Development of Novel Fast-Disintegrating Tablets by Direct Compression Using Sucrose Stearic Acid Ester as a Disintegration-Accelerating Agent

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It was attempted to produce novel furosemide (FS) fast-disintegrating tablets by direct compression. The combination of FS, microcrystalline cellulose, croscarmellose sodium and xylitol was used as the basic formulation, and sucrose stearic acid ester (SSE) was chosen as an additional additive. The tablets with SSE were prepared by the simple addition of SSE, using a lyophilized mixture of FS and SSE or using a FS/SSE mixture obtained by evaporation of their ethanol solution. Only the tablets, produced using the FS/SSE mixture obtained by organic solvent (ethanol) evaporation, showed hardness of more than 30 N and a disintegration time of less than 20 s, which were the properties suitable for fast-disintegrating tablets. These properties were considered to result from well-mixed and fine-powdered SSE and FS.

Key words fast-disintegrating tablet; sucrose stearic acid ester; furosemide; hardness; disintegration time

Tablets are the most common oral solid dosage forms, because they are convenient to carry, the duration of action of the contained drugs can be controlled[1,2] and their taste or smell can be improved.[3,4] Although powder or capsule dosage forms are also useful orally, they have the drawback of attaching to the throat or pharynx, indicating that tablets have superior usability; however, elderly people and children often have difficulty swallowing conventional tablets or capsules.[5] In particular, patients with oesophageal problems require oral dosage forms that can be swallowed more easily. Various studies have been performed to solve these problems, and fast-disintegrating tablets have been found to be one of the most useful dosage forms.[6,7] For fast-disintegrating tablets, a small amount of saliva is sufficient for disintegration of the tablet in the oral cavity. Namely, as water is not necessary to swallow the drug, patients can take medicine without a source of portable water, which is another advantage of fast-disintegrating tablets.

Various techniques can be used to prepare fast-disintegrating tablets. Lyophilization or molding techniques are used to produce fast-disintegrating tablets,[8—10] but they often result in a lack of hardness due to their highly porous structure, leading to complex processing or being difficult to carry; therefore, recently, simple direct compression methods have drawn attention as a convenient way to produce fast-disintegrating tablets.[11,12] Tablets produced with appropriate disintegrants often show properties of fast disintegration. The disintegration time is dependent on the properties and load of drugs and additives.[12—14] In the present study, it was attempted to produce a fast-disintegrating tablet of a diuretic, furosemide (FS),[15,16] which is also used as an antihypertensive. As treatment with FS is often related to the limit of water intake of patients with edema, fast-disintegrating tablets, which can be taken without water, may be excellent to treat such patients. Furthermore, sucrose stearic acid esters (SSEs), which have been examined as a lubricant in making compressed tablets,[17] were focused on in this study, because some SSEs show good wettability, which might lead to improvement of fast disintegration or dissolution.[18] In the basic formulation of this study, microcrystalline cellulose (MC) and croscarmellose sodium (CC) were used as the tablet diluent and disintegrant, respectively, and xylitol (XL) was added as an agent to mask the taste of FS. The effects of SSE on hardness and disintegration characteristics of the compressed tablets were examined.

Experimental

Materials Furosemide (FS) was purchased from Sigma-Aldrich (St. Louis, U.S.A.). Microcrystalline cellulose (MC: Avicel PH-302) and croscarmellose sodium (CC: Ac-Di-Sol) were obtained from Asahi Kasei Co. (Tokyo, Japan). Xylitol (XL) was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). A sucrose stearic acid ester with an HLB of 16 (Code S-1670; Mitsubishi-Kagaku Foods Co., Tokyo, Japan) was used as SSE throughout this study. All other chemicals were of reagent grade.

Preparation of Tablets 1) Basic Tablets (Type A): The formulation of the basic tablets is shown in Table 1. FS, MC, CC and XL were sieved using a screen of 60 mesh, mixed thoroughly, put into a flat-bottomed cylinder (inner diameter=10 mm), and compressed using a cylindrical pestle with a flat end surface at 4 kN for 30 s using a manual press, Shimadzu SSP-10 A (Shimadzu Co., Kyoto, Japn) to produce tablets (10 mm diameter) of a circular disk.

2) Tablets Produced by Simple Addition of SSE (Type B): FS, MC, CC, XL and SSE were sieved in the same manner as above. The composition of each tablet formulation is described in Table 2. In this method, FS, MC, CC and XL were fixed at 20, 134, 6 and 40 mg, respectively, per tablet, and then a certain amount of SSE was simply added, mixed thoroughly and compressed in the same manner as above.

