Thermal stability of amorphous sugar matrix, dried from methanol, as an amorphous solid dispersion carrier

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Abstract

Developing a technique to disperse hydrophobic ingredients homogeneously in a water-soluble solid matrix (solid dispersion) is one of the topics that have been extensively investigated in the pharmaceutical and food industries. Recently, we have devised a novel solid dispersion technique (surfactant-free solid dispersion), in which a preliminarily amorphized sugar was dissolved in an organic media containing hydrophobic component, without using any surface active substances, and then vacuum dried into the amorphous solid mixture [Food Chem., 197 (2016) 1136; Mol. Pharm., 14 (2017) 791]. In this study, the physicochemical properties, especially thermal stability of the surfactant-free amorphous solid dispersion, were investigated.

Keywords: solid dispersion; amorphous sugar; surfactant-free; vacuum drying; glass transition temperature

1. Introduction

To date, many attempts have been made to improve the solubility of hydrophobic drugs in physiological fluids [1,2]. One promising approach for improving the water solubility of a hydrophobic drug is the use of an "amorphous solid dispersion (ASD)"[3-5], in which hydrophobic drug molecules are dispersed at the molecular level in the carrier matrix comprised of water-soluble substance. When a medicine in the ASD is taken into a human body, the dissolution of the carrier matrix is accompanied by the release of hydrophobic drug molecules [6]. The concentration of the dissolved drug temporarily increases much above the equilibrium solubility (over-dissolution), possibly resulting in the improvement of the bioavailability of the hydrophobic drug [6]. In the solid dispersion of hydrophobic drugs, an amphiphilic polymer such as polyvinylpyrrolidone and hydroxypropyl methylcellulose is frequently used as the carrier matrix [6,7], and a combination of a surfactant with an amorphous carbohydrate matrix has also been reported to be effective for the stable dispersion of drugs [8,9]. On the other hand, we recently developed a new ASD technique that does not involve the use of a surface active agent [10]. In this method, (i) sugar is amorphized and (ii) added to an organic solvent containing a hydrophobic substance, followed by homogenization. (iii) The homogenized solution is then dried to a solid (surfactant-free solid dispersion). The amorphized sugar can be dissolved in an organic solvent such as methanol to a greater extent than a crystalline one. Hydrophobic drugs (Indomethacin, ibuprofen, gliclazide, nifedipine) can be stably embedded in the surfactant-free solid dispersion without any detectable segregation and exhibited marked over-dissolution at the initial stage of the dissolution in water [11].

The stability of the dispersion state of drug molecules in an amorphous carrier matrix is also an important quality aspect of the ASD besides the drug dissolution behavior in water: When hydrophobic drug molecules segregate from the amorphous carrier matrix, the over-dissolution of the drug is mostly precluded. The segregation of hydrophobic drug molecules is caused by the glass-to-rubber transition of the carrier matrix, and the glass transition temperature (T_g) of amorphous carrier matrix therefore is considered to correspond to the drug dispersion stability. In this study, first the T_g values of the surfactant-free solid dispersion were measured and compared to those for authentic freeze-dried ones. As a result, the T_g value of amorphous sugar matrix obtained from an organic solvent (methanol) was found to be significantly lower than that from an aqueous solution and furthermore indicated to be increased, as the result of a heat treatment, to as high as that for the water-originated one. Hence, at the next step, the methanol-originated amorphous sugars were heated under different conditions, including temperature and period, and analyzed for the T_g value and the drug dissolution behavior in water. The mechanism of the markedly low T_g for the methanol-originated amorphous sugars as well as what happens in the heat-treatment were investigated.

2. Materials and Methods

2.1. Materials

α-Maltose, maltitol, palatinose, and trehalose were purchased from Wako Pure Chemical Industries, Ltd., (Osaka, Japan). Indomethacin (γ-form of the crystal) and ibuprofen (Wako Pure Chemical Industries) were used as hydrophobic drugs. Methanol was obtained from Wako Pure Chemical Industry.

