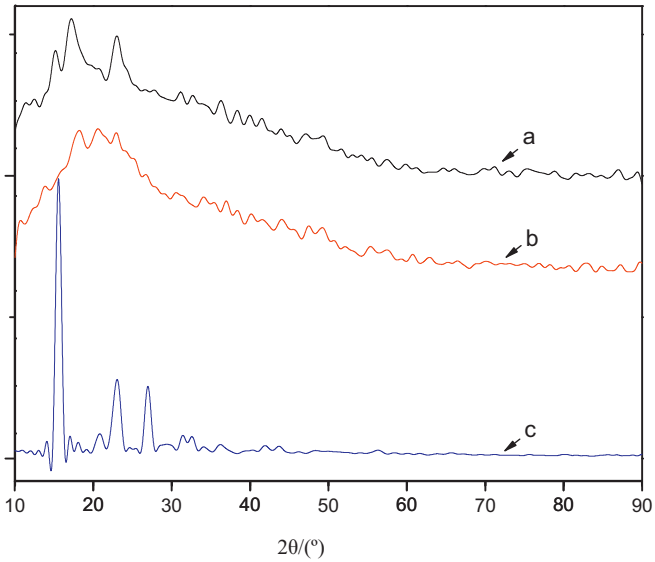

Fig. 3. XRD spectra of CMCS (a), SD2 (b) and acetylsalicylic acid (ASA) (c).

