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Evaluation of a novel sugar coating method for moisture protective tablets

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Abstract

A novel method of manufacturing one-step dry-coated (OSDRC) tablets, which we recently invented, was used to produce sugar-coated tablets protected from moisture without the need for a conventional complicated sugar coating process. Amorphous sucrose was selected for the outer layer of the OSDRC tablets as sugar-coated layer. The isothermal crystallization behavior and characteristics such as water vapor permeability, tensile strength, and disintegration time of compressed amorphous sucrose were investigated. Water vapor adsorption measurements showed the crystallization behavior of amorphous tablets to be similar to that of amorphous powder, although it was affected by compression pressure. We found that the crystallized amorphous sucrose after compression at 200 MPa was moisture protective, and the water vapor permeability coefficient was decreased to 1/2000 or less compared with a tablet prepared with a lactose–microcrystalline cellulose (MCC) mixture, hydroxypropylmethylcellulose (HPMC), and sucrose crystal. The water vapor permeability and physicochemical characteristics were influenced by the amorphous content or additive content. It was confirmed that a new sugar-coated tablet using amorphous sucrose and OSDRC technology was moisture protective, therefore, it was concluded that the novel sugar coating method was very useful to obtain a moisture protective tablet.

Keywords: Dry-coated tablets; Sugar coating; Sucrose; Amorphous; Moisture permeation

1. Introduction

Several pharmaceutical approaches have been used to improve compliance by making changes to the natural characteristics of drugs. Aronson and Hardman (1992) reported the primary reasons for noncompliance of drug therapy to be the unpleasant smell or taste of drugs and difficulty in swallowing. Therefore, it is important to mask odor and taste and to make drugs easy to handle and swallow in order to improve acceptance, palatability, and compliance. The stabilization of drugs is also important because many drugs are sensitive to moisture and thus protected by moisture-proof packaging and desiccants. Stabilizing drugs using pharmaceutical technologies which do not require such desiccants would be a significant advancement for both pharmacists and patients.

Pharmaceutical coating is an important process widely used to improve the physical and chemical properties of dosage forms. Sugar-coated tablets have excellent characteristics such as stabilization of drugs and ease of swallowing compared with film-coated tablets. Sugar-coated tablets have an elegant appearance and provide protection against the hydrolysis and oxidative degradation of drugs since the outer layer consists of sugar crystals having low gas permeability and low water vapor permeability. In addition, the coating can mask the unpleasant taste and odor of drugs. However, conventional sugar coating has several problems such as a complicated manufacturing process, difficulties in controlling coating conditions, the long time needed to manufacture the tablet, and the high moisture content of the coating layer.

In general, sugar-coated tablets are manufactured using a sugar solution or sugar suspension, therefore, the formation of a water-proofing and sealing layer is required to prevent water from entering the core. Additionally, a subcoating layer, a smoothing layer, and a syrup coating layer are applied in turn, making the manufacturing process long and complicated. A thin-layer sugarless coating using film coating technology has been developed in order to solve the problems of conventional sugar coating and shorten the manufacturing time (Ohmori et al., 2004a,b).

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Although these coating methods involve spraying aqueous solutions, the press coating method (dry coating method) is a very useful technique for drugs unstable in moisture, since dry coating does not use an aqueous solution (Otsuka and Matsuda, 1994; Thomas et al., 1998). Dry-coated tablets are composed of a core and outer layer. Therefore, the characteristics of these tablets are determined by the properties of the outer layer. We considered if the dry coating was applicable to sugar coating, it would be possible in a short time to produce tablets which have stability against humidity and the lowest moisture content.

The conventional method of manufacturing dry-coated tablets first requires the preparation of core tablets. The core tablets are placed into a die filled with powder for the coating layer. The powder for the outer layer is filled around the core tablets. Then the powder for the outer layer with the core tablets inside is compressed to make a tablet. In this method, the core-tablet supply system has problems such as non-core and off-center which causes variation in the thickness of the coating layer.

We have previously reported a one-step dry-coated tablet manufacturing method (the OSDRC system) as a new technology that solves these problems (Ozeki et al., 2001, 2002). Since the OSDRC system does not require the preparation of core tablets, it is possible to make dry-coated tablets in a single run. Moreover, it is practically difficult to produce dry-coated tablets with a side outer layer thickness of less than 1.5 mm by conventional manufacturing methods. However, we demonstrated that it was possible to make dry-coated tablets with a side outer layer thickness of 1 or 0.5 mm using the OSDRC system (Ozeki et al., 2004a,b). Additionally, dividable dry-coated tablets which had a double core surrounded by an outer layer were developed. The original characteristics such as moisture protection are expected to be maintained after the tablet has been divided because each core containing active ingredient is completely covered by an outer layer.

We considered a novel method of manufacturing sugar-coated tablets for moisture protection using OSDRC technology. Our original concept was to use amorphous sucrose as the outer layer, produce dry-coated tablets and then form a sugar-coated layer through crystallization of the amorphous sucrose. Although a number of fundamental studies of amorphous materials have been carried out to clarify their properties, i.e., crystallization behavior and stability, and to understand the influence on products (Saleki-Gerhardt and Zografi, 1994a; Shamblin and Zografi, 1999), very little research has been done on the characteristics of compressed amorphous sucrose.

In this study, first, we investigated the isothermal crystallization behavior of compressed amorphous sucrose and the physicochemical characteristics such as tensile strength and water vapor permeability of the crystallized form. Second, the effects of amorphous content and additives on the characteristics were investigated. Finally, the moisture protection property of new sugar-coated tablets prepared using OSDRC technology was confirmed.

The purpose of the study is to clarify the possibility of manufacturing new sugar-coated tablets, for attaining moisture protection and the masking of unpleasant tastes and odors, using the newly developed OSDRC technology and an amorphous substance.