2.2. Methods

Vacuum Foam Drying and Heat Treatment The amorphous sugar cake that had been freeze-dried from an aqueous solution [12] was added to a methanol solution, containing a model hydrophobic drug, at the concentration of 100 mg/mL. Immediately thereafter, a 100 µL aliquot of the mixture solution was transferred to a 1.5 mL-polypropylene tube and the resulting solution was then dried under a reduced pressure of around ca. 1 Torr and centrifugation at 30±1˚C for 60 min (methanol-originated sample), using a TOMY Micro Vac MV-100 centrifugal concentrator (TOMY SEIKO Co., ltd., Tokyo, Japan). At this initial drying stage, foaming was minimal. After a 60 min period of initial drying, the residue was punctured with a steel needle, followed by the secondary vacuum drying for an additional 30 min [11]. The subsequent vacuum drying reliably resulted in foaming [11]. These series of procedures had preliminarily been indicated to be indispensable for drying the sample sufficiently (< 0.01 g-MeOH/g-dry matter) within a convenient drying period [11].

The obtained dried sample was alternatively transferred in a glass vial and then heated in a drying oven. The sample vials were sealed with heat-resistant caps to avoid the water sorption in the drying oven. The heating temperature and period were varied from 30 to 120˚C and from 0 to 120 min.

Differential Scanning Calorimetry Differential scanning calorimetry (DSC) analyses of amorphous sugar matrices, obtained from methanol as well as water, were carried out, using a TA Q2000 calorimeter (TA instruments Co., New Castle, DE) equipped with RCS90 cooling system (TA instruments Co.) in the same procedures as was used in our previous study [11]. From the obtained DSC curves, the T_g of the sample was determined as the onset of the corresponding thermal event.

Fourier Transform Infrared Ray Spectroscopy IR spectra for amorphous sugar samples were measured by means of a diffuse diffraction method using an FTIR in the same ways as was used in our previous study [13]. In order to semi-quantitatively estimate the degree of formation of hydrogen bonding in an amorphous sugar matrix, the peak wavenumbers of sugar O-H stretching vibration bands of amorphous sugar samples were analyzed. The IR

band due to sugar O-H stretching vibration (3200~3500 cm^{-1}) was smoothed at 80 points to determine the peak wavenumber.

Specific Molar Volume Analysis A ten mL of methanol or water was put in a 20 mL graduated cylinder, and 0.1~2 g (0.3~6 mmol) of amorphous sugar cake that had been freeze-dried from water and then thoroughly dehydrated over P$_2$O$_5$ [12] was then added to the methanol. α-Maltose was used as a sugar since it can be highly dissolved in methanol from amorphous state compared to the other sugars [10]. The freeze-dried amorphous α-maltose was absolutely dissolved by gently inverting the graduated cylinder several times. After removing bubbles on the cylinder wall, the change in the volume (*dV*) was determined and converted into the apparent partial mole volume of sugar (v_{sugar}) by being divided by the amount of the added sugar (*n g*) (Eq. (1)).

$$v_{sugar} = dV/n \qquad (1)$$

Dissolution Behavior of Hydrophobic Drugs from Solid Dispersion Samples The prepared surfactant-free solid dispersions of model hydrophobic drugs were added to a known amount of water (final drug conc.: 50 µg/mL for indomethacin, 500 µg/mL for ibuprofen) and the suspension was stirred at 200 rpm with a 1.5-cm magnetic stirring bar at 37±1˚C. A 200~1,000 µL aliquot of the suspension was withdrawn and then filtered with 0.2 µm pore size filter (Nihon Millipore K.K., Tokyo, Japan). The concentration of the dissolved model drug was typically measured by UV-vis absorption at specific wavelengths (indomethacin: 318 nm; ibuprofen: 233 nm).

3. Results and Discussion

The DSC thermograms for the surfactant-free solid dispersion sample, obtained by vacuum foam drying from methanol solution, showed single heat capacity shift due to glass-to-rubber transition but no endothermic peak. This demonstrates that the surfactant-free solid dispersion sample was fully amorphous and methanol was fully removed during the vacuum foam drying.