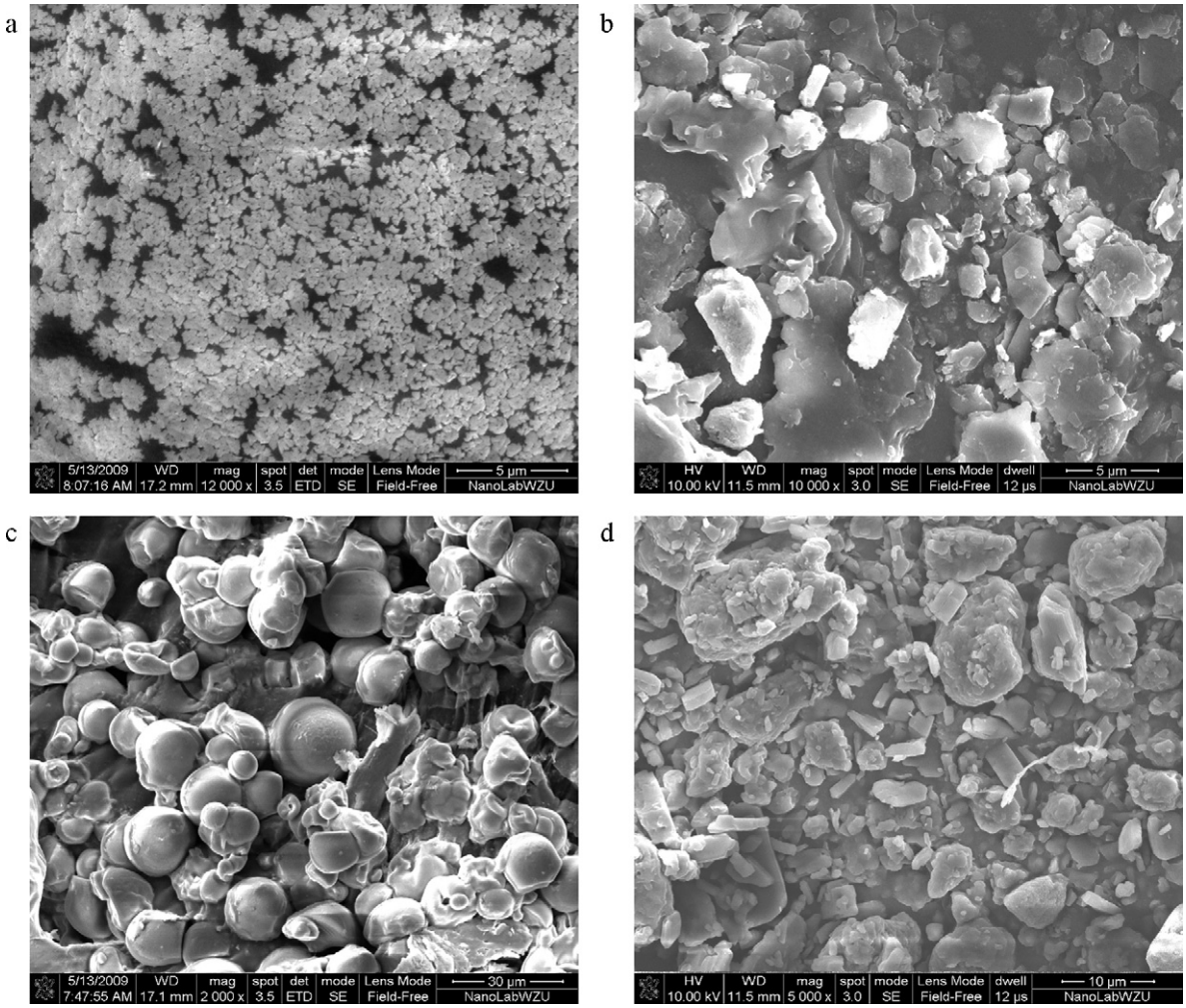

Fig. 4. SEM images of (a) nano-size CMCS (DS = 1.15), (b) SD2 composed of nano-size CMCS (DS = 1.15) and acetylsalicylic acid (ASA), (c) micro-size CMCS (DS = 0.36) and (d) SD3 composed of micro-size CMCS (DS = 0.36) and acetylsalicylic acid (ASA).

nano-sized flake carboxymethyl cassava starch, compared to the SD1 using native starch as excipient.

3.2.2. SEM analysis of solid dispersions (SD2, SD3)

SEM images of CMCS with different substitution degree (DS = 0.36, 1.15) and the solid dispersions composed of these CMCS were presented in Fig. 4.

SD2 was prepared using nano-sized CMCS flakes as carrier. Nano-sized CMCS flakes were most in shape of hexagon with smooth surface and uniform particle size of 100–400 nm, as shown in Fig. 4(a). After preparation of solid dispersion, significantly alteration of the granular structure of the carboxymethylated starch was observed in Fig. 4(b). These solid dispersions showed layered structure composed of nano- and micro-sheets with nano-size thickness and irregular edge length and width. Compared to native cassava starch granules, an increasing surface area of these nano- and micro-sheets were available for acetylsalicylic acid molecules in the solid dispersions attaching to the surface of starch particles or inserting into the starch crystalline region. The amorphous state or small particle size of the drug, with an increasing surface area for improved wetting might improve the dissolution rate of the drug (Chow et al., 1995; Dai et al., 2007). Therefore, this nanometer CMCS might be a better carrier for solid dispersion than native cassava starch. And the results were consistent with the XRD conclusion. What is more, micron grade CMCS was used in solid dispersion to further confirm this conclusion.

SD3 was prepared involving micro-size CMCS with relatively low substitution degree of 0.36. The SEM images of the micro-size CMCS (SD = 0.36) and SD3 were shown in Fig. 4(c) and (d). CMCS granules were round in shape with the size of 8–28 μm, as shown in Fig. 4(c). The surface of CMCS granules looked like much more coarse than that of native cassava starch for the carboxymethylation process (Wang et al., 2008). This rough surface of CMCS had better dispersion capability for the drug than the smooth surface of native starch particles. The image of SD3 was irregular particle as shown in Fig. 4(d). And the drug in the SD3 prepared by the carrier had better dispersion. But this micro-size CMCS was not good enough. When its size decreased to nano-size, the carrier had better dispersion capability for the drug. These results suggested that the nanoscale CMCS was a kind of good carrier for solid dispersion, which also provided new option on selecting nano-sized excipients for solid dispersions.

