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Improvement in Solubility of Poorly Water Soluble Drug by Cogrinding with Highly Branched Cyclic Dextrin

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Key words: ball mill, cogrinding, glibenclamide, highly branched cyclic dextrin, poorly water-soluble drug

Abstract

We investigated the enhancement of the solubility of glibenclamide (GCM), a poorly water soluble anti-diabetes drug, by cogrinding it with highly branched cyclic dextrin (HBCD) using a ball mill. Highly branched cyclic dextrin (HBCD) is a novel cyclic glucan produced from waxy corn starch by the cyclization reaction of a branching enzyme. When GCM crystals were coground with HBCD for 2 h, the solubility of GCM was improved to 12.4 μg/ml, while the concentration of HBCD was 5.0 mg/ml. Additionally, the GCM solubilized with HBCD was chemically stable in aqueous solution for at least 1 week at room temperature. The peak intensity assigned to crystalline GCM disappeared after cogrinding it by observing its powder X-ray diffraction pattern, which means that the crystalline structure of GCM could be disrupted. In the DSC measurement, the ground mixture showed a single endothermic peak, even though a temperature depression of the endothermic peak due to GCM crystal was observed. After the cogrinding, two sharp peaks assigned to sulfonylurea and benzoyl carbonyl stretching bands varied to broaden the peak to around 1640 cm^{-1} in the C = O stretching region. These results suggested the formation of solid dispersion between GCM and HBCD.

Introduction

Highly branched cyclic dextrin (HBCD) is a novel cyclic glucan produced from waxy corn starch by the cyclization reaction of a branching enzyme [1, 2]. It is highly soluble in water and has a relatively low propensity for retrogradation compared to that of commercial dextrins [3]. So far, a number of investigations have been conducted on the improvement of the physicochemical properties of various drugs by mixing with cyclodextrins, a typical cyclic glucan consisting of 6, 7 and 8 glucopyranose units [4, 5]. The branched cyclic dextrin has not only a cyclic structure, such as cyclodextrins, but a long external glucan chain in its molecule (Figure 1). However, little is known about the physicochemical interaction between HBCD and chemical compounds.

Poorly water soluble drugs often show low bioavailability when administered orally, since the dissolution rate of the drugs in the gastrointestinal tract can usually be a rate-limiting step [6, 7]. Size reduction of drug particles by grinding can increase their surface area, which may enhance the dissolution rate and consequently the bioavailability of pharmaceutical materials. Furthermore, the cogrinding of drug substances with other ingredients is considered a useful method to prepare an inclusion complex [8], solid dispersion [9] and nanoparticles [10, 11]. We previously reported on the improvement of the dissolution behavior of fullerene, which is extremely water insoluble, by cogrinding with large-ring cyclodextrins [12].

In the present study, we investigated the enhancement of the solubility of glibenclamide (GCM), a poorly water soluble anti-diabetes drug, by cogrinding it with HBCD in the solid state. The molecular status of GCM in the ground mixture was evaluated using powder X-ray diffraction (XRD), IR spectrum and differential scanning calorimetry (DSC).

Experimental

Materials

Highly branched cyclic dextrin (HBCD) was provided by Nihon Shokuhin Kako Co. Ltd. (Tokyo, Japan). All