Table 1. Glass Transition Temperatures (T_g) for amorphous sugar matrices, dried from methanol, as well as for Freeze-Dried from water

sugar	T_g (°C)	
	from water	*from methanol*
α-maltose	90±1	36±1 (1st scan)
		72±2 (2nd scan)
palatinose	62±2	21±1
trehalose	102±3	37±3
maltitol	46±2	9±2

Table 1 compares the T_g values of differently dried matrices of sugars. The T_g values for the sugar matrices dried from methanol are ~50˚C lower than those for the samples dried from
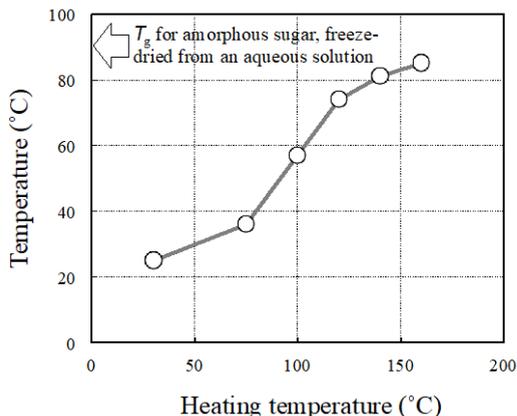
Fig. 1. Influences of heating temperature on T_g values for surfactant-free solid dispersion, obtained from methanol. α-Maltose and indomethacin (1% v/v) were used as sugar and hydrophobic drug, respectively.

aqueous solutions. Considering the fact that the methanol-originated samples had been thoroughly dried, as described above, the T_g value for an amorphous sugar matrix can be deduced to strongly varied, depending on the original solvent type.

As shown in Table 1, when the methanol-originated sugar matrix was scanned twice, the T_g value is markedly increased, suggesting that the thermal treatment may improve the physical stability of the sugar matrix dried from methanol. Hence, the influences of temperature and duration of heating on the methanol-originated sample were investigated.

Figure 1 shows the T_g values for different heating temperatures. As the heating temperature (Fig. 1) and period (data not shown) increase, the T_g increases and appears to reach the value for the water-originated sample.

The dissolution of hydrophobic drugs in water from the heat-treated solid dispersion sample as well as from the unheated ones were measured (Fig. 2). Both the heated and unheated solid dispersion samples show typical "spring and parachute" dissolution curves [14]. Namely, the concentration of dissolved drug jumps up to much above the equilibrium solubility at the early stage ("spring") and then decreases to reach the equilibrium value ("parachute"),
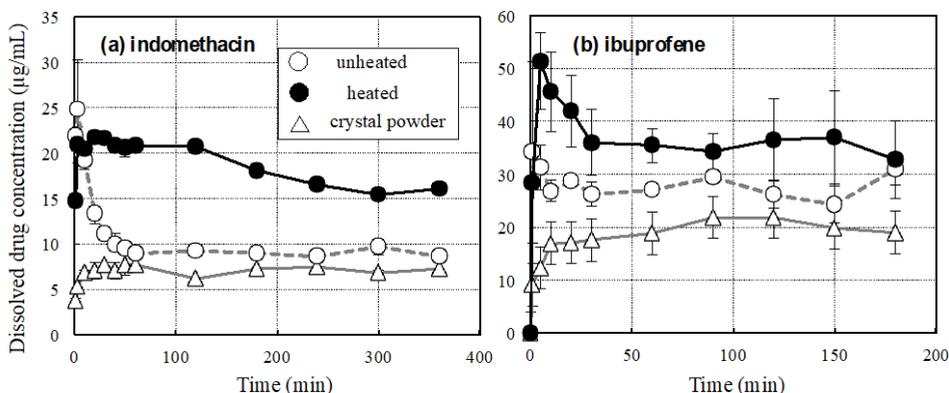

Fig. 2. Dissolution profiles of (a) indomethacin and (b) ibuprofene in water from unheated and heated surfactant-free solid dispersion as well as crystalline powders of model drugs. α-Maltose was used as sugar, and the drug content in the solid dispersion sample was 1% w/w. The amounts of model drug added to the water were 50 μg/mL for (a) indomethacin and 500 μg/mL for (b) ibuprofene. The heat-treatment was conducted at 120°C for 60 min.

whereas the crystalline drug exhibits gradual increase toward the saturation concentration. When compared between the heated and unheated solid dispersions of indomethacin, the decrease in the dissolved indomethacin concentration after the over-dissolution is markedly slowed down as the result of the heat-treatment although the attained maximum dissolved concentration of indomethacin is slightly lowered. On the other hand, in the case for ibuprofen, the attained maximum dissolved concentration is slightly increased as the result of the heat-treatment while the slowing down of the "parachute" process is less significant than in the case for indomethacin. Considering these, the heat-treatment of the surfactant-free solid dispersion, originated from methanol, can be deduced to serve to improve the aqueous dissolution of hydrophobic drug, the effect and extent of which vary depending on the drug type.