2. Materials and methods

2.1. Materials

Powdered Sucrose (JP grade) was obtained from Mitsui Sugar Co., Ltd. (Japan). To study the effect of particle size, powdered sucrose was classified using air jet sieving (MDS-LT, Nippon Pneumatic Mfg. Co., Ltd., Japan), then two fractions were used—Fa: $d_{50} = 9.4$ μm and Fb: $d_{50} = 49$ μm. Hydroxypropylcellulose (HPC-M, Nippon Soda Co., Ltd., Japan) was used as an ingredient. Light anhydrous silicic acid (ADSOLIDER-101, FREUND Co., Japan) was used as a glidant. Magnesium stearate (Taihei Chemical Co., Ltd., Japan) was used as a lubricant. Microcrystalline cellulose (MCC; CEOLUS PH-101), lactose monohydrate (Pharmatose 200M), and hydroxypropylmethylcellulose (HPMC; TC-5RW) were obtained from Asahi Kasei Chemicals Co. (Japan), DMV Japan Co. (Japan), and Shin-Etsu Chemical Co., Ltd. (Japan), as references, respectively. All excipients were sieved through a 200 M (75 μm) screen prior to use, and mixing of the powder was performed by shaking in a plastic bag. All other chemicals were of analytical grade.

2.2. Preparation of amorphous sucrose

Crystalline sucrose was dissolved in deionized water (20%, w/v), and the solution was spray-dried utilizing a rotary atomizing spray drier (Skytech, Japan). The spray-drying conditions were as follows: the inlet temperature was 150 °C, outlet temperature was 85 ± 5 °C, rotational velocity of the atomizer was 15,000 rpm, and feeding rate of the solution was about 30 mL/min. Spray-dried (SD) particles were kept in a glass vial and stored in a desiccator below 20% relative humidity (RH) at room temperature. The resultant SD particles were uniform spherical particles about 20 μm in mean diameter. The amorphous state of SD sucrose was verified by a halo pattern in a powder X-ray diffraction analysis (MiniFlex, Rigaku, Japan) and an exothermic peak in a differential scanning calorimetric (DSC) analysis.

2.3. Preparation of tablets

Compression of the powder was performed using the universal tension and compression tester (Autograph AG-IS, Shimadzu Co., Japan). The weighed sample (45–100 mg) was compressed using a die with an 8–12 mm internal diameter and flat-faced punches at a fixed compressing velocity of 5 mm/min under various pressures (50–300 MPa). The punches and the die wall were lubricated with a small amount of magnesium stearate using a brush before compression. The amount of sample was adjusted to create the same thickness, and the pressure was varied according to the purpose of the experiments.

2.4. Differential scanning calorimetry

Differential scanning calorimetric measurements were performed by Diamond DSC (Perkin-Elmer, USA), which were calibrated with indium. Samples (about 10 mg) were carefully loaded into an aluminum pan with a pin-holed lid and scanned at a heating rate of 10 °C/min between 40 and 210 °C under a dry nitrogen purge.

2.5. Water vapor adsorption

Water vapor adsorption characteristics were measured using a microbalance system (MB-300G, VTI, USA). Samples of approximately 10–230 mg were placed in the microbalance pan, which was kept at 25 °C by a thermal jacket.

2.6. Water vapor permeation

Water vapor permeation (WVP) measurements of tablets were performed gravimetrically based on the increase in weight of the cells. The cell consisted of a glass bottle, filled with 5 g of calcium chloride to produce a gradient for water vapor permeation. The top of the cell was an opened circular hole 10 mm in diameter. A tablet was fixed on the cell by an adhesive. The cell was kept in 75% RH and 25 °C, prepared with a saturated salt solution, and weighed at regular intervals. It was confirmed that there was no permeation of water vapor through the adhesive using aluminum foil instead of tablets beforehand.

2.7. Measurement of tensile strength

Tablet crushing strength (H) was measured using a force gauge (Portable Checker PC-30, Okada Seiko Co., Ltd., Japan). The diameter and thickness of tablets were measured with a micrometer. The tensile strength (T) was calculated using the following equation:

$$T = \frac{2H}{\pi dL}$$

where H (N) is the crushing strength, and d (mm) and L (mm) are the diameter and thickness of the tablet, respectively.

2.8. Porosity

The porosity of the tablet (ε) was calculated using the following equation:

$$\varepsilon\,(\%) = \left(1 - \frac{M}{V\rho}\right) \times 100$$

where M (g) is the tablet weight, V (cm^3) the tablet volume, and ρ (g/cm^3) is the true density of the powder. The diameter and thickness of the tablet for calculation of tablet volume were measured with a micrometer.

2.9. Measurement of plastic energy

Plastic energy was measured using a universal tension and compression tester (Rheo meter CR-500DX, Sun Scientific Co., Ltd., Japan). The tablet was put on the two bridges at a distance of 5 mm and compressed perpendicularly to its surface. The applied force was recorded as a function of distance. The data acquisition was terminated when the tablet fractured, and plastic energy was defined as the area under the force–distance curve.

2.10. Measurement of pore size distribution and surface area

The pore size distributions of tablets were determined by both a low- and high-pressure mercury porosimeter (PoreMaster 60GT, Quantachrome Instruments, USA). Pores can be measured from 4 nm (pressure = 400 MPa) up to 200 μm (pressure = 0.01 kPa).

The technique can be used to estimate the surface area of samples.

2.11. Scanning electron microscopy (SEM)

The upper surface of tablets was observed with a scanning electron microscope (JSM T330A, JEOL Ltd., Japan) at an accelerating voltage of 10 kV. Prior to analysis, the sample was sputter coated with a thin layer of gold.

2.12. Preparation of OSDRC tablets

We prepared tablets according to the OSDRC technology we reported previously (Ozeki et al., 2001, 2002). A schematic outline of the manufacturing process is shown in Fig. 1. The OSDRC system consists of an upper-center punch (a1; 6 mm in diameter), a lower-center punch (b1; 6 mm), an upper-outer punch (a2; 8 mm), and a lower-outer punch (b2; 8 mm). In this study, we used a single set of flat-faced punches and die for OSDRC, and compressed the powder using the universal tension and compression tester (Autograph AG-IS, Shimadzu Co., Japan). The compression conditions were as follows: the compression velocity was 5 mm/min, final compression pressure was 200 MPa, weight of the core was 80 mg, and total weight of the tablet was 230 mg.

