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Formulation design of a novel fast-disintegrating tablet

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Abstract

As our society is becoming increasingly aged, the development of an appropriate dosage form for the elderly patients is mostly desirable. A novel fast-disintegrating tablet was investigated in this study as a user-friendly dosage form for the aged. Advantages of this formulation have sufficient hardness and can be manufactured by commonly used equipment. Saccharides can be divided into high- and low-compressibility categories, and an appropriate material for fast-disintegrating tablets was created by taking advantage of this fact. To improve the compressibility of low-compressibility saccharides, particle modification was conducted by coating and granulating a low-compressibility saccharide with a high one to enable the production of a fast-disintegrating tablet. Another discovery was that the high-compressibility saccharide used as a binder solution was present in an amorphous state after the granulation process. The crystal change from amorphous to crystal state intentionally by a conditioning process after compression enabled to increase tablet hardness by strengthening adhesion between particles. The conditioning process made it possible to achieve sufficient hardness while maintaining the fast disintegration time. As a result, this fast-disintegrating tablet that can be manufactured by commonly used equipment, can be used for the dosing of a wide range drugs.

Keywords: Fast-disintegrating; Saccharide; Compressibility; Amorphous; Conditioning process

1. Introduction

Due to a society that is becoming increasingly aged, the development of an appropriate dosage form for the elderly is most desirable. Because the changes in various physiological functions associated with aging including difficulty in swallowing, current dosage forms, like capsules, are impractical.

Recently, new jelly formulations like xerogel (Itou et al., 1994) and fibroin (Hanawa et al., 1995) have been proposed, and Ohta Pharmaceuticals has marketed a stick-type "Air-push jelly" formulation in Japan (Dairaku and Togashi, 2003). Although a jelly formu-

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lation is easy to take because it contains water, many issues, like chemical stability and drug-release properties, must be addressed. Jellies are also not considered to be candidates for widespread use because of their low versatility.

Honda and Nakano (1998) reported that a half of the patients surveyed experienced difficulty in taking medication and felt that a tablet was a better and easier formulation compared to other formulations such as capsules or powders. Sugihara et al. (1986) reported that the degree of ease when taking a tablet depended on its size. He reported that the size of tablet that was easiest to swallow was 7–8 mm, but the size easiest to handle was one larger than 8 mm. Therefore, since a tablet size that is both easy to take and easy to handle is difficult to achieve, tablets have some intrinsic problems as dosing formulations for the elderly.

The most desirable formulation for use by the elderly is one that is easy to swallow and easy to handle. Taking these requirements into consideration, attempts have been made to develop a fast-disintegrating tablet (Chang et al., 2000). Since such a tablet can disintegrate in only a small amount of water in the oral cavity, it is easy to take for any age patient, regardless of time or place. For example, it can be taken anywhere at anytime by anyone who do not have easy access to water. It is also easy to dose the aged, bed-ridden patients, or infants who have problems swallowing tablets and capsules. Recently, many companies have researched and developed various types of fast-disintegrating dosage forms. Cardinal Health was the first company to develop and market a fast-disintegrating, freeze-dried porous wafer known as Zydis (Seager, 1998; Katou et al., 1993). CIMA also marketed an effervescent tablet known as OraSolve (Wehling et al., 1991). Others include Eisai and Ethypharm, who developed the EMP tablet (Tushima, 2001) and Flashtab (Cousin et al., 1995), respectively. However, some of these technologies have disadvantages. New equipment, such as freeze-driers and specially molded tableting machines, were required for their production. Furthermore, these formulations were difficult for the aged to handle because of inadequate strength. The objectives of this study are to produce a fast-disintegrating tablet, which has sufficient hardness for handling and can be manufactured by commonly used production methods and equipment.

2. Materials and methods

2.1. Materials

The D-mannitol (Towa Chemical Industry, brand name: Mannit P), lactose (HMS, brand name: Lactose IMP), glucose (Nippon Shokuhin Kako), sucrose (Nisshin Seito), erythritol (Nikkenn Chemicals, brand name: Erythritol 100M), xylitol (Towa Chemical Industry, brand name: Xylit P), maltose (Hayashibara, brand name: Sanmalt), sorbitol (Towa Chemical Industry), trehalose (Hayashibara, brand name: Toreha powder), multitol (Towa Chemical Industry, brand name: Amalty MR) and magnesium stearate (Nippon Oil & Fats) were used in this study. Acetaminophen (Yoshitomi Pharmaceutical Industries Ltd.) was used as the model drug.