At present stage, the mechanism for the improvement of aqueous dissolution of hydrophobic drugs by heating is obscure. However, this study indicates that the heat-treatment can overcome the low T_g of amorphous sugar (carrier) matrix, dried from methanol, and possibly the instability of over-dissolution of hydrophobic drugs. Hence, the possible mechanism for the markedly low T_g for the methanol-originated amorphous sugars and what happened in the heat-treatment were further investigated.

The IR spectra for the amorphous sugar matrices dried from methanol and water were compared (Fig. 3), indicating that the peak position of the absorption due to O-H stretching vibration for the methanol-originated sample (3350 cm^{-1}) was much lower than that for the water-originated one (3388 cm^{-1}). Accordingly, more sugar-sugar hydrogen bondings may be formed in the amorphous sugar matrix dried from methanol than in that from water. On the other hand, when the methanol-originated sample was heated (at 120°C for 60 min), the peak frequency of O-H stretching vibration was positively shifted toward the value for the water-originated sample (Fig. 3).
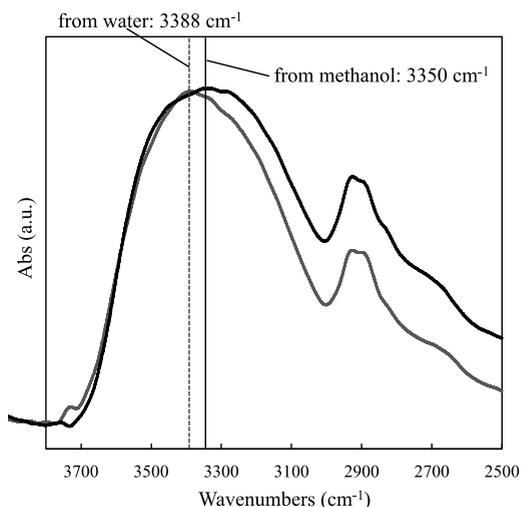

Fig. 3. IR bands for sugar O-H stretching vibration for amorphous matrices, dried from methanol and water. The peak wavenumbers of the IR bands are shown in the figures.

From the volumetric measurements of the methanol and aqueous solution containing different amount of amorphous sugar (α-maltose), the occupied volume of sugar molecule in methanol and water were calculated to be 133 mL/mol and 188 mL/mol, respectively. This

indicates that a sugar molecule may have considerably compact conformation in methanol relative to in water.

Sugar molecule in a poor solvent may change its conformation so as to decrease the solvent-contacting surface area. The lower permittivity of methanol than that of water may allow intramolecular hydrogen bonding in the disaccharide molecule, which would also reduce the occupied volume of a sugar molecule. Consequently, the partial molar volume of α-maltose in methanol is considered to be markedly smaller than in water, as shown above.

When assumed that the sugar molecules in the matrix dried from methanol, more or less, maintain their compact conformation before being drying, the methanol-originated matrix is considered to have smaller mean intermolecular distance and thus greater extent of hydrogen bondings, as indicated by the lower frequency of sugar O-H stretching vibration. It would also follow that the smaller volume assigned to each sugar molecule provides the lower T_g where the free volume of sugar molecule reaches a critical value (Table 1). Furthermore, the markedly small occupied volume of sugar molecule in the matrix obtained from methanol may be accompanied by the distortion of the sugar molecule. The relaxation of sugar molecule to less awkward conformation is thus considered to be time-dependent and accelerated with increasing temperature, as shown in Fig. 1.