3) Tablets Produced Using a Lyophilized Mixture of FS and SSE (Type C): First, FS, MC, CC, XL and SSE were sieved in the same manner as above. The composition of each tablet formulation is described in Table 3. SSE was dissolved in water at 50 °C, and FS (0.5 g) was added and stirred overnight, and the resultant mixture was lyophilized. The lyophilized mixture of FS and SSE was mixed with all the other powders thoroughly, and compressed in the same way as above.

4) Tablets Produced Using the FS/SSE Mixture Obtained by Evaporation of the Solvent (Ethanol) (Type D): First, FS, MC, CC, XL and SSE were

Table 1. Basic Formulation of FS Tablets without SSE (Type A Tablets)

Component	Formulation			
	A-1	A-2	A-3	A-4
FS (mg)	20	20	20	20
MC (mg)	174	154	134	114
CC (mg)	6	6	6	6
XL (mg)	—	20	40	60

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sieved in the same manner as above. The composition of each tablet formulation is described in Table 4. FS and SSE were mixed and dissolved in ethanol, and the solvent was evaporated with a rotary evaporator. The residue was dried under nitrogen gas, and then dried completely under reduced pressure overnight. The resultant mixture of FS and SSE was mixed with all the other powders thoroughly, and compressed in the same manner as above.

Physical Characterization of Tablets In order to measure the strength of the tablets, the side of the cylindrical tablet was sandwiched softly between the flat platens of a Kiya-type hardness meter (Fujiwara Scientific Co., Ltd., Tokyo, Japan), and pressed gradually. The hardness observed immediately before crushing was measured. Further, the disintegration time was examined with a disintegration tester, NT-60H (Toyama Sangyo, Co., Ltd., Osaka, Japan).

Observation of Powder Features FS and SSE and their mixture obtained by evaporation of the solvent, ethanol, were observed by scanning electron microscopy (SEM) and differential scanning calorimetry (DSC). For the SEM measurement, each powder was thinly coated with platinum using a JEOL JFC-1600 Auto Fine Coater (JEOL Ltd., Tokyo, Japan) and observed using a JEOL JSM-5600LV scanning electron microscope (JEOL Ltd., Tokyo, Japan), and micrographs were taken. In the DSC measurement, the sample (10 mg) was heated from 50 to 190 °C at 15 °C/min in air atmosphere using Al_2O_3 as a reference with a Rigaku TAS200 thermal analytical system (Rigaku Co., Tokyo, Japan).

Statistical Analysis Comparison was performed using the unpaired *t*-test, and significant difference was set as $p<0.05$.

Results and Discussion

Basic Formulation (Type A Tablets) Disintegration time is one of the most important properties when evaluating fast-disintegrating tablets. Considering the disintegration time of commercial fast-disintegrating tablets,[19] it can generally be proposed that the disintegration time should be less than 20 s, which is considered to be an acceptable period during which patients feel no concern about intraoral disintegration of the tablets. On the other hand, although porous or freeze-dried tablets are generally regarded as appropriate for fast disintegration, they are often fragile; therefore, they are difficult to package, take out from the package and carry without breaking. Strength, therefore, is required as the other most important property for the fast-disintegrating tablets. Several patents indicate that tablets should have a hardness of more than 3 kg (29.4 N)[20—22] or 30 N[23] in order to ensure that they can be automatically packaged, taken out of a press-through package without breaking, or carried in a bottle without breaking. Considering these features, a hardness of more than 30 N and a disintegration time of less than 20 s were used as criteria to evaluate the tablet qualities.

The hardness and disintegration time of the basic formulation, that is, type A tablets, are shown in Fig. 1. The effect of XL on hardness and disintegration time is described in Fig. 2. The addition of XL gradually lowered hardness in a linear manner, but quite markedly prolonged the disintegration time linearly. Although the tablet with no XL exhibited good physical characteristics as a fast-disintegration tablet, the taste of the drug remained to be improved, and in order to solve the problem of tablet taste, 20% (w/w) or more XL (A-3 and A-4 in Table 1) was required (data not shown). Thus, in the following experiment, tablet A-3 was chosen as the control tablet, which did not contain SSE.