2.2. Evaluation of saccharides

All saccharides were used in the supplied state. From each saccharide 150 mg was weighed and then compressed to an 8 mm round compact at 50 kg/cm^2 using the hydraulic press. The hardness ($n = 3$–5) was measured using a tablet hardness meter (Schleuniger). The disintegration time in the mouth was measured by taking the time required for the complete disintegration of a tablet by saliva in the mouth of healthy male adult volunteers ($n = 3$) without water.

2.3. Measurement of surface free energy

The liquid penetration rate was measured by using KRUSS K121 at 25 °C. The stainless tube packed with powder was lowered into liquid and the time was started to record when the liquid was contacted with the powder. The weight of liquid penetrated into the powder bed was recorded against time. The penetration rate constant was calculated by the Washburn equation. Hexane, tetrachloromethane, chloroform, dichloromethane, ethanol, *N*,*N*-dimethylformamide, benzylalcohol were used as probe solvents having different polarity. The surface free energy of saccharides was calculated from Owens, Wendt, Rable, and Kaelble's equation using the contact angle between liquid and powder.

$$\frac{1+\cos\theta}{2}\frac{\gamma_L}{\sqrt{\gamma_L^d}} = \sqrt{\gamma_S^p}\cdot\sqrt{\frac{\gamma_L^p}{\gamma_L^d}} + \sqrt{\gamma_S^d}$$

where θ is the contact angle, γ_L and γ_S are the surface free energy of the liquid and the solid, respectively, and p and d represent polar and dispersion component of the surface free energy, respectively.

2.4. Preparation of the fast-disintegrating tablet

Mannitol and other excipients were granulated with maltose solution (15%, w/w) in a fluidized-bed granulator (Uni-glatt, Ohgawara Seisakusho) in an approximately 400-g batch size. The granulation conditions were: a spray rate of 10 g/min, a spray pressure of 1.5 kg/cm^2, and a bed temperature of 30–35 °C. After mixing the granules with magnesium stearate, the mixture was compressed using a rotary tableting machine (Hata Seisakusho).

Next, if the conditioning was needed, the tablets were kept for 24 h at 25 °C 70% RH using a thermostatic chamber (Tabaiespec Co. Ltd., PR-35C), followed by a further period of 3 h at 30 °C 40% RH using the same equipment.

2.5. Powder X-ray diffraction measurement

The powder X-ray diffraction patterns were measured using an X-ray diffractometer (RINT1400, Rigaku) with Cu anode material. The diffraction pattern was measured with a voltage of 40 kV and a current of 40 mA in the area of $5^\circ < 2\theta < 40^\circ$ at an angular speed of 3° min^{-1}.

2.6. Calculation of the crystallinity of maltose

The crystallinity of maltose was calculated from the results of thermal analysis. The mixture of maltose and mannitol known to comprise the crystal maltose was used to prepare the calibration curve between the endothermic peak area derived from maltose and the contents of crystal maltose. The endothermic peak area was measured using a differential scanning calorimeter (DSC6100, Seiko Instruments). The crystallinity of maltose was calculated using this calibration curve from the endothermic peak area derived from the maltose in each sample. The sample for measurement was prepared by grinding tablets using a mortar, which were left in a thermostatic chamber (Tabaiespec Co. Ltd., PR-35C) maintained at 25 °C 70% RH and were then sampled at a predetermined time.

About 10 mg of sample was weighed in a standard open aluminum pan, and an empty pan of the same type was utilized as the reference. Samples were heated from 20 to 200 °C at a heating rate of 5 °C/min, while being purged with dry nitrogen.

2.7. Measurement of change in adsorbed moisture and hardness during the conditioning process

Tablets were left in a thermostatic chamber (Tabaiespec Co. Ltd., PR-35C) maintained at 25 °C 70% RH or 30 °C 40% RH, and were sampled at a predetermined time. The adsorbed moisture was calculated from the change in the mean weight of 100 tablets. The hardness ($n = 5$) was measured using a tablet hardness meter (Schleuniger).

3. Results and discussion

3.1. Characteristics of saccharide and particle modification

In order to produce fast-disintegrating tablets with commonly used production methods and equipments, the raw material used should have a quick disintegration rate in the mouth and a high compressibility in order to yield an adequate hardness when compressed.