4. Conclusion

Amorphous sugar can be temporarily dissolved in methanol and dried into amorphous powders from methanol, which was applied to the surfactant-free solid dispersion of hydrophobic drugs (surfactant-free solid dispersion). However, the T_g of the methanol-originated sample was much lower than that of amorphous sugar dried from water. More hydrogen bonds are formed in the amorphous matrix dried from methanol than in the matrix dried from water. The specific characteristics of the methanol-originated sample were reduced as the result of heating: The T_g and degree of hydrogen bonding for the surfactant-free solid dispersion sample were respectively increased and reduced close to those for amorphous sugar dried from water by heating under appropriate conditions. The heat treatment was indicated to improve aqueous dissolution of hydrophobic drugs (indomethacin and ibuprofen) from the surfactant-free solid dispersion. The comparison of the apparent sugar molar volumes in methanol and water suggested that the occupied volume of sugar molecules in methanol was ~30% smaller than that in water. The markedly lower T_g and higher extent of hydrogen bonding for the methanol-originated amorphous sugar matrix were deduced to closely relate to the highly compact and possibly awkward conformation of sugar molecules in methanol.

5. References

[1] Lipinski, C. A. Poor aqueous solubility-an industry wide problem in drug discovery. *Am. Pharm. Rev*. 2002, *5*, 82-85.

[2] Amidon, G. L. Drug derivatization as a means of solubilizations: Physical and biochemical strategies. In *Techniques of Solubilization of Drug*; Yalkowsky SH, Eds.; Marcel Dekker: New York, 1991, pp 183-211.

[3] Leuner, C.; Dressman, J. Improving drug solubility for oral delivery using solid dispersions. *Eur. J. Pharm. Biopharm.* 2000, *50*, 47-60.

[4] Ilevbare, G. A.; Liu, H.; Edgar, K. J.; Taylor, L. S. Maintaining supersaturation in aqueous drug solutions: impact of different polymers on induction times. *Cryst. Growth Design* 2013, *13*, 740-751.

[5] Li, B.; Konecke, S.; Harich, K.; Wegiel, L.; Taylor, L. S.; Edgar, K. J. Solid dispersion of quercetin in cellulose derivative matrices influences both solubility and stability. *Carbohydr. Polym.* 2013, *92*, 2033–2040.

[6] Huang, Y.; Dai, W-G. Fundamental aspects of solid dispersion technology for poorly soluble drugs. *Acta. Pharm. Sinica B* 2014, *4*, 18-25.

[7] Chadha, R.; Kapoor, V. K.; Kumar, A. Analytical techniques used to characterize drug-polyvinylpyrrolidone systems in solid and liquid states - An overview. *J. Sci. Ind. Res*. 2006, *65*, 459-469.

[8] Jie, L.; Jianming, C.; Yi, L.; Jing, S.; Fuqiang, H.; Zongning, Y.; Wei, W. Glyceryl monooleate/Poloxamer 407 cubic nanoparticles as oral drug delivery Systems: I. In vitro evaluation and enhanced oral bioavailability of the poorly water-soluble drug simvastatin. *AAPS PharmSciTech* 2009, *10*, 960-966.

[9] Yadav, B. V.; Yadav, A. V. Pharmaceutical application of supercritical fluid technique: an overview. *J. Pharm. Res.* 2009, *29*, 31-44.

[10] Satoh, T.; Hidaka, F.; Miyake, K.; Yoshiyama, N.; Takeda, K.; Matsuura, T.; Imanaka, H.; Ishida, N.; Imamura, K. Surfactant-free solid dispersion of fat-soluble flavour in an amorphous sugar matrix, *Food Chem.* 2016, *197*, 1136–1142.

[11] Takeda, K.; Gotoda, Y.; Hirota, D.; Hidaka, F.; Sato, T.; Matsuura, T., Imanaka, H.; Ishida, N.; Imamura, K. Surfactant-free solid dispersions of hydrophobic drugs in an amorphous sugar matrix dried from an organic solvent. *Mol. Pharm.* 2017, *14*, 791–798.

[12] Imamura, K.; Maruyama, Y.; Tanaka, K.; Yokoyama, T.; Imanaka, H.; Nakanishi, K. True density analysis of a freeze-dried amorphous sugar matrix. *J. Pharm. Sci.* 2008, *97*, 2789–2797.

[13] Imamura, K.; Ogawa, T. ; Sakiyama, T. ; Nakanishi, K. Effect of types of sugar on the stabilization of protein in the dried state. *J. Pharm. Sci.* 2003, *92*, 266-274.

[14] Brouwers, J.; Brewster, M. E.; Augustijns, P. Supersaturating drug delivery systems: the answer to solubility-limited oral bioavailability? *J. Pharm. Sci*. 2009, *98*, 2549–2572.