3. Results and discussion

3.1. Crystallization behavior of compressed amorphous sucrose

For the purpose of preparing a sugar-coated outer layer for dry-coated tablets by crystallizing compressed amorphous sucrose, the crystallization behavior of amorphous sucrose was investigated as a first step. It is possible to follow the crystallization of amorphous sucrose by examining the weight changes related to the adsorption and desorption of water vapor (Carstensen and Scoik, 1990; Stubberud and Forbes, 1998).

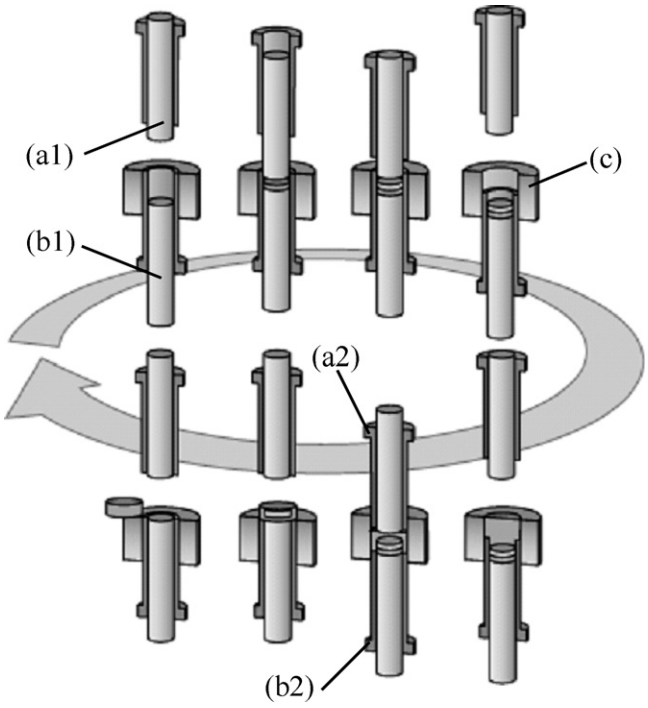

Fig. 1. Schematic diagram of the OSDRC system: (a1) upper-center punch, (a2) upper-outer punch, (b1) lower-center punch, (b2) lower-outer punch, and (c) die.

Fig. 2 shows the weight changes of compressed amorphous sucrose (tablet) stored at 25 °C and 51% RH.

Upon exposure to 25 °C and 51% RH, the amorphous sucrose tablet demonstrated rapid water vapor adsorption, reaching a peak soon afterwards. The water vapor adsorption rate was about the same in each amorphous sucrose tablet specimen. After a slight induction time, the weight decrease associated with water vapor release occurred. As in the case of amorphous sucrose

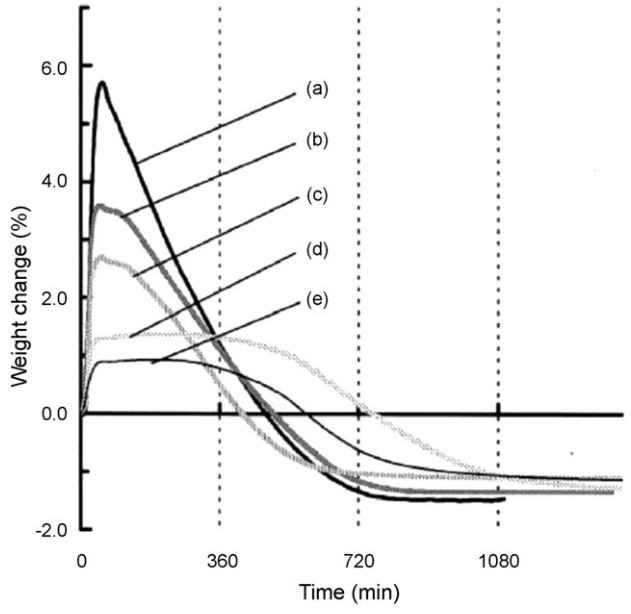

Fig. 2. Water vapor adsorption profiles of amorphous sucrose tablets as a function of storage time at 25 °C under 51% RH, compressed at different pressure: (a) powder, (b) 50 MPa, (c) 100 MPa, (d) 200 MPa, and (e) 300 MPa.

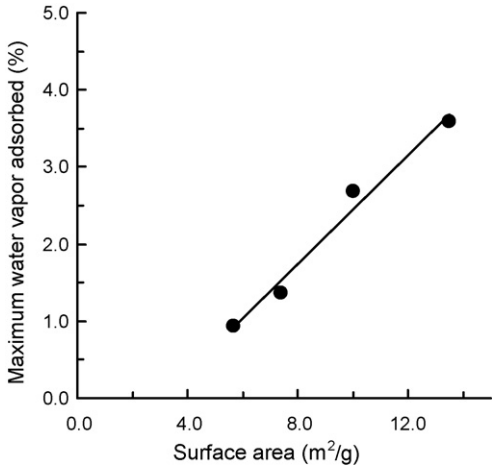

Fig. 3. Relationship between maximum water vapor adsorption and surface area of amorphous sucrose tablets before crystallization.

powder, this basic behavior shows that the nuclei were generated when the water vapor adsorption reached a peak and the water vapor was released in association with the sucrose crystal formation (Makower and Dye, 1956). The weight change indicated a negative value at that time because the moisture contained in the amorphous substance at the initial state was also released. The amorphous sucrose compressed at 200 MPa was exposed to 40% RH and 25 °C, 51% RH and 25 °C, and 75% RH and 25 °C to investigate the influence of humidity on the hygroscopic behavior. The water vapor adsorption was proportional to the storage humidity (data not shown). Thus, the crystallization conditions were set at 51% RH and 25 °C in the subsequent experiments.