3.3. Solubility study

Dissolution experiments were carried out in phosphate buffer pH 7.4. And the results were shown in Fig. 5. The pure drug showed a release of 33.1% at the end of 30 min, while SD2 showed 70.7% drug release in 30 min. After 1 h, the pure drug showed a release of 49.2% and SD2 showed 73.2% drug release. Both the pure drug and SD2 had a rapid increase in the percent drug dissolution in 1 h. In comparison with the dissolution of pure drug, the dissolution rate of SD2 composed of nano-sized flake carboxymethyl cassava starch was considerably higher. The enhanced dissolution of SD2 might be due to many factors such as particle size reduction, lack of crystallinity of pure drug, reduction in interfacial tension between hydrophobic drug, increased wettability and effective surface adsorption of drug on hydrophilic carrier (Maulvi et al., 2011; El-Badry et al., 2009).

But with the release time going on to 60 min, the dissolution rate of the drug decreased to a very low release. The SD2 only showed a release of 79.1% even with 48 h drug release. This might be due to the firm adsorption of drug on nano-sized flake CMCS, which had a very large surface area and could be responsible for the firm adsorption of drug.

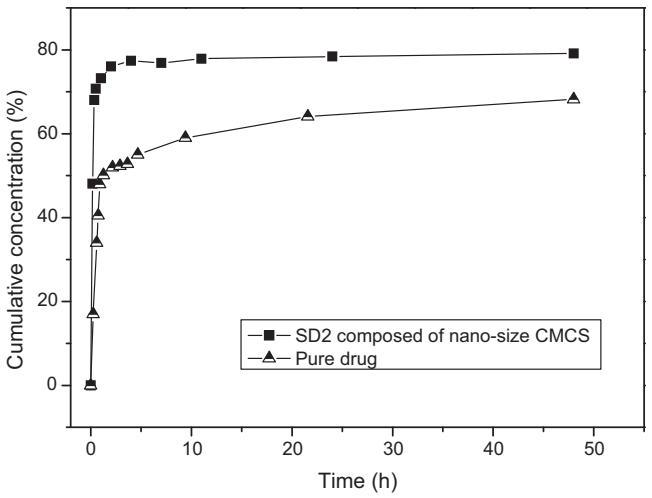

Fig. 5. Dissolution profiles of solid dispersion in phosphate buffer pH 7.4. (a) SD2 composed of nano-size CMCS (DS = 1.15) and acetylsalicylic acid (ASA) and (b) pure drug of acetylsalicylic acid (ASA).

4. Conclusion

In this paper, the characteristics and solubility of solid dispersions composed of nano or micro-sized CMCS were investigated. Both SD2 and SD3 had much better dispersion of acetylsalicylic acid molecules in nano- or micro-sized flake carboxymethyl cassava starch, compared to the SD1 using native starch as excipient. But SD3 prepared from micro-sized CMCS was not good enough compared to SD2. When the size of CMCS decreased to nano-size, the carrier had better dispersion capability for the drug. And the dissolution rate of SD2 composed of nano-sized flake carboxymethyl cassava starch was considerably higher than that of pure drug. These results indicated that the nanoscale CMCS was a kind of good and new carrier for solid dispersion to improve the solubility of poorly water-soluble drugs.

Excipients were vital components of drug formulations. However, the development of new excipients was slow, a fact partly related to cost and regulatory hurdles to demonstrate that they were safe for human use (Baldrick, 2010). Later research of our group will examine whether nano-sized flake CMCS has the potential to be a safe pharmaceutical excipient based on publicly available data and aims to assist in limiting nonclinical testing needed to include the material in future drug formulations. What is more, the stability of the solid dispersions needs further research, since the solid dispersion is an unstable system and the structure of SD would change in the storage process (Mooter et al., 2001; Weuts et al., 2003).

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