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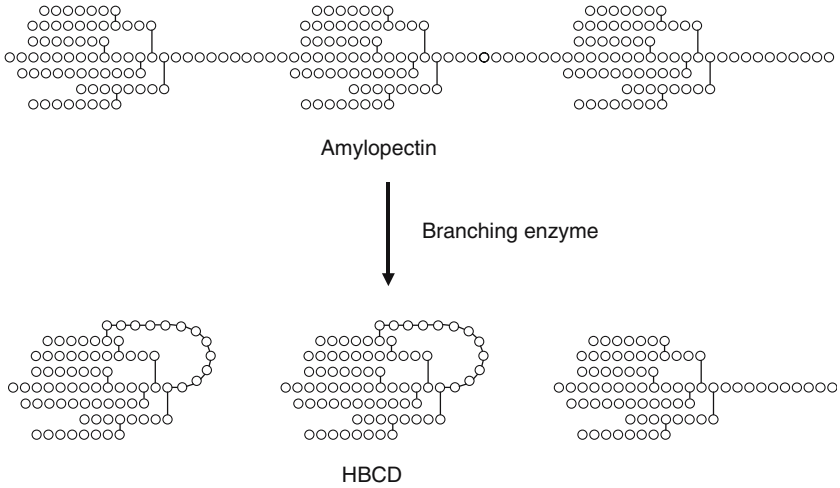

Figure 1. Schematic representation of the HBCD produced by the cyclization reaction of branching enzyme from amylopectin [3]. Open circles along with holizontal and curved lines indicate α-1,4 glucan chains. Vertical lines indicate α-1,6 branch linkages.

other chemicals and solvents were of reagent grade and purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan), and used without further purification.

Preparation of grinding mixture

A physical mixture (PM) of GCM and HBCD was prepared at a ratio of 1:5 (weight ratio) using pestle and mortar. For the preparation of a ground mixture (GM), 15 mg of physical mixture was loaded into a 5 ml shade glass vial with balls (diameter 5 mm) and coground using a Desktop Ball Mill (V-1M, Irie, Tokyo, Japan) for 2 h at 150 rpm at room temperature.

Determination of solubilized glibenclamide

After cogrinding, 15 mg of GM was dispersed in 3 ml distilled water, and incubated with gentle shaking for 1 h at 25 °C. The suspensions of GM were then filtrated through a 0.45 μm membrane (Millipore, Bedford, MA, USA). The filtrate was subjected to HPLC analysis (LC-2000, Jasco, Tokyo, Japan). The HPLC conditions were as follows: mobile phase, acetnitrile – 50 mM phosphate buffer (13:7); column, Inertsil ODS-3 (5 μm, 4.6 mm i.d. X 150 mm); flow rate, 1.0 ml/min; column temperature, room temperature; UV detection, 233 nm.

Powder X-ray diffractometry (XRD)

Powder XRD was carried out with a Geigerflex Rad-II (Rigaku, Tokyo, Japan). Measurements were performed at 35 kV, 25 mA and at a scanning speed of 6 min^{-1} with a Cu–Kα radiation source.

Infrared spectroscopy

A model 230 FT-IR spectrometer (Jasco, Tokyo, Japan) was used. The measurements were carried out using the KBr method.

Differential scanning calorimetry (DSC)

DSC curves were obtained on the DSC 8230 (Rigaku, Tokyo, Japan). About 3 mg of powdered sample were put into an aluminum crimped pan and measured at a scanning speed of 5 °C min^{-1} under a nitrogen gas flow.

Results and discussion

In order to study the effect of cogrinding on the molecular state of GCM in the solid state, powder XRD was employed for a ground mixture of GCM and HBCD. Since HBCD had no crystalline structure, diffraction peaks of crystalline GCM were observed at 2θ, 11.8, 19.0, 21.6 and 23.2° (Figure 2a, b). New diffraction peaks, implying the formation of a crystalline complex, did not appear. The peak intensity assigned to crystalline GCM disappeared after cogrinding, as shown in Figure 2c. This suggested that the crystalline structure