Maximum water vapor adsorption was dependent on compression pressure. In other words, the higher the compression pressure, the smaller the maximum water vapor adsorption. Fig. 3 shows the relationship between maximum water vapor adsorption and the surface area of the amorphous sucrose immediately after compression. It was demonstrated that maximum water vapor adsorption was dependent on the surface area of the compressed product. Saleki-Gerhardt et al. (1994b) reported that the detected water vapor adsorption was dependent on the amorphous content. In this regard, we conducted a DSC analysis to investigate whether or not the decrease in maximum water vapor adsorption due to compression is attributable to the decrease in amorphous amount due to crystallization. Fig. 4 shows the DSC of amorphous sucrose immediately after compression at 200 and 300 MPa and that of sucrose stored at 25 °C and 51% RH and after a certain amount of water vapor release. The compressed product demonstrated the same exothermal peak as that of the powder, indicating that crystallization did not occur due to the compression pressure. Also, all the amorphous sucrose was crystallized after storage.

Kawakami et al. (2006) reported that the melting behavior of crystallized amorphous sucrose is different from that of intact sucrose crystals. That is, crystals with an incomplete lattice are formed depending on the moisture content just before crystallization. However, in this experiment, the result of the DSC analysis indicated that the endothermic peak that occurred in

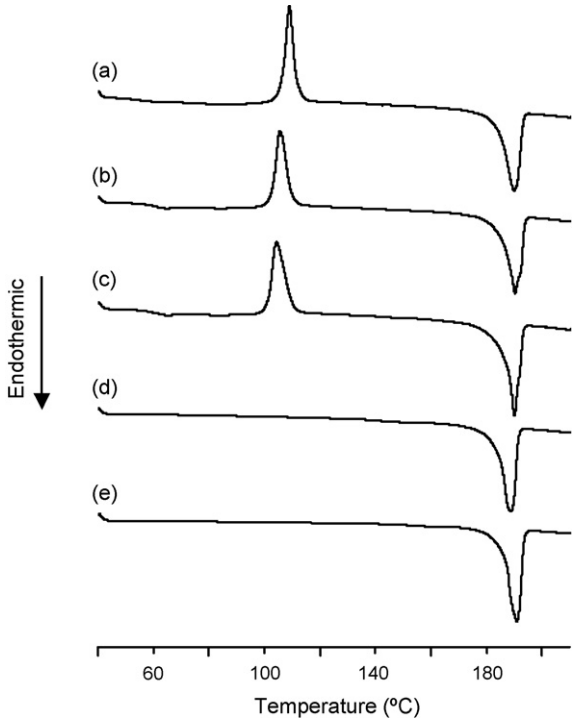

Fig. 4. DSC thermographs of sucrose samples: (a) intact amorphous sucrose powder, (b) amorphous sucrose tablet compressed at 200 MPa, (c) at 300 MPa, (d) amorphous sucrose tablet stored at 25 °C under 51% RH for 2 days, and (e) sucrose crystal.

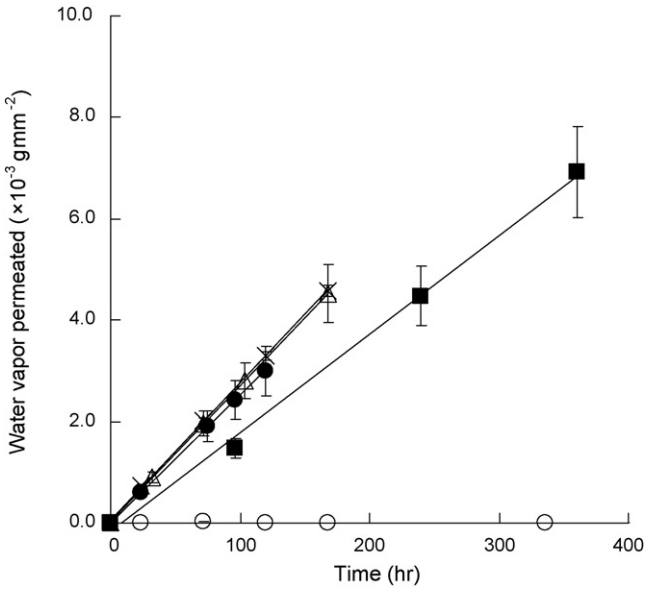

Fig. 5. Water vapor permeation profiles of tablets composed of various excipients as a function of time at 25 °C under 75% RH. Compression pressure is 200 MPa. Excipients: (●) HPMC, (■) lactose–MCC (7:3), (△) sucrose crystal (d_{50} = 49 μm), (×) sucrose crystal (d_{50} = 9.4 μm), and (◯) crystallized amorphous sucrose after compaction. The bars represent the S.D. for three determinations.

association with melting shifted slightly to the lower temperature side but mostly corresponded with the intact crystals (Fig. 4). Therefore, it was considered that almost intact crystals were formed by this process.

3.2. Characteristics of compressed amorphous sucrose

3.2.1. Water vapor permeability

Lasoski and Cobbs (1959) reported that moisture did not penetrate the sucrose crystals, so we expected moisture protection of compressed sucrose and investigated its water vapor permeability. The compressed amorphous sucrose was crystallized, and the water vapor permeation of the crystallized sucrose was compared with that of compressed sucrose crystal, compressed lactose–MCC (7:3), and compressed HPMC generally used as excipients and film components. Fig. 5 shows the relationship between water vapor permeation and time. Water vapor permeation demonstrated a linear increase against time in each case. Table 1 (Exp. nos. 1–5) shows the permeability coefficient calculated using Eq. (1) on the basis of this linear slope.

$$Q = \frac{K\,\Delta p\,At}{l} \tag{1}$$

where Q (g) is the amount of water permeated, K (g h^{-1} mm^{-1} mmHg^{-1}) the water vapor permeability coefficient, Δp (mmHg) the vapor pressure difference, A (mm^2) the area of cell opening, t (h) the time, and l (mm) is the thickness of the tablet.

There is no marked difference in the water vapor permeability coefficient between HPMC, lactose–MCC (7:3), and sucrose crystal. Considering that moisture does not penetrate the sucrose crystal, the permeation was expected to decrease when fine crystals were used. However, no barrier function was observed in the compressed crystals 10 μm or less in diameter. On the other hand, it was discovered the water vapor permeability coefficient of compressed and crystallized amorphous sucrose was 0.1 or less, which was 1/2000 or less that of compressed lactose–MCC (7:3). The decrease seemed to be attributable to the blocking of the water vapor diffusion route due to amorphous crystallization in addition to no water vapor permeation through crystals. Considering that the water vapor permeability coefficient of a conventional sugar-coated layer is 3.6 (Maekawa et al., 1975), it was demonstrated that the same function as the sugar-coated layer could be provided by the crystallization of amorphous sucrose. Accordingly, a tight continuous layer of sucrose crystals is expected to be formed by crystallization after compression.

