Studies of Rapidly Disintegrating Tablets in the Oral Cavity Using Co-ground Mixtures of Mannitol with Crospovidone

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We attempted the development of rapid oral disintegration tablets by direct compression using co-ground mixture of D-mannitol and crospovidone. The co-ground mixture was prepared with a vibration rod mill. The tablets were formed by compression using a single punch-tableting machine after addition of the co-ground mixture to non-ground D-mannitol, crospovidone and magnesium stearate. Regarding the properties of tablets, hardness and the time of disintegration were measured. The particle diameter and specific surface area of the co-ground mixture were measured. The tablets manufactured from a physical mixture of 30% (w/w) co-ground mixture of D-mannitol and crospovidone (mixed ratio 9 : 1) with 65.5% (w/w) of non-ground mannitol, 4% (w/w) of crospovidone, and 0.5% (w/w) of magnesium stearate had good properties for rapidly disintegrating tablets in the oral cavity. They showed the hardness of 4.9 kg and disintegration time of 33 s. We found that adding co-ground mixture of D-mannitol and crospovidone is useful in enhancing hardness of the tablets that could not be achieved by addition of their individually ground mixture. The improvement in the hardness of the tablets was also observed when other saccharides and disintegrants were used. This method was proved to be applicable in the manufacture of tables of ascorbic acid, a water-soluble drug and nifedipine, a slightly water soluble drug; and the dissolution rate of nifedipine from the tablets in water was remarkably improved. The particle sizes of D-mannitol in the co-ground mixture were smaller than that of the individually ground mixture, resulting in a larger specific surface area of the co-ground mixture than that of the individually ground mixture. Therefore, it was presumed that crospovidone acted as a grinding assistant for D-mannitol in the co-grinding process, enhancing the hardness of tablets by increasing the contact area among powder particles.

Key words rapidly disintegrating tablets; co-ground mixture; crospovidone; D-mannitol; direct compression

In the present aging society, easy-to-use dosage forms for elderly patients, whose swallowing function is often decreased, are in a great demand. It was shown that conventional tablets, capsules, and liquid or syrup preparations were not always easy-to-use dosage forms for elderly patients because of their decreased motor function.[1,2] To deal with the demand, great efforts have been made to develop paste preparations and rapidly disintegrating tablets in the oral cavity, using jelly, water-absorbing and swelling gelated materials, or water-soluble polymers.[3,4]

The rapidly disintegrating tablets in the oral cavity are of very practical use because they can be swallowed with a small amount of water or saliva. Such tablets have been produced by various methods; Namely, 1) drying after filling the pockets of the press through pack (PTP) with dispersed solution of the drug,[5—7] 2) drying after low-pressure compression of humid powder granules containing the drug,[8—10] 3) compression of dry powder granules containing the drug[11—13] and, shaping by direct compression after mixing excipients and the drug.[14]

The tablets manufactured by any of the above methods are composed of the drug and saccharides, which disintegrate in a small amount of water or saliva in the oral cavity within about 30 s. Direct compression is the most convenient method however, since no special manufacturing facilities or granulation process is required.

We found that rapidly disintegrating tablets can be easily manufactured by adding a co-ground mixture of mannitol and crospovidone to the mixture of both compounds before shaping. Mannitol is a water-soluble sugar alcohol with poor compactibility while crospovidone is an insoluble polymer with high swelling capacity. We investigated the effect of the ratio of these compounds in the mixture and the time of grinding on the hardness of tablets and the time required for the tablets to disintegrate in the oral cavity. Using ascorbic acid and nifedipine as model drugs, we examined the physical properties of the tablets. Furthermore, we clarified the mechanism of enhancement of the hardness of the tablets when the co-ground mixture of mannitol and crospovidone was added.