At first, various saccharides, which are generally used as formulation additives, were examined as the raw material for fast-disintegrating tablets. The in vivo disintegration time in the mouth and the hardness of the tablets obtained by compressing various saccharides were measured, as shown in Table 1. The results showed that mannitol, lactose, and glucose, etc. had quick disintegration time, but very low hardness. On the other hand, maltose and multitol, etc. exhibited high hardness, but a significantly slow disintegration time. Given these results, we determined that no raw material that simultaneously satisfied both of the aforementioned characteristics could be found. However, one unexpected observation was made: saccharides could be divided into two groups. One group consisted of low-compressibility saccharides that exhibited quick disin-

Table 1
Compression characteristics of various saccharides

Ingredients	Hardness (kp)	In vivo disintegration time (s)
Mannitol	0	<10
Lactose	0	<10
Glucose	0.2	<10
Sucrose	0.5	<10
Erythritol	0	<10
Xylitol	0	<10
Maltose	6.8	>30
Sorbitol	2.2	>30
Trehalose	3.4	>30
Maltitol	2.5	>30

tegration time in the mouth when made into tablets. The other group consisted of high-compressibility saccharides that yielded adequate hardness.

To clarify the mechanism which affects the compressibility of saccharides, the surface free energy of each saccharide was analyzed by Owens–Wendt plot which was obtained from the measurement of wet rates of various saccharides. Fig. 1 shows the surface free energy of dispersive component and polar component of the low- and high-compressibility saccharides. The high-compressibility saccharides had the surface free energy of very high-polar component compared to those of the low-compressibility saccharides. Furthermore, a lot of hydroxyl group was observed on the particle surface of high-compressibility saccharides by IR measurement, namely the surface free energy of very high-polar component was derived from the hydroxyl

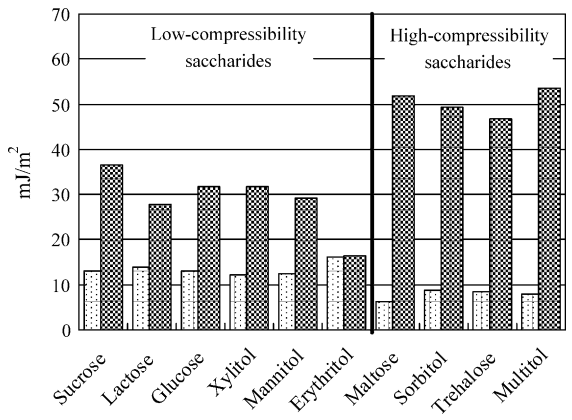

Fig. 1. Surface free energy of dispersive component and polar component of the low- and high-compressibility saccharides. Surface free energy of dispersive component (⬚) and polar component (▩).

group on the particle surface and this hydrophilic substituent would have affected on the cohesive property of each particles, which enhanced the compressibility of saccharides. Consequently, it was found that the surface free energy of polar component have affected on the difference of compressibility of saccharides.

Attempts were made to create a new material that exhibited the two desirable characteristics. We improved the compressibility of the low-compressibility saccharide so that an adequate hardness could be obtained while maintaining its quick disintegration time by coating and granulating a low-compressibility saccharide with a high-compressibility saccharide.

The tablet characteristics prepared by the combination of low- and high-compressibility saccharides was evaluated as shown in Table 2 (Formulation A). Mannitol was used as the low-compressibility saccharide and maltose was used as the high-compressibility saccharide and as the binder for granulation. Mannitol was granulated with maltose solution in a fluidized-bed granulator, which is a commonly used equipment. Mannitol's low compressibility characteristic was improved by granulating using a maltose binder. After compression, an adequate hardness of 5.9 kp, and the low friability of 0.65% were obtained while maintaining the quick disintegration time of about 20 s. This new combination material exhibited both adequate hardness and quick disintegration in the mouth, and had the appropriate properties for a fast-disintegrating tablet. Attempts to create a new material exhibiting the two characteristics based on a new finding was successfully concluded, and particle modification, which took advantage of basic saccharide chemistry, enabled the production of a fast-disintegrating tablet using common methods and manufacturing equipments.