3.2.2. Physicochemical characteristics

For the purpose of investigating the applicability of amorphous sucrose to tablets, the physicochemical characteristics of compressed amorphous sucrose were investigated. Fig. 6 shows the changes in tensile strength before and after crystallization of amorphous sucrose compressed at various pressures. The tensile strength before crystallization increased in proportion to the compression pressure up to 200 MPa but remained at a constant level when the pressure exceeded 200 MPa. Compared with the state before crystallization, the tensile strength after crystallization did not change at 50 MPa but decreased at 100 MPa or higher. Table 2 (Exp. nos. 1–4) shows the porosity of tablets

Table 1
The water vapor permeability coefficients of various tablets

Exp. no.	Samples	Compression pressure (MPa)	Water vapor permeability coefficient, K ($\times 10^{-9}$ g h^{-1} mm^{-1} mmHg^{-1})[a]
1	HPMC	200	1054.3 ± 132.3
2	Lactose/MCC (7:3)	200	765.9 ± 100.4
3	Sucrose crystal (d_{50} = 49 μm)	200	931.2 ± 147.6
4	Sucrose crystal (d_{50} = 9.4 μm)	200	1005.9 ± 24.5
	Amorphous sucrose		
5		200	0.4 ± 0.3
6		50	10.3 ± 5.3
7		100	6.8 ± 4.1
8		300	0.8 ± 0.0
	Amorphous sucrose/sucrose crystal[b]		
9	10%[c]	200	542.6 ± 23.5
10	20%[c]	200	57.2 ± 8.3
11	50%[c]	200	16.2 ± 1.9
12	75%[c]	200	0.6 ± 0.2
	HPC/amorphous sucrose[b]		
13	10%[d]	200	29.2 ± 12.1
14	20%[d]	200	61.7 ± 3.9
	PVP/amorphous sucrose[b]		
15	10%[e]	200	202.2 ± 23.6
16	20%[e]	200	397.2 ± 51.2

[a] Each data represents the mean ± S.D. for three experiments.
[b] Physical mixture.
[c] Amorphous sucrose content.
[d] HPC content.
[e] PVP content.

Table 2
The porosity of tablets before and after crystallization

Exp. no.	Samples	Compression pressure (MPa)	Porosity (%)[a]	
			Before crystallization	After crystallization
	Amorphous sucrose			
1		50	32 ± 0	33 ± 0
2		100	24 ± 1	28 ± 0
3		200	14 ± 1	19 ± 1
4		300	11 ± 1	11 ± 1
	Amorphous sucrose/sucrose crystal[b]			
5	0%[c]	200	13 ± 1	13 ± 1
6	10%[c]	200	13 ± 1	12 ± 1
7	20%[c]	200	13 ± 1	13 ± 1
8	50%[c]	200	13 ± 1	14 ± 1
9	75%[c]	200	13 ± 1	17 ± 1
	HPC/amorphous sucrose[b]			
10	10%[d]	200	19 ± 0	24 ± 1
11	20%[d]	200	22 ± 0	26 ± 1
	PVP/amorphous sucrose[b]			
12	10%[e]	200	16 ± 1	20 ± 2
13	20%[e]	200	18 ± 0	20 ± 0

[a] Each data represents the mean ± S.D. for five experiments.
[b] Physical mixture.
[c] Amorphous sucrose content.
[d] HPC content.
[e] PVP content.

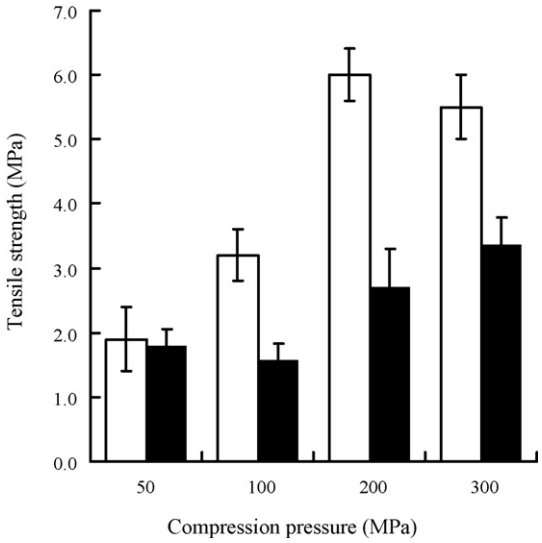

Fig. 6. Tensile strength of amorphous sucrose tablets as a function of compression pressure before (open columns), and after storage at 25 °C under 51% RH for 2 days (closed columns). The bars represent the S.D. for five determinations.

before and after crystallization. The decrease in tensile strength was attributed to the increased porosity as Tye et al. (2005) reported.

The tensile strength decreased more when the storage humidity was higher, indicating the influence of the difference in the crystal formation process attributable to the difference in storage conditions (data not shown).

It is considered that a tensile strength of about 1 MPa is necessary for a tablet to be distributed without any problems. The preparation of OSDRC tablets by crystallization of amorphous sucrose is expected to satisfy this criterion and to produce a tablet of sufficient strength. Furthermore, the disintegration time of the tablet (that serves as the outer layer) was about 1.5 min, and so a sufficiently quick dissolution of a drug from the OSDRC tablet was expected.