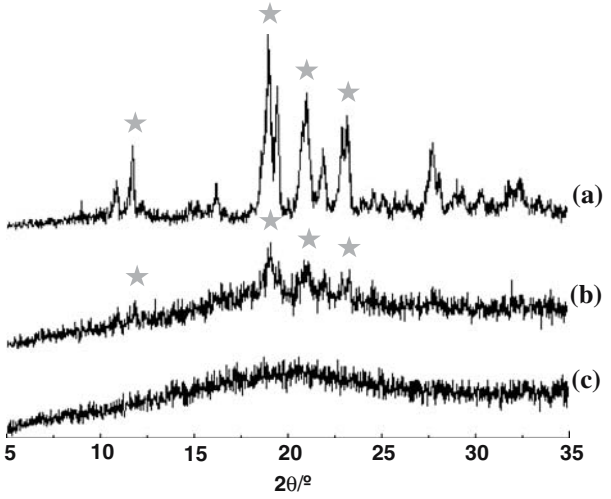

Figure 2. Changes in powder XRD patterns of physical mixtures consisting of HBCD and GCM; (a) GCM intact, (b) physical mixture, (c) ground mixture.

of GCM was disrupted, and that GCM molecules were substantially dispersed into amorphous HBCD in a solid state.

Figure 3 shows the thermal behavior of GCM coground with HBCD as investigated by DSC. The physical mixture showed a single endothermic peak corresponding to the fusion of GCM crystals at 170 °C. The ground mixture also showed a single endothermic peak, even though a temperature depression of the endothermic peak due to GCM crystals was observed. The decrease in the area of the GCM melting peak suggested that most of the GCM molecules were molecularly dispersed in the amorphous HBCD. The result agreed well with that of powder XRD, suggesting the formation of a solid dispersion between GCM and HBCD.

For a structural characterization of ground mixture, IR spectroscopy was employed. In the IR spectra for both GCM alone and physical mixture, characteristic bands were observed at 3367 and 3314 cm^{-1}, corresponding to the amide stretching band (Figure 4a, b). Two sharp peaks were also observed at 1720 cm^{-1} and 1623 cm^{-1}, assigned to the sulfonylurea carbonyl stretching and benzoyl carbonyl stretching band, respectively. After cogrinding, a general reduction in the intensity of the bands and a loss of spectral resolution were observed, both effects being attributable to the drug amorphization process (Figure 4c). The amide stretching bands almost disappeared in the zone between 3300 and 3400 cm^{-1}. In addition, the sulfonylurea and benzoyl carbonyl stretching bands varied to broaden the peak to around 1640 cm^{-1} in the C=O stretching region. This indicated that the hydrogen bonding feature in the HBCD-GCM system was changed due to molecular interaction induced by the grinding process. It is well known that the formation of hydrogen bonding causes a lower frequency shift in carbonyl stretching bands. When the carbonyl group becomes free, the carbonic stretching bands move to a 40–50 cm^{-1} higher frequency [13]. In this study, the observed band shifts were less than 20 cm^{-1}, suggesting that the intermolecular hydrogen bonds were collapsed imperfectly or that intermolecular hydrogen bonds other than those between drug molecules were formed by the grinding.

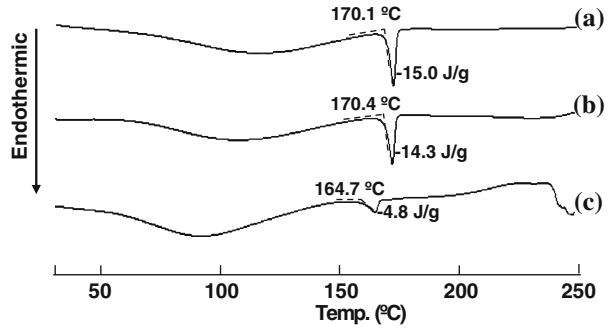

Figure 3. Effect of cogrinding on DSC curves of GCM; (a) GCM intact, (b) physical mixture, (c) ground mixture.