3.2. Improvement of tablet characteristics

Another new observation was that maltose used as the high-compressibility saccharide was present in an amorphous state after granulation. Fig. 2 shows the X-ray diffraction patterns of the mixture of lactose and maltose. Although the typical diffraction peaks of maltose were observed in the physical mixture (sample b), the diffraction peaks derived from maltose in the granule disappeared (sample c). This means that the maltose used as a binder is initially present in the amorphous

Table 2
Formula and tablet characteristics

	Formulation A	Formulation B	Formulation C	Formulation D
Formula				
Acetaminophen	–	–	–	250.0
Mannitol	283.5	141.7	141.7	74.8
Lactose	–	–	–	90.0
Maltose	15.0	7.5	6 + 1.5[a]	22.5
Aspartame	–	–	–	9.0
Menthol flavor	–	–	–	1.4
Mg-st	1.5	0.8	0.8	2.3
Total weight (mg)	300	150	150	450
Tablet characteristics—initial state				
Compression force (kg/punch)	303	188	–	150
Diameter (mm)	10	8	8	11
Hardness (kp)	5.9	0.9	1.1	1.7
Thickness (mm)	–	3.60	3.60	6.41
Friability at 100 rounds (%)	0.65	–	–	–
In vivo disintegration time (s)	20	10–15	10–15	15–20
Tablet characteristics—after conditioning				
Hardness (kp)	–	4.0	4.0	5.8
Thickness (mm)	–	3.60	3.60	6.41
Friability at 100 rounds (%)	–	1.0	0.94	0.93
In vivo disintegration time (s)	–	10–15	10–15	15–20

[a] Six milligrams maltose: binder solution; 1.5 mg maltose: powder seed.

state after the granulation process. Given this, a hypothesis was set up to attempt to intentionally increase the hardness and maximize the utility of the new discovery. Specifically, attempts were made to convert the amorphous maltose to the crystalline state by use of a conditioning process. The recrystallization of maltose was observed by conditioning the granule containing amorphous maltose at 25 °C 70% RH (sample d). This crystal change would increase tablet strength. It was also expected to shorten the disintegration time in the mouth while maintaining adequate hardness.

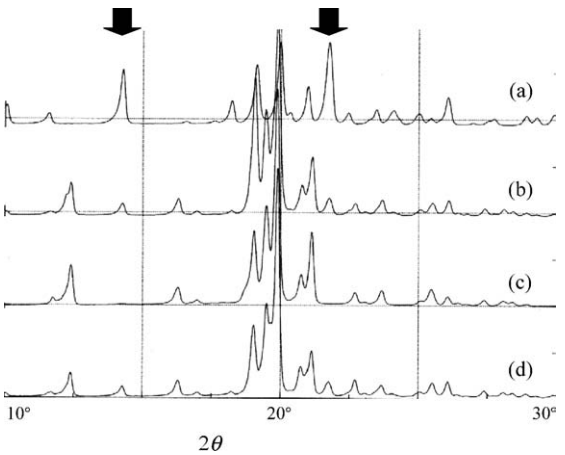

Fig. 2. X-ray diffraction patterns: (a) intact maltose, (b) physical mixture of lactose and maltose, (c) lactose granulated with maltose and (d) granule after conditioning.

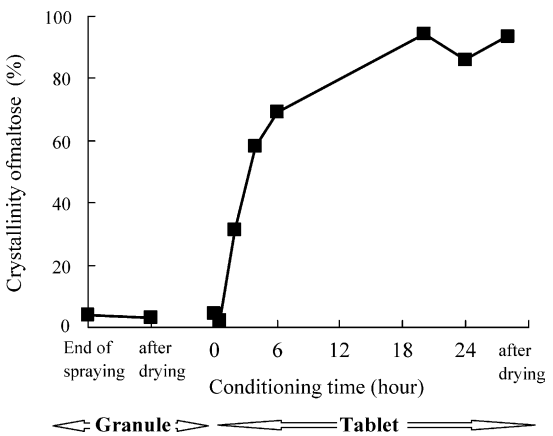

Fig. 3. Change in crystallinity of maltose in tablets during the granulation and conditioning process.

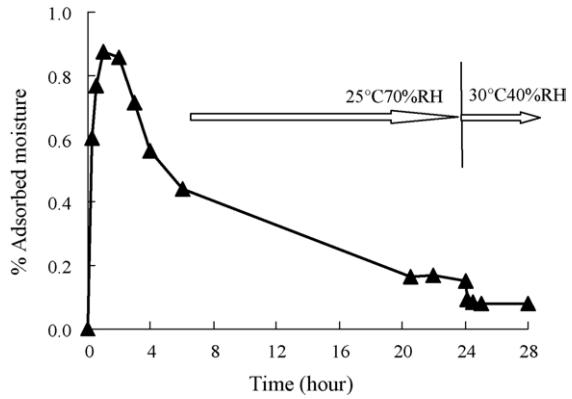

Fig. 4. Adsorption curve of tablets during the conditioning process under 25 °C 70% RH and 30 °C 40% RH.