3.2.3. *Pore size distribution and microstructure*

Fig. 7 shows the pore distribution determined by mercury porosimeter. The pore distribution of compressed sucrose crystal and compressed amorphous sucrose before crystallization was biphasic and specific to 0.5–1 μm. The same distribution was observed when fine crystals were used. However, unlike the pore distribution demonstrated by the compressed sucrose crystal and compressed amorphous sucrose before crystallization, 0.5–1 μm pores disappeared while 0.05 μm pores were generated in the compressed and crystallized amorphous sucrose. However, the generation of larger pores measuring 100 μm was also observed. Consequently, it is considered that the porosity increased and the tablet strength decreased in the compressed and crystallized amorphous sucrose. However, considering the dramatic decrease in water vapor permeation, the distribution of pores in a layer about 700 μm thick is not assumed to be homogenous. The pore distribution of a conventional sugar-coated layer is 0.03 μm or less (Takeda, 1976), which corresponds to the distribution of

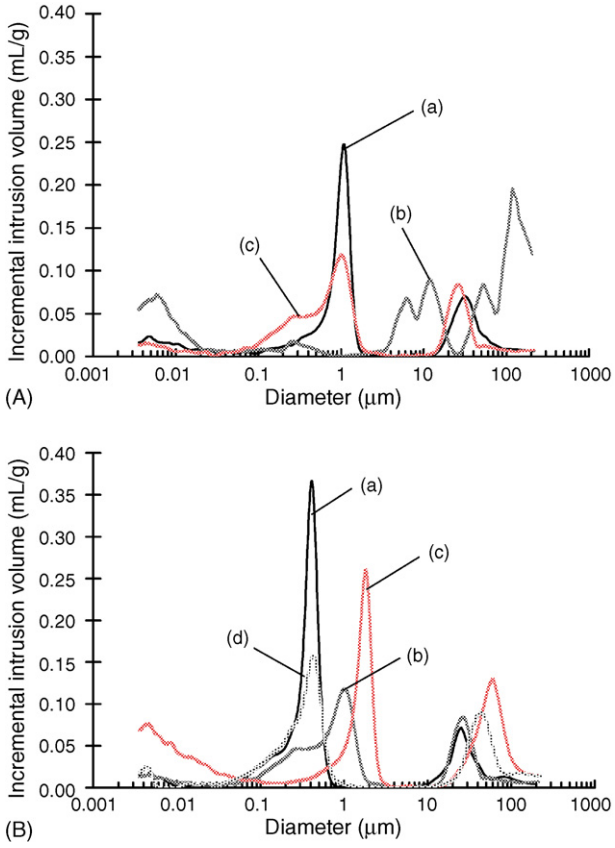

Fig. 7. Pore size distributions of tablets composed of various sucrose samples, obtained by mercury porosimetry: (A)—(a) amorphous sucrose, (b) crystallized amorphous sucrose after compaction, and (c) sucrose crystal (d_{50} = 49 μm); (B)—(a) sucrose crystal (d_{50} = 9.4 μm), (b) sucrose crystal (d_{50} = 49 μm), (c) HPMC, and (d) lactose–MCC (7:3).

finer pores of compressed and crystallized amorphous sucrose in this experiment.

A significant pore distribution at 1 μm was also observed in the case of lactose–MCC and HPMC which demonstrated high water vapor permeability (Fig. 7B), indicating substantial involvement of these pores in water vapor permeation.

The changes in the microstructure of the tablet's surface before and after crystallization were investigated by SEM. Fig. 8 shows the microstructure of the surface. When compression was performed at 50 MPa, spherical particles that were spray-dried over the tablet were densely filled and only slight deformation was observed before crystallization. However, under a pressure of 200 MPa, fusion and cohesion between the particles were clearly observed. The particles were completely fused to form a smooth surface when a pressure of 300 MPa was applied. Thus, the fusion and cohesion at particle–particle interface to form a continuous phase of amorphous sucrose are affected by the compression pressure. This is partly because the binding force of amorphous particles is strong (Hancock and Shamblin, 2001), and the increased local temperature around the regions promotes the fusion of particles due to interparticulate friction during compression. On the other hand, crystals were formed, demonstrating some unevenness after crystallization. Under a

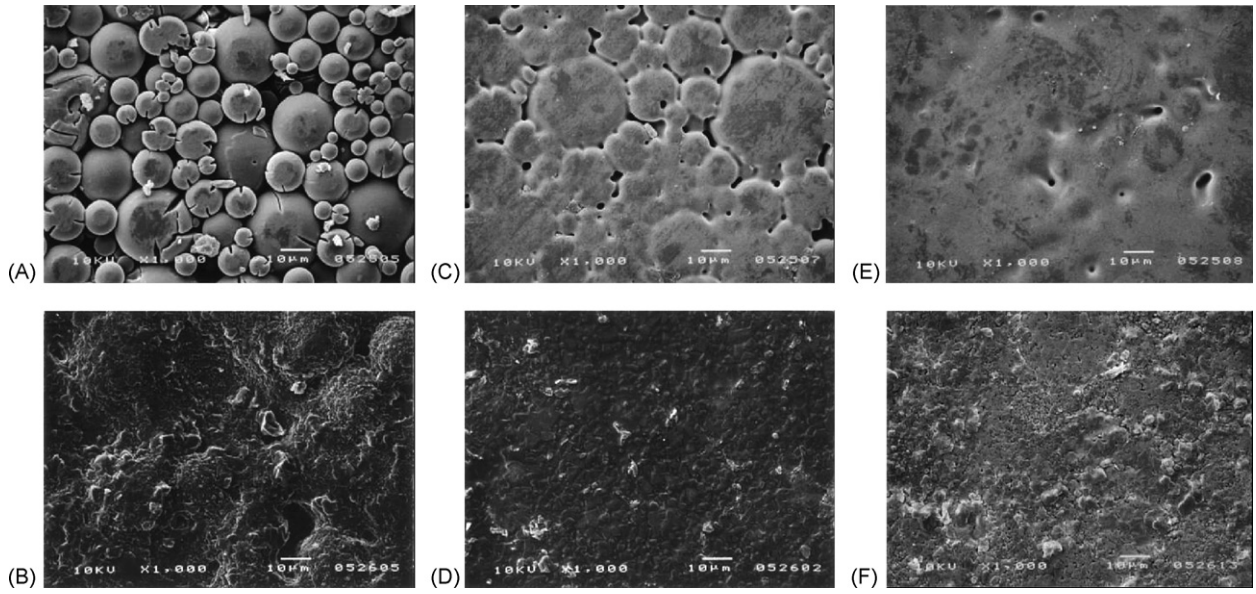

Fig. 8. Scanning electron micrographs of the upper surface of amorphous sucrose tablets compressed at 50 MPa [(A) before and (B) after storage at 25 °C under 51% RH for 2 days], 200 MPa [(C) before and (D) after storage at 25 °C under 51% RH for 2 days], and 300 MPa [(E) before and (F) after storage at 25 °C under 51% RH for 2 days].

pressure of 50 MPa, the fusion of amorphous spherical particles occurred with crystallization.