The solubility of GCM was increased with increasing cogrinding time, as shown in Figure 5. When GCM crystals were coground with HBCD for 2 h, the solubility of GCM was improved to 12.4 μg/ml, while the concentration of HBCD was 5.0 mg/ml. Additionally, the GCM solubilized with HBCD was chemically stable in aqueous solution for at least 1 week at room temperature. Ball-milling would be preferable in this case, though the enhancement of solubility was achieved to some extent by cogrinding with pestle and mortar. The aggregation of the powdered sample occurred in the case of manual-milling with the pestle and mortar, since the ground mixture changed to a sticky material after 15 min of grinding. Dry milling of hydrophobic drugs usually causes an aggregation of drug particles and

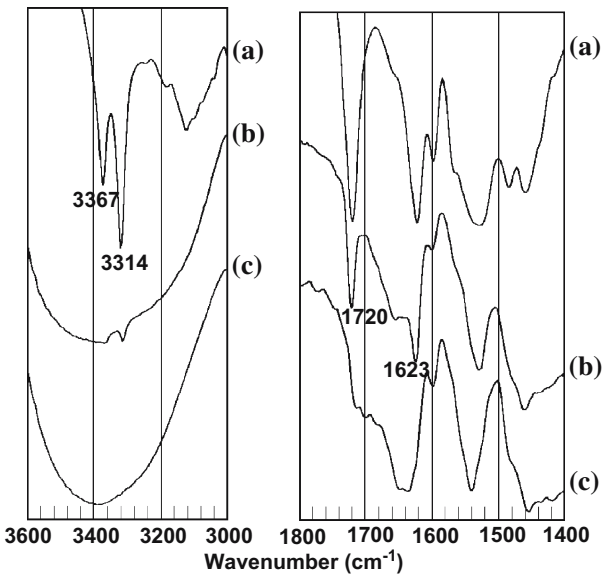

Figure 4. Effect of cogrinding on IR spectra of mixtures consisting of HBCD and GCM; (a) GCM intact, (b) physical mixture, (c) ground mixture.

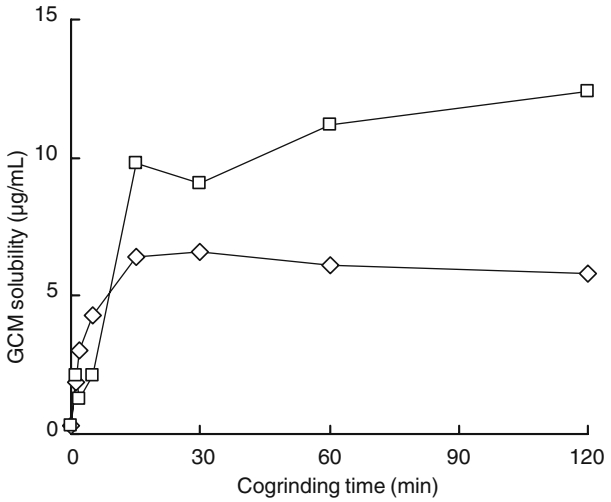

Figure 5. Comparison of grinding methods in the improvement of the solubility of GCM; □ coground with ball-mill, ◇ coground with pestle and mortar.

results in the limitation of size reduction [14, 15]. Co-grinding with other ingredients could reduce adhesion between the powdered sample and milling materials. In addition, continuous mechanical shear stress would be required for the interaction between drugs and ingredients.

Cogrinding of polyvinyl pyrrolidone (PVP) and glisentide, which is an antidiabetic drug similar to GCM, provided improved dissolution behavior for glisentide. A high energy-mill was utilized for the mechanical treatment of glisentide by cogrinding with PVP, and a progressive drug amorphization was the main factor responsible for the improving of glisentide is dissolution performance [16]. Accordingly, HBCD would work for the amorphization of a drug like PVP, which is a hydrophilic polymer, during the cogrinding process.

Conclusion

In the present study, we found that the major factor for improving GCM solubility was not transformation into another crystalline form, but the amorphization of GCM induced by cogrinding with HBCD. Further enhancement is expected by employing higher-powered grinding methods. Anyhow, the present results suggested that HBCD could be useful as a new solubilizing agent.

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