Tablets Obtained by Simple Addition of SSE (Type B Tablets) SSE-containing tablets, except for B-5, exhibited slightly less than 30 N hardness (Fig. 3). Although B-5 exhibited hardness of more than 30 N, it showed a longer disintegration time (more than 44 s) (Fig. 3). B-2 and B-3 showed disintegration times of 17.9 and 19.7 s, respectively. The effect of SSE on hardness and disintegration time is summarized in Fig. 4. The addition of a small amount of SSE promoted the disintegration rate, but slightly lowered hardness. The addition of SSE at 0.1% (w/w) was the optimal condi-

Table 2. Formulation of FS Tablets Prepared by Simple Addition of SSE (Type B Tablets)

Component	Formulation					
	A-3	B-1	B-2	B-3	B-4	B-5
FS (mg)	20	20	20	20	20	20
MC (mg)	134	134	134	134	134	134
CC (mg)	6	6	6	6	6	6
XL (mg)	40	40	40	40	40	40
SSE (mg)	—	0.1	0.2	2	5	10

Table 3. Formulation of FS Tablets Prepared Using Powder Obtained by Freeze-Drying of the Aqueous FS/SSE Mixture (Type C Tablets)

Component	Formulation								
	A-3	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8
FS (mg)	20	20	20	20	20	20	20	20	20
MC (mg)	134	134	134	134	134	134	134	134	134
CC (mg)	6	6	6	6	6	6	6	6	6
XL (mg)	40	40	40	40	40	40	40	40	40
SSE (mg)	—	0.04	0.12	0.2	0.4	0.8	2	4	8

Table 4. Formulation of FS Tablets Prepared Using Powder Obtained by Solvent Evaporation of the FS/SSE Mixture in Ethanol (Type D Tablets)

Component	Formulation					
	A-3	D-1	D-2	D-3	D-4	D-5
FS (mg)	20	20	20	20	20	20
MC (mg)	134	134	134	134	134	134
CC (mg)	6	6	6	6	6	6
XL (mg)	40	40	40	40	40	40
SSE (mg)	—	0.1	0.2	2	5	10

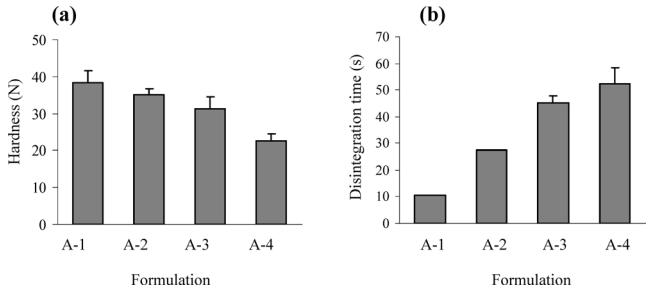

Fig. 1. Hardness (a) and Disintegration Time (b) of Basic Formulations (Type A Tablets)

The results are expressed as the mean±S.D. (n=5 for a; n=6 for b).

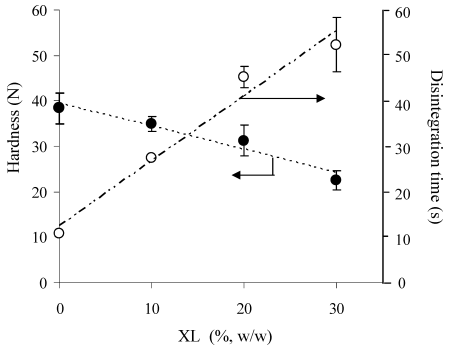

Fig. 2. Effect of XL on Hardness (●) and Disintegration Time (○) of Basic Formulations (Type A Tablets)

Linear curve fitting was conducted for the mean values. Hardness (N)=−0.513×(XL, %)+39.5 (R=0.97). Disintegration time (s)=1.43×(XL, %)+12.5 (R=0.99).

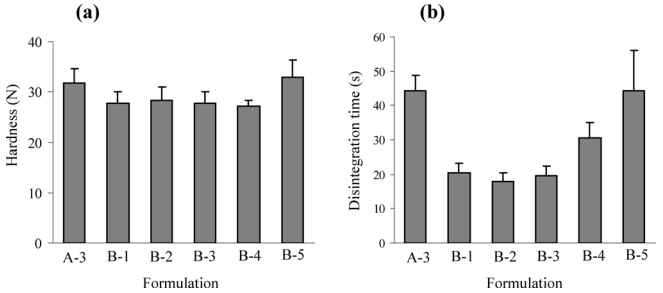

Fig. 3. Hardness (a) and Disintegration Time (b) of Tablets Produced by Simple Addition of SSE (Type B Tablets)

The results are expressed as the mean±S.D. (n=5 for a; n=6 for b).