3.3. Effect of the amorphous content on characteristics

3.3.1. Water vapor permeability

To find out how much amorphous sucrose is required initially to prevent water vapor permeation, sucrose crystals prepared by adding amorphous sucrose at various ratios were compressed and then crystallized. As shown in Table 1 (Exp. nos. 3, 5, and 9–12) and Fig. 9, water vapor permeation was dependent on the amorphous sucrose content and was indicated by two straight lines with 20% as the border. When the amount of amorphous sucrose was less than 20%, the water vapor permeability coefficient dramatically increased. According to the theory of percolation, when two different powder substances are used, there is a percolation threshold at which the nature of one substance is replaced by that of the other, thereby changing the physicochemical characteristics. This threshold is observed at an amount of 20–30% in many cases (Rohera et al., 1987). In this experiment, 20% served as the percolation threshold. A continuous layer was expected to be formed when the amount exceeded 20%. It is considered that the sucrose crystals that are present at the initial state in amorphous sucrose are adhered by a solid bridge in association with crystallization. However, with an amount of 20% or less, the amorphous particles formed an intermittent layer so that the permeation rapidly increased because of the presence of areas where a solid bridge of crystals could not be formed.

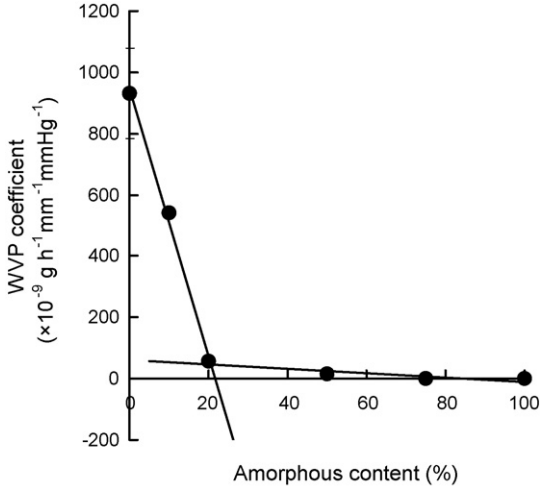

Fig. 9. Effect of amorphous content on water vapor permeability (WVP) coefficients of crystallized amorphous sucrose after compaction. The bars represent the S.D. for three determinations.

The diameter of the crystals and amorphous particles used in this experiment was 49 and 20 μm, respectively. According to the ordered mixture theory (Hersey, 1974), water vapor permeability drops if the particle diameter of amorphous sucrose is smaller than that of the sucrose crystal even through the amount of amorphous sucrose added is smaller.

3.3.2. Physicochemical characteristics

Fig. 10 shows the influence of amorphous content on tensile strength before and after crystallization. Tensile strength before crystallization hardly changed when the amorphous content was 20% or less but an increase in proportion to the amorphous content was observed in excess of 20%. The result sufficiently reflected the percolation threshold observed in the case of water vapor permeation. Similarly, a change occurred in tensile strength after crystallization with 20% as the borderline.

When tensile strength before and after crystallization was compared, it was found to increase after crystallization when the amorphous content was 20% or less but there was no difference at 50%. On the other hand, the presence of amorphous

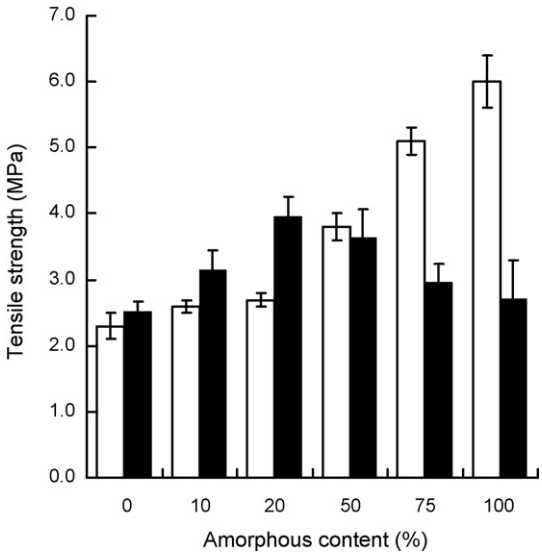

Fig. 10. Tensile strength of amorphous sucrose tablets as a function of amorphous content before (open columns), and after storage at 25 °C under 51% RH for 2 days (closed column). The bars represent the S.D. for five determinations.

content in excess of 50% decreased tensile strength in association with crystallization. Elamin et al. (1994) reported that tablet strength increased when the milled crystals were stored under humid conditions. Sebhatu et al. (1994) stored 15% amorphous lactose at 57% RH and reported that tablet strength increased because of the presence of the amorphous portion. Therefore, the increase in the strength of a tablet is caused by a solid bridge of crystals in association with the crystallization of amorphous sucrose. The presence of a small amount of amorphous indicates an increase in tablet strength. When the amount added exceeds 50%, it is considered that a decrease in tablet strength occurs due to increased porosity [Table 2 (Exp. nos. 3 and 5–9)].

3.4. Effect of additives on characteristics

3.4.1. Water vapor permeability

For the purpose of providing plasticity to sucrose, HPC and PVP which are extensively used water soluble polymers were added, and their influence on water vapor permeation was investigated. As shown in Table 1 (Exp. nos. 13–16), the addition of HPC or PVP increased water vapor permeation. However, compared with PVP, the influence of HPC was smaller. Since the increase in water vapor permeation occurs by the diffusion of water molecules through the polymer, the result indicated that more diffusion occurred in PVP than in HPC. The permeation was proportional to the amount added with the addition of 10 and 20% PVP or HPC. According to the percolation theory, a continuous layer of additive is not expected to form when the amount added is 20% or less (Kuny and Leuenberger, 2003; Amin and Fell, 2004), the characteristics of sucrose are retained, and water vapor permeation decreases. However, an increase in permeation actually occurred even when the amount added was 10%. This is because water molecules diffused in the polymer and permeated through the gaps of sucrose even though a continuous layer of additive had not formed.

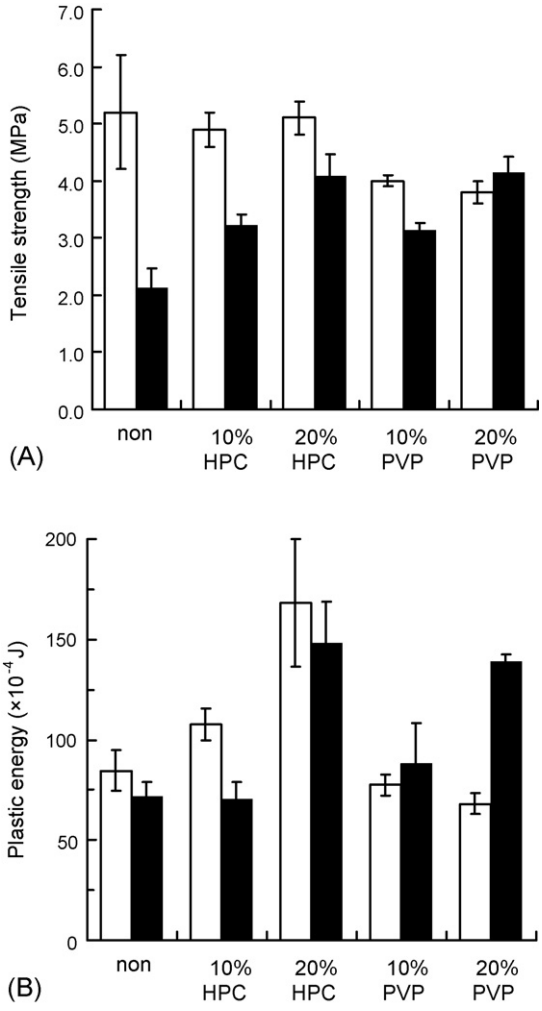

Fig. 11. Physical properties of amorphous sucrose tablets as a function of additive content before (open columns), and after storage at 25 °C under 51% RH for 2 days (closed column): (A) tensile strength and (B) plastic energy. The bars represent the S.D. for five determinations.

3.4.2. Physicochemical characteristics

Fig. 11(A) shows the changes in tensile strength before and after crystallization and Fig. 11(B) shows the changes in plastic energy. It was confirmed that the plasticity of HPC before crystallization was dependent on the amount added. After crystallization, the addition of 20% was necessary to obtain plasticity. Since the addition of polymer influences water vapor permeability, it is necessary to select an additive with a higher plasticizing effect or to design complex particles of amorphous sucrose—plasticizer.

3.5. Investigation of the characteristics of OSDRC tablets

A new sugar-coated tablet was prepared using amorphous sucrose as an outer layer and fructose (hydroscopic substance) as a core by OSDRC technology in order to investigate its characteristics. The physicochemical characteristics of the tablet were: a thickness of 3.98 ± 0.04 mm, tablet strength of 78.5 ± 3.1 N, disintegration time of 4.5 ± 0.1 min, and friability of 0.4%, all of which are favorable for a solid dosage form. For the purpose of

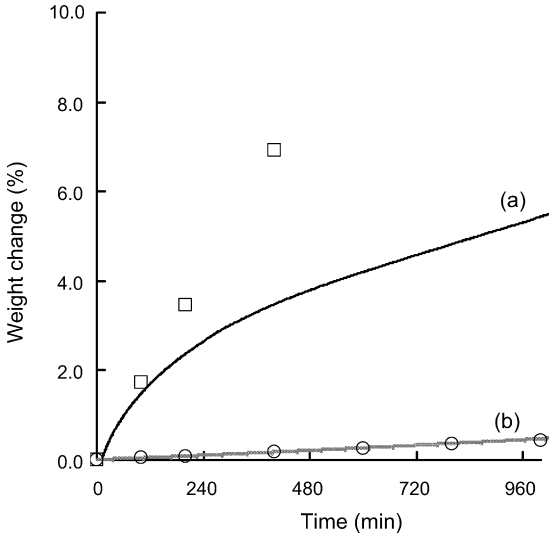

Fig. 12. Water vapor permeation profiles of OSDRC tablets containing fructose as a model hygroscopic substance: (a and □) outer layer—HPMC and (b and ◯) outer layer—crystallized 50% amorphous sucrose after compression. Open symbols represent values predicted from the WVP coefficient.

confirming the moisture protection of the tablet, the water vapor adsorption behavior on storage at 25 °C and 75% was investigated. The results are shown in Fig. 12. When HPMC was used as an outer layer ingredient, the measured value was not matched by the calculated value. This is considered attributable to the very high hygroscopicity and deliquescence of fructose employed as a core, which resulted in a difference from the value calculated from the permeability coefficient. In the case of the new sugar-coated tablet, the measured value corresponded with the calculated value, therefore, the protection from moisture was confirmed.

4. Conclusion

It was demonstrated that water vapor permeation could be sufficiently reduced in the compressed and crystallized amorphous sucrose in comparison with the compressed product of crystals themselves or film component, etc. The water vapor permeability and physicochemical characteristics were influenced by the amorphous content or amount of additive. These changes were suggested to be attributable to the changes in pore distribution caused by crystallization.

A novel method of manufacturing sugar-coated tablets using an amorphous substance and OSDRC technology is available not only for moisture protection but also for masking odor and taste, and which is expected to improve patient compliance. Further research in the future is expected to assess the influence of amorphous particle diameter, additives, and crystallization conditions on water vapor permeability and physicochemical characteristics during the manufacturing process.

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