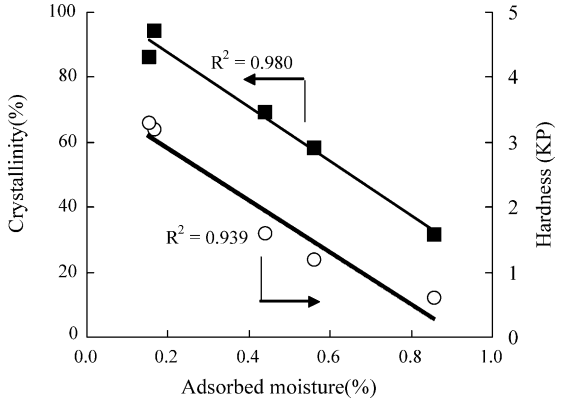

Fig. 6. Correlation between adsorbed moisture and the crystallinity of maltose and hardness.

Fig. 3 shows the change in the crystallinity for maltose during the granulation and conditioning processes after compression (Formulation B). It was confirmed that maltose was in the amorphous state during the granulation process. After compression, when tablets containing amorphous maltose was conditioned at 25 °C 70% RH, the maltose gradually changed into a crystalline state, which took about 18 h to complete. Figs. 4 and 5 show the changes in adsorbed moisture and hardness, respectively, during the conditioning process. The adsorbed moisture was calculated from the weight change of the tablets. The adsorbed moisture increased rapidly for the first 2 h, and the tablet adsorbed about 0.9% of its original weight in moisture. Tablet hardness decreased slightly during this time.

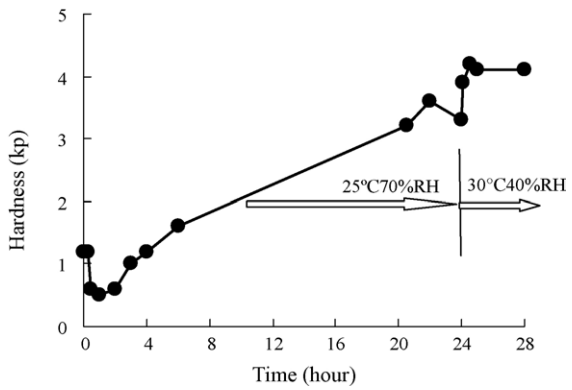

Fig. 5. Change in tablet hardness during the conditioning process under 25 °C 70% RH and 30 °C 40% RH.

After 2 h, desorption was observed. This was caused by the change of maltose into the crystalline form from the amorphous state. Tablet hardness increased gradually and concurrently with the desorption. At the end of this process, the hardness had increased from about 1 kp to reach 4 kp (a four-fold greater hardness). Although the tablet had a very low hardness at first as shown in Table 2 (Formulation B), adequate hardness and the low friability were achieved after the conditioning and change to the crystalline form, and the quicker disintegration time of about 10 s was obtained.

A good correlation was observed between the crystallinity of maltose, the adsorbed moisture, and tablet hardness after 2 h, as shown in Fig. 6. The correlation coefficients between adsorbed moisture and crystallinity and that between adsorbed moisture and hardness were 0.980 and 0.939, respectively, which is very high correlation. Specifically, it was proved that maltose's change to the crystalline form by the conditioning lead to the increase of tablet hardness with concurrent desorption.

The mechanism for increasing hardness is thought to be as follows. Before the conditioning, the amorphous maltose exists on the surface of the mannitol particle. During the conditioning process, the amorphous maltose adsorbs moisture. When the crystallization of maltose occurs, particles adhere to each other strongly, and as a result, the tablet hardness increases. Consequently, the conditioning process makes it possible to increase hardness while maintaining quick disintegration.

3.3. Reduction of treatment time by addition of maltose seed

Although the conditioning was actually useful to achieve sufficient hardness while keeping its quick disintegration, the conditioning took >18 h at least and the reduction of treatment time was required to apply to practical production. It was considered the acceleration of maltose's crystallization by addition of maltose seed was the best way to shorten the processing time. So, a part of maltose (1% amount for tablet weight) was used in powder state as seed and the rest (4% amount for tablet weight) was used as binder solution as usual. The mixture of mannitol and 1% of powder maltose was granulated with maltose solution as shown in Table 2 (Formulation C). After compression, tablets were treated in the same way as Formulation B.