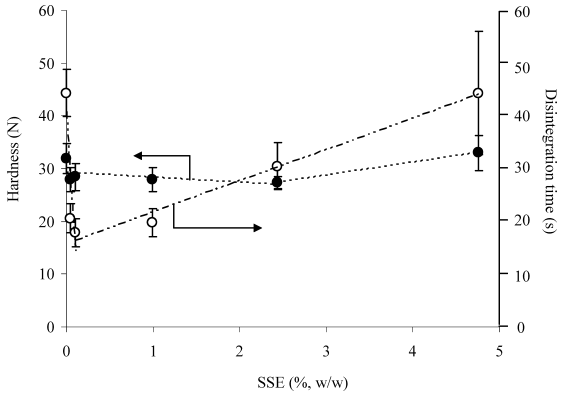

Fig. 4. Effect of SSE on Hardness (●) and Disintegration Time (○) of Tablets Produced by Simple Addition of SSE (Type B Tablets)

Linear curve fitting was conducted for the mean values. Hardness (N)=−0.953×(SSE, %)+29.3 (R=0.55; SSE: 0—2.44%). Disintegration time (s)=−264×(SSE, %)+40.8 (R=0.91; SSE: 0—0.1%); disintegration time (s)=5.93×(SSE, %)+15.8 (R=0.99; SSE: 0.1—4.76%).

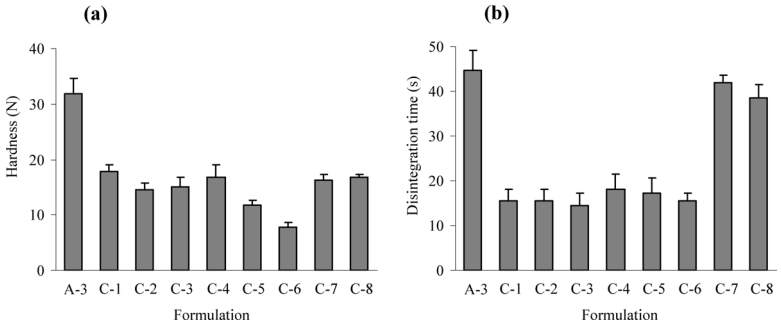

Fig. 5. Hardness (a) and Disintegration Time (b) of Tablets Produced Using Lyophilized Mixture of FS and SSE (Type C Tablets)

The results are expressed as the mean±S.D. (n=5 for a; n=6 for b).

tion to achieve the shortest disintegration time. SSE facilitated compaction with a low content such as 0.1% (w/w), but in the disintegration test, more addition of SSE appeared to increase a wet viscous layer around particles and prevent the degradation of the tablet. The resultant disintegration time at 0.1% (w/w) SSE is acceptable because it is less than 20 s, but the hardness of 28 N was less than the criterion value.

Tablets Obtained by Compression Using Lyophilized Mixture of FS and SSE (Type C Tablets) FS was suspended in SSE aqueous solution and lyophilized to achieve a better uniform state of both substances. In the freeze-dried mixture, SSE was found to surround FS particles better, because the tendency of FS to aggregate easily was suppressed. Tablets produced using the lyophilized mixture displayed a short disintegration time in many formulations (C-1 to C-6), as shown in Fig. 5; however, all the tablets showed less than 20 N hardness. The influence of SSE on the hardness or disintegration rate was not simple, and the effect changed around the SSE content of 1% (w/w) (Fig. 6). When lyophilization was used for preparation of the mixture, it was presumed that the physical states of SSE and/or FS in the resultant mixture would be different from the simple mixture of SSE and FS. Namely, the physical states of the lyophilized mixture might not be suitable for the binding among powder, though those states or features were not examined. The details will be a future subject. Thus, the lyophilization method was not appropriate from the viewpoint of tablet hardness.

Tablets Obtained by Compression Using the FS/SSE

Mixture Obtained by Ethanol Evaporation (Type D Tablets) Compositions of each compound were the same as those in Type B tablets. In Type D tablets, ethanol was chosen as an organic solvent to prepare a uniform mixture of FS and SSE. SSE and FS could be dissolved in ethanol, and ethanol was evaporated completely. The tablets produced using this mixture showed no reduction of hardness, and the disintegration time shortened with the addition of a small amount of SSE (Fig. 7). Tablet hardness was remained greater than 30 N except for D-5. As compared with Type B tablets, hardness was significantly higher at 0.05—2.4% (w/w) SSE ($p<0.05$). The disintegration time sharply decreased by addition of small amount of SSE, and the disintegration time was lowest with an SSE content of 0.1% (w/w) (Fig. 8). The disintegration time then increased in a linear manner in the range of SSE content of 0.1—4.8% (w/w) (Fig. 8). Formulations D-1, D-2 and D-3 exhibited a disintegration time of less than 20 s. In particular, D-2 exhibited the shortest disintegration time (15 s). As compared with Type B tablets, disintegration time decreased significantly at 0.1—4.8% (w/w) SSE ($p<0.05$). Thus, the addition of SSE at 0.05—1% (w/w) was appropriate in terms of both hardness and disintegration time. Thus, in the present production of tablets with SSE, Type D tablets, obtained using the FS/SSE mixture prepared by ethanol evaporation, were the best formulations, and the SSE content of 0.05—1% (w/w) was suitable to satisfy the criteria of the hardness and disintegration rate. In this study, although the criteria for hardness and disintegration time were set at 30 N and 20 s, further better conditions might be required to ensure that the tablets are more physically durable and orally disintegrated more rapidly. Further studies on formulations and preparative methods might be necessary in the future.

The physicochemical characteristics were investigated by SEM and DSC in order to explain the suitability of the FS/SSE mixture prepared by ethanol evaporation. In the examination, the FS/SSE (9 : 1, w/w) mixture prepared by ethanol evaporation, almost corresponding to the composition of D-3, was used. The particle shape of the mixture was different from that of original FS, and the particle surface of the mixture rather resembled that of SSE alone (Fig. 9), suggesting SSE might coat the FS particles. SEM micrographs showed the mean particle sizes (Green diameter) of FS, SSE and the mixture were 6.3 ± 2.6, 5.4 ± 2.9 and $3.8\pm1.3\,\mu$m (each, $n=70$) (Fig. 9). Therefore, the particles of the mixture were somewhat smaller than the particles of the original SSE and FS. The DSC graph of the mixture showed endothermic peaks of SSE and FS, and no new peaks (Fig. 10). The SSE and FS in the mixture appeared to physically maintain the solid state of original SSE or FS to a fair extent.[24] Thus, SSE and FS were considered to mix well by the manner in which SSE surrounded FS particles, and the resultant SSE-FS agglomerates showed a somewhat smaller size than the original SSE and FS. The good mixing and smaller states were considered to give good compaction and permeation of aqueous solution to the tablets, which were related to effective hard-

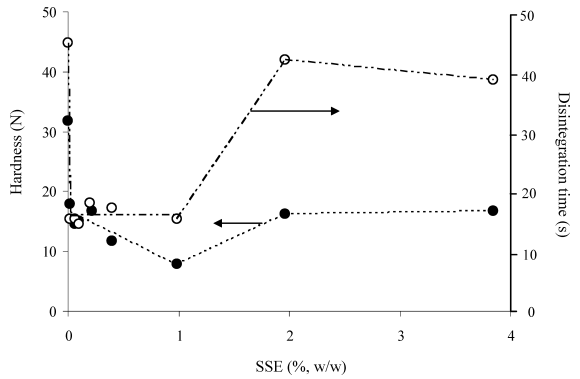

Fig. 6. Effect of SSE on Hardness (●) and Disintegration Time (○) of Tablets Produced Using Lyophilized Mixture of FS and SSE (Type C Tablets)

Linear curve fitting was conducted for the mean values. Hardness (N) = −9.21×(SSE, %)+16.7 ($R=0.91$; SSE: 0.02—0.99%). Disintegration time (s) = −0.153×(SSE, %)+16.0 ($R=0.04$; SSE: 0.02—0.99%).

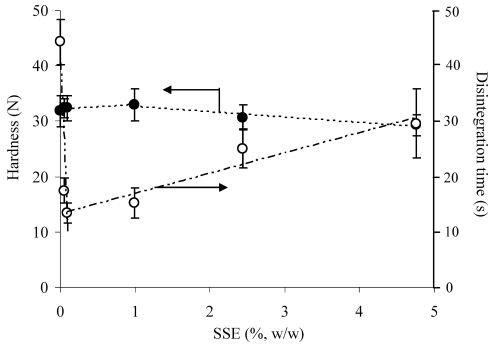

Fig. 8. Effect of SSE on Hardness (●) and Disintegration Time (○) of Tablets Produced Using the FS/SSE Mixture Obtained by Ethanol Evaporation (Type D Tablets)

Linear curve fitting was conducted for the mean values. Hardness (N) = 0.842×(SSE, %)+32.1 ($R=0.86$; SSE: 0—0.99%); hardness (N) = −0.945×(SSE, %)+33.5 ($R=0.97$; SSE: 0.99—4.76%). Disintegration time (s) = −309.0×(SSE, %)+40.5 ($R=0.92$; SSE: 0—0.1%); disintegration time (s) = 3.68×(SSE, %)+13.2 ($R=0.97$; SSE: 0.1—4.76%).

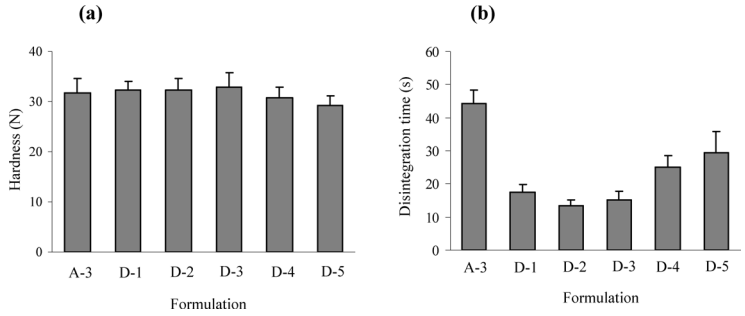

Fig. 7. Hardness (a) and Disintegration Time (b) of Tablets Produced Using the FS/SSE Mixture Obtained by Ethanol Evaporation (Type D Tablets)

The results are expressed as the mean±S.D. ($n=5$ for a; $n=6$ for b). (a) $p<0.05$ against Type B at 0.1—4.8% (w/w) SSE; (b) $p<0.05$ against Type B at 0.05—2.4% (w/w) SSE.

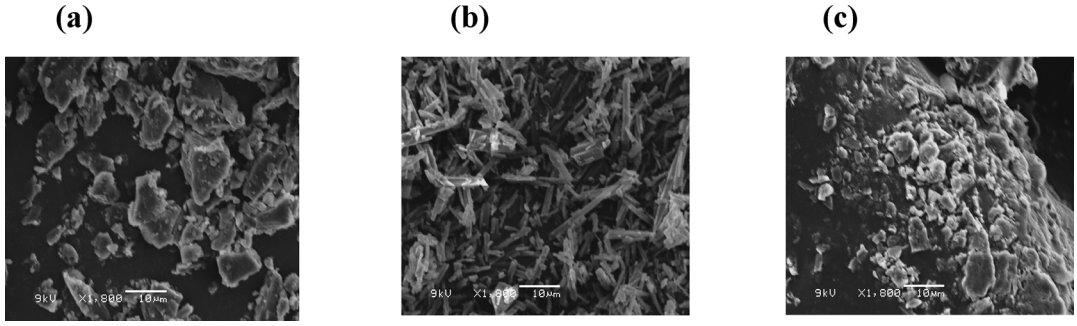

Fig. 9. SEM Micrographs of SSE (a), FS (b) and FS/SSE (9 : 1, w/w) Mixture Obtained by Ethanol Evaporation (c)
The length of each white bar is 10 μm.

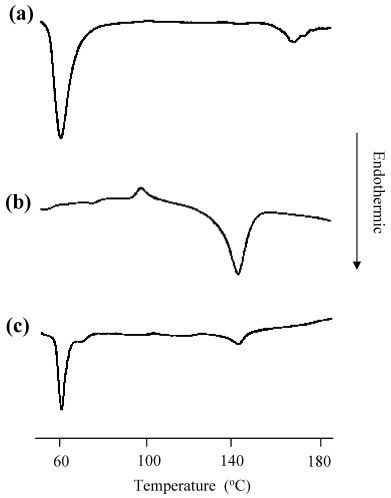

Fig. 10. DSC Graphs of SSE (a), FS (b) and FS/SSE (9 : 1, w/w) Mixture Obtained by Ethanol Evaporation (c)
The vertical axis (heat flow) is shown on an arbitrary scale.

ness and fast disintegration rate, respectively. As the results in SEM and DSC indicated the physical features of SSE and FS in Type D tablets were basically similar from those in Type B tablets, overall properties in hardness and disintegration were considered to be similar between Type B and D tablets. Namely, the addition of more than 0.1% (w/w) SSE in Type D tablets was presumed to increase a wet viscous layer around particles and prevent the