Experimental

Materials As saccharides, mannitol (Towa Chemical Co., Ltd., Japan), erythritol (fine powder 100M, Nikken Chemicals Co., Ltd., Japan), xylitol (Towa Chemical Co., Ltd., Japan), lactose (DMV Co., Ltd., Japan), and glucose (Matsutani Chemical Industries Co., Ltd., Japan) were used. As disintegrants, crospovidone (PVPP, Polyplasdone® XL, ISP Ltd., Japan), croscarmellose sodium (Ac-Di-Sol, Asahi Kasei Co., Ltd., Japan), low substituted hydroxypropylcellose (L-HPC LH-21, Shi-Etsu Chemical Co., Ltd., Japan), sodium carboxymethyl starch (Na-CMS, Primojel®, Matsutani Chemical Industries Ltd., Japan), and partly pre-gelatinized starch (PCS, Asahi Kasei Co., Ltd., Japan) were used. Ascorbic acid (Wako Pure Chemical Industries Ltd., Japan) was used as a water-soluble model drug and nifedipine (Wako Pure Chemical Industries Ltd., Japan) was used as the slightly water soluble model drug. Magnesium stearate (Mg-St, Sakai Chemical Co., Ltd., Japan) was used as the lubricant.

Preparation of Tablets Tablets were manufactured by direct compression (Fig. 1). After co-grinding mannitol and crospovidone in a vibrating sample mill (T1-100, CMT Co., Ltd., Japan), non-ground mannitol and Mg-St, or non-ground mannitol, crospovidone, and Mg-St were added to produce a physical mixture of them. The physical mixture was compressed using a single punch tablet machine (J4, Iuchi-Seieido Co., Ltd., Japan) at the compression force of 1000 kgf to produce flat-faced tablets with a diameter of 8 mmϕ and weight of 200 mg. The other tablets were prepared similarly by replacing mannitol with erythritol, xylitol, or lactose and crospovidone with Ac-Di-Sol, L-HPC, Na-CMS, or PCS. Compression was performed following addition of ascorbic acid to be contained 60% (w/w) of the total weight at and after co-grinding and nifedipine 2.5% (w/w) after co-grinding.

Determination of Hardness of Tablets The hardness of tablets was de-

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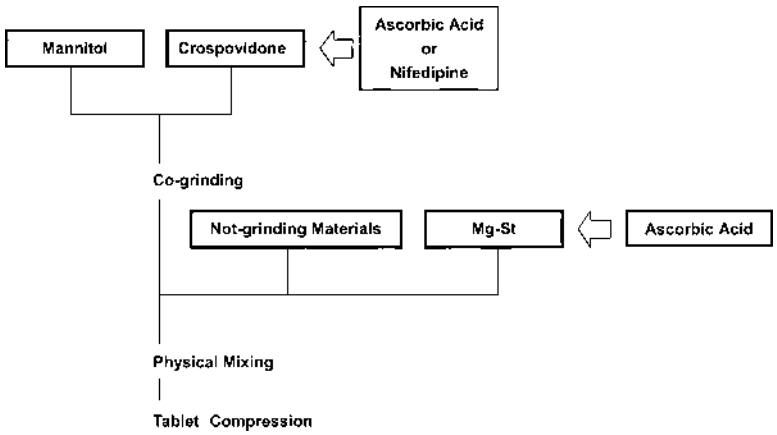

Fig. 1. Preparation Procedure of Rapidly Disintegrating Tablet

Table 1. Formulation of Tablets Containing Co-ground Mixture

	Materials (Percentage by weight)	Formulation No.				
		F01	F02	F03	F04	F05
Non-grinding	Mannitol	96.5	89.5	79.5	69.5	59.5
Grinding	Mannitol	—	7.0	17.0	27.0	37.0
	Crospovidone	3.0	3.0	3.0	3.0	3.0
	Magnesium stearate	0.5	0.5	0.5	0.5	0.5

termined by using a hardness tester (TBH 28 ERWEKA Co., Ltd.).

Disintegration in Oral Cavity The time required for the tablets to disintegrate with saliva was determined by holding the tablets in the mouth. The time required for complete disintegration of the tablet in the mouth was measured. The test was performed in 3 healthy male adults. Male aged from 28 to 39.

Dissolution Test Dissolution test was examined in water (900 ml, 37 °C) using a dissolution tester (NTR-VS3, Toyama Sangyo Co., Ltd., Japan) with a puddle rotation at 50 rpm. After placing a tablet containing 5 mg of nifedipine in water, the solution was filtered through a cellulose acetate filter of 0.2 μm pore size (Dismic®, Toyo Roshi Kaisha Ltd., Japan) and diluted with water. The absorbance (wavelength, 236 nm) was measured using a spectrophotometer (UV-2200A, Shimadzu Corp., Japan).

Determination of Mean Particle Size The mean particle size (D_{90}) was determined using a particle counter (SALD-1100, Shimadzu Corp., Japan) after suspending mannitol, crospovidone, or the co-ground mixture (mannitol/crospovidone: 9/1 (w/w)) in water or ethanol solution saturated with mannitol (about 50 ml, at room temperature).

Determination of Specific Surface Area The specific surface area was determined using an automatic surface area analyzer (Gemini 2360, Shimadzu Corp.) after pre-treatment of mannitol, crospovidone, individually ground mixture, and co-ground mixture (mannitol/crospovidone: 9/1 (w/w)) at 50 °C under reduced pressure for 1 h.

Results and Discussion

Effect of the Co-ground Mixture We first investigated how the ratio and amount of the co-ground mixture of mannitol and crospovidone would affect the hardness and disintegration time in the oral cavity. Table 1 shows the formulation of experimentally manufactured tablets. The hardness of the tablets increased as the amount of the co-ground mixture was increased. The hardness of the tablets in which 30% (w/w) (F04) of the co-ground mixture was added was about 7 kg, however, it did not increase any further when the amount of co-ground mixture was increased (F05) (Fig. 2). The disintegration time was about 60 s for all formulations that contained the co-ground mixture, regardless of the amount of the co-ground mixture added.

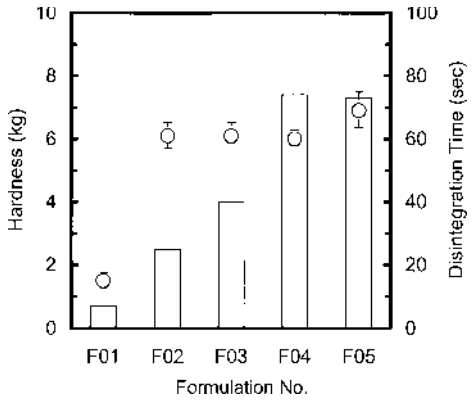

Fig. 2. Effect of Co-ground Mixture on Hardness and Disintegration Time
□, hardness; ○, disintegration time.

Based on the above results, we investigated the effect of the co-ground mixture on the properties of the tablets, using the co-ground mixture of mannitol and crospovidone and the individually ground mixture of each component. Figure 3 shows the hardness and disintegration time in relation to grinding. The hardness of the tablets containing the co-ground mixture increased with the time of grinding, while that of the tablets containing the individually ground mixture changed almost didn't change. The time of disintegration was prolonged proportionally to the time of grinding in both formulations. As a result, we found that the hardness of the tablets was remarkably increased by the co-ground mixture of mannitol and crospovidone. It was found that the co-ground mixture not only increased the hardness but also prolonged the time of disintegration of the tablet, and that these

effects were enhanced by the grinding time. Not less than 5 kg of the hardness and not more than 60 s of the disintegration were chosen. The grinding time was fixed at 20 min in subsequent experiments.

Application to Manufacture of Rapidly Disintegrating Tablets We attempted to manufacture rapidly disintegrating tablets by further adding non-ground crospovidone as we succeeded in enhancing the hardness of the tablets by adding co-ground mannitol and crospovidone. The ratios of co-ground and individually ground mannitol and crospovidone were fixed at 27% (w/w) and 3% (w/w), respectively, and that of Mg-St at 0.5% (w/w). After adding 0—4% (w/w) of non-ground crospovidone, tablets were compressed after further adding non-ground mannitol to make tablets with final weight of 200 mg (Table 2). Figure 4 shows the hardness and disintegration time of the resultant tablets. As the ratio of non-ground crospovidone increased, the hardness of the tablets made of the co-ground mixture decreased. However, a hardness of more than 5 kg was maintained even if tablets contained 4% (w/w) of non-ground crospovidone. The hardness of the tablets made of the individually ground mixture increased, but only to 3 kg. The disintegration time decreased in proportion to the ratio of non-ground crospovidone in both formulations, with no remarkable difference being observed between addition of the co-ground and individually ground mixtures. The tablets to which 4% (w/w) of crospovidone was added along with the co-ground mixture (F09) showed a hardness of 4.9 kg and a disintegration time of 33 s, proving that it is satisfactorily applicable to the manufacture of rapidly disintegrating tablets.

Crospovidone is produced as amorphous, spherical particles with a large specific surface area by spray drying and it is known to be a powder with excellent fluidity and compression compactibility.[15,16] In the tablets with low hardness containing the individually ground mixture, the hardness was, therefore, presumed to improved as the ratio of non-ground crospovidone was increased. On the contrary, the hardness of tablets already hard enough decreased after the addition of the co-ground mixture. It is presumed that this was because the binding force of non-ground crospovidone is weaker than that of the co-ground mixture.

We then investigated the hardness and disintegration of tablets experimentally manufactured according to the F09 formulation shown in Table 2, using various kinds of saccharides and disintegrants. Using erythritol, xylitol, lactose and glucose as poor compactibility saccharides, the effect of co-grinding was investigated (Fig. 5A). The tablets containing erythritol were compressed under a compression pressure of 1000—1400 kgf because of its remarkably poor compactibility. All tablets showed a hardness of more than 3 kg; increase in the hardness of tablets by addition of the co-ground mixture was observed regardless of the type of saccharide. The disintegration time, however, was remarkably delayed being more than 60 min in the tablets that contained xylitol, lactose or glucose. The delay might have been due to the increased viscosity of the saturated solution when dissolved in spite of the higher solubility in water of xylitol and glucose compared with mannitol.[11] Regarding lactose, other factors might have affected the disintegration time because solubility and viscosity of the saturated solution are equivalent to those of mannitol.[11] The possibility, however, remains that tablets with a hardness of more than 3 kg and disintegration time of about 30 s may be available with varied compression pressure

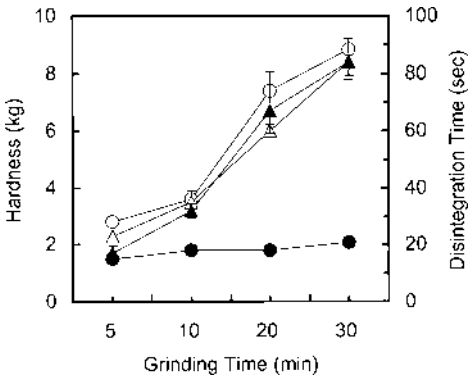

Fig. 3. Effect of Grinding Time on Hardness and Disintegration Time

○, ●, hardness; △, ▲, disintegration time. Open symbols, co-grinding; closed symbols, individually grinding.

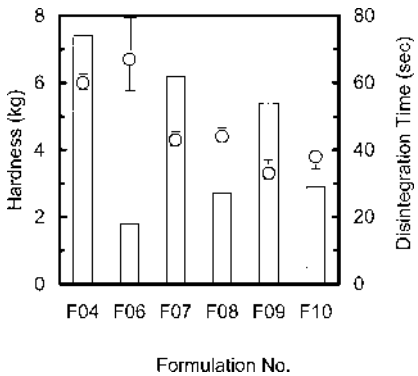

Fig. 4. Effect of Grinding Time on Hardness and Disintegration Time

□, hardness; ○, disintegration time.

Table 2. Formulation of Tablets Containing Additional Disintegrant

	Materials (Percentage by weight)	Formulation No.					
		F04 Co-grinding	F06 Individually grinding	F07 Co-grinding	F08 Individually grinding	F09 Co-grinding	F10 Individually grinding
Non-grinding	Mannitol	69.5	69.5	67.5	67.5	65.5	65.5
	Crospovidone	—	—	2.0	2.0	4.0	4.0
Grinding	Mannitol	27.0	27.0	27.0	27.0	27.0	27.0
	Crospovidone	3.0	3.0	3.0	3.0	3.0	3.0
	Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5

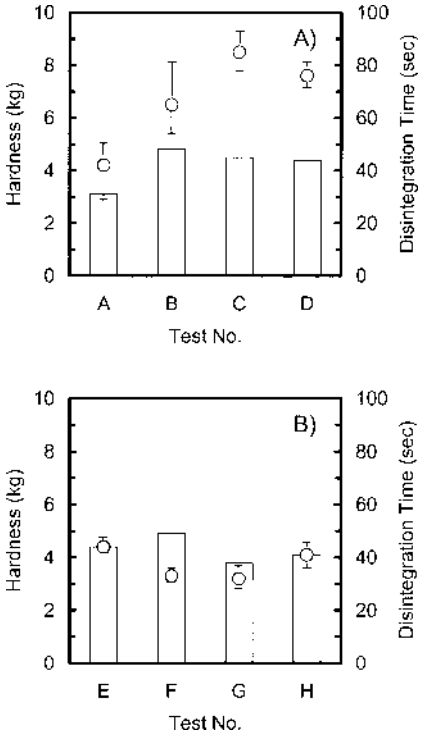

Fig. 5. Effect of Saccharides and Disintegrants on Hardness and Disintegration Time

□, hardness; ○, disintegration time. A, erythritol; B, xylitol; C, lactose; D, glucose; E, croscarmellose sodium; F, low substituted hydroxypropylcellose; G, sodium carboxymethyl starch; H, partly pregelatinized starch. Compress pressures of A and others were 1400 and 1000 kgf, respectively.

and ratio of crospovidone when xylitol, lactose or glucose is used. Figure 5B shows the hardness and disintegration time of the tablets when Ac-Di-Sol, L-HPC, Na-CMS, or PCS was used as disintegrants and the co-ground mixture of mannitol was added. All tablets showed the hardness of 3—5 kg and a disintegration time of 30—45 s; no remarkable variation of the tablet properties was observed regardless of the kind of disintegrant employed.

The above results also suggested that disintegrants other than crospovidone could be used in the manufacture of rapidly disintegrating tablets by adding the co-ground mixture.

Application to Water-Soluble and Slightly Soluble Drugs We investigated the applicability of ascorbic acid, a water-soluble drug and nifedipine, a slightly soluble drug, to the manufacture of rapidly disintegrating tablets containing the co-ground mixture. As shown in Fig. 1, ascorbic acid was added with non-ground mixture (mannitol, crospovidone, and Mg-St) and nifedipine during the co-grinding process of mannitol and crospovidone. Ascorbic acid was added at the ratio of 60% (w/w) (120 mg per tablet) and nifedipine at 2.5% (w/w) (5 mg per tablet). Figure 6 shows the hardness and disintegration time of the resultant tablets. The tablet containing ascorbic acid showed a hardness of more than 3 kg and disintegration time of about 50 s even when added at the ratio of 60% (w/w), though ascorbic acid has a compactibility, as low as that of mannitol. The tablet containing 2.5% (w/w) of nifedipine showed favorable results: that is, a hardness of about 5 kg and disintegration time of about 30 s.

We also investigated the dissolution of slightly soluble

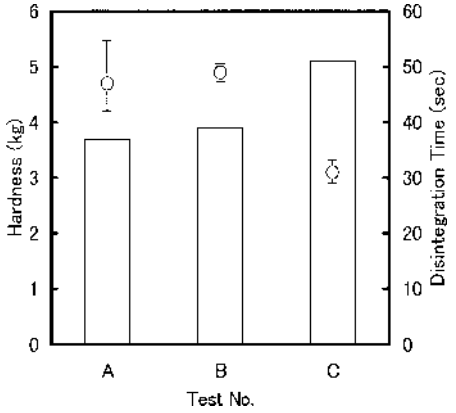

Fig. 6. Effect of Tablets Containing Drug on Hardness and Disintegration Time

A, ascorbic acid (after co-grinding, 60% (w/w)); B, ascorbic acid (at co-grinding, 60% (w/w)); C, nifedipine (at co-grinding, 2.5% (w/w)).

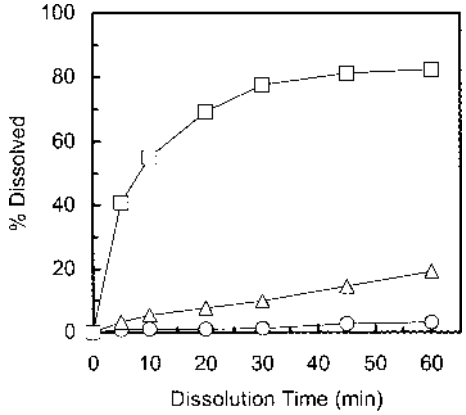

Fig. 7. Dissolution Profiles of Nifedipine Powder and Tablets

○, nifedipine powder; △, nifedipine tablet (non-grinding); □, nifedipine tablet (co-grinding).

drugs from the tablets manufactured by this method that may contribute to improve the dissolution of these drugs on account of incorporated co-grinding process. Figure 7 shows the dissolution in water from non-ground nifedipine powder and the tablets that manufactured by adding non-ground nifedipine powder with the non-ground mixture or during co-grinding process. Dissolution was not satisfactorily improved by only adding nifedipine powder to the non-ground mixture. The dissolution of nifedipine was remarkably improved when nifedipine powder was added during the co-grinding process, showing a dissolution rate of 80% in 30 min. Enhancement of the absorption of slightly soluble drugs to the organism by improving their dissolution has been studied by several methods: complex formation by adding excipients to a pharmaceutical preparation, solid dispersion, co-grinding, *etc.*[17] The manufacturing method we found can improve the dissolution of slightly soluble drugs from the tablets without requiring an additional process, by only using the co-grinding the components to improve the hardness of tablets.

From the above results, the tablets manufactured by this method were found to rapidly disintegrate in the oral cavity even if water-soluble or slightly soluble drugs were added to the co-ground mixture.

Physical Properties of the Co-ground Mixture We in-

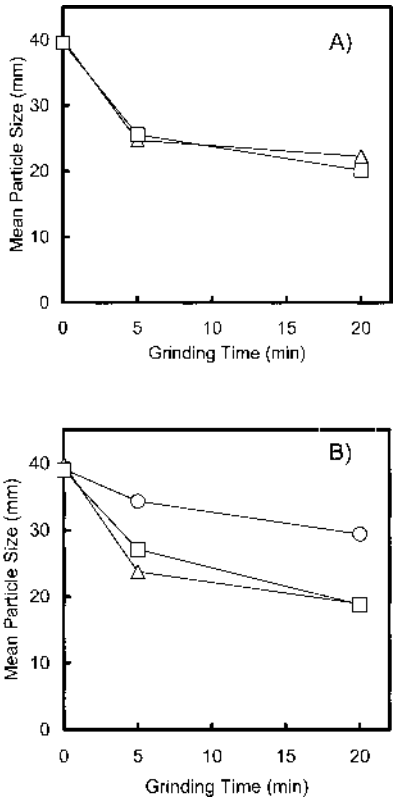

Fig. 8. Effect of Grinding Time on Mean Particle Diameter (D_{90})

A, in water; B, in ethanol solution with saturated mannitol. ○, mannitol (individually grinding); △, PVPP (individually grinding); □, mannitol/PVPP=9/1 w/w (co-grinding).

vestigated the physical properties of the co-ground mixture of mannitol and crospovidone. The mean particle size (D_{90}) was first determined after suspending the individually ground mannitol and individually ground and co-ground mixture of crospovidone with mannitol [mannitol/crospovidone: 9/1 (w/w)] in water or saturated ethanol solution with mannitol. In water, the size of swollen particles of crospovidone was determined since it is insoluble in water (Fig. 8A); and in saturated ethanol solution, the particle size of mannitol alone or that of mannitol together with swollen crospovidone was determined (Fig. 8B). In the determination in water, the size of the particle of crospovidone was found to decrease during the grinding process, regardless of whether it was individually ground or co-ground, becoming to about 20 μm in 20 min. In the determination in saturated ethanol solution with mannitol, the size of individually ground and co-ground mixture particles became about 20 μm while that of the individually ground mixture of mannitol became about 30 μm in 20 min. Considering that mannitol consisted of 90% (w/w) of the co-ground mixture, the particle of mannitol when co-ground with 10% (w/w) of crospovidone could be further decreased by about 10 μm.

The specific surface area of mannitol, crospovidone, and their individually ground and co-ground mixtures (mannitol/crospovidone: 9/1 (w/w)) was determined (Fig. 9). The specific surface area increased more than twice than that of these individually ground mixtures. Since the particle size and specific surface area are directly correlated, the results corresponded to the particle size obtained above.

The above results suggest that crospovidone acted as a

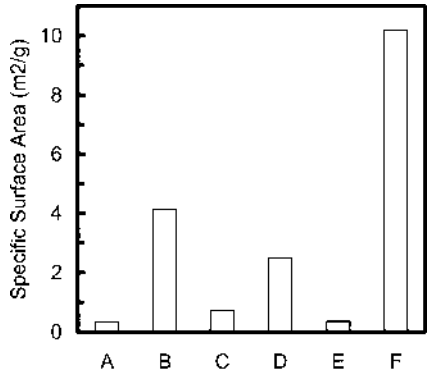

Fig. 9. Effect of Co-grinding on Specific Surface Area

A, mannitol (non-grinding); B, mannitol (grinding); C, PVPP (non-grinding); D, PVPP (grinding); E, mannitol/PVPP=9/1 w/w (non-grinding); F, mannitol/PVPP=9/1 w/w (co-grinding).

grinding assistant when mannitol and crospovidone are co-ground, resulting in a decrease in the particle size and increase in the specific surface area of the whole co-ground mixture. The hardness of the tablets might have been increased on account of the increase in the contact area among powder particles.[18] It may be presumed that disintegration of the tablets decreases because dispersed mannitol helps to wet crospovidone.[19]

Conclusion We were able to prepare tablets that rapidly disintegrated in the oral cavity, with a hardness of about 5 kg and disintegration time of about 30 s, by direct compression. It was attained by physically mixing the co-ground mixture of mannitol and crospovidone with their non-ground mixture (mannitol, crospovidone and Mg-St) before compression. The hardness of tablets was presumed to be improved because crospovidone might have acted as a co-grinding agent for mannitol. It was also suggested that saccharides other than mannitol and disintegrants other than crospovidone could be used with this method in the manufacture of rapidly disintegrating tablets. This method as found to be applicable in the manufacture of both water-soluble and slightly soluble drugs and the dissolution of slightly soluble drugs from the tablets could be remarkably improved by adding such drugs during the co-grinding process.

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