Figs. 7 and 8 show the changes in adsorbed moisture and hardness, respectively, during the conditioning process. The desorption rate and the increase rate of tablet hardness were accelerated as expected and the effect of maltose seed was proved. Since the good correlation between the crystallinity of maltose and tablet hardness was found as shown in Fig. 4, it was presumed that the recrystallization rate of maltose was accelerated by addition of seed and treatment time would be cut in half.

Regarding tablet characteristics, the hardness after treatment indicated around 4.0 kp which was the same as the formulation without seed (Formulation B) and other tablet characteristics such as in vivo disintegration time and friability of Formulation C also showed the similar values to Formulation B, namely it was confirmed that there is no difference in tablet characteristics between without and with maltose seed. Consequently, the addition of maltose seed made it possible to shorten the treatment time by acceleration of crystallization rate of maltose while keeping the same tablet characteristics.

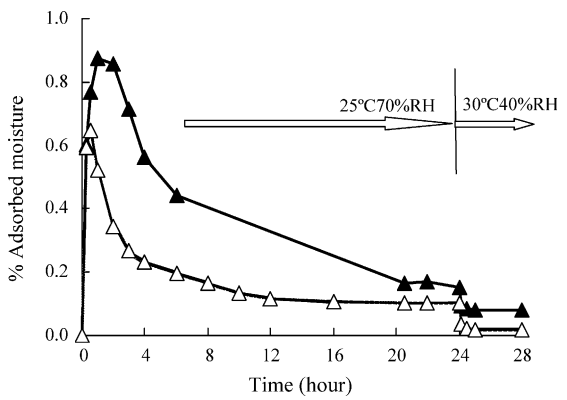

Fig. 7. Effect of maltose seed on adsorption curve of tablets during the conditioning process under 25 °C 70% RH and 30 °C 40% RH. No maltose seed (▲), 1% maltose seed (△).

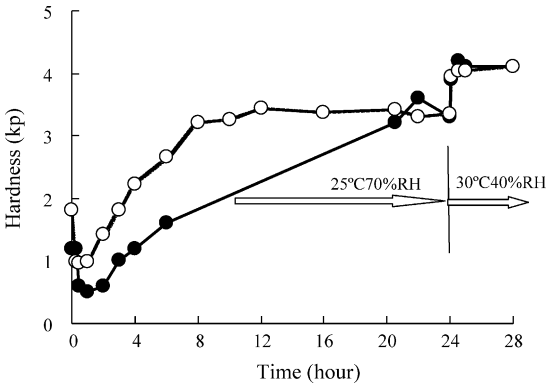

Fig. 8. Effect of maltose seed on change in tablet hardness during the conditioning process under 25 °C 70% RH and 30 °C 40% RH. No maltose seed (●), 1% maltose seed (○).

3.4. Application to acetaminophen as model drug

Next, the novel, fast-disintegrating system was applied to an actual drug to verify its practical use. The tablet characteristics containing a high dose acetaminophen as the model drug were evaluated as shown in Table 2 (Formulation D). Mannitol and lactose were used as the low-compressibility saccharide and maltose was used as the high one and as the binder for granulation. Aspartame and menthol flavor were used as masking agent for the bitter taste of acetaminophen. All materials were granulated with maltose solution in fluidized-bed granulator. After compression, tablet had a low hardness of 1.7 kp in the initial state, but it had very quick disintegration time of around 20 s. After the conditioning, tablet hardness increased to 5.8 kp and exhibited adequate hardness, while keeping the same quick disintegration time of around 20 s. Consequently, the tablet containing acetaminophen manufactured under this system showed adequate hardness and very quick disintegration time simultaneously. It was also confirmed that

this system, which was produced using commonly used production steps and equipment could be applied to a wide range of drugs and had tremendous application potential.

In conclusion, the process for producing the novel, fast-disintegrating tablet consisted of two new concepts, was established. The first concept was the creation of an appropriate material for a fast-disintegrating tablet: the combination of low- and high-compressibility saccharides based on the physicochemical property of saccharides. The second concept was that the conditioning process, using maltose's crystalline change made it possible to achieve sufficient hardness while keeping its quick disintegration. As a result, this system can produce a fast-disintegrating tablet by commonly used production methods and equipment, and can also be applied to a wide range of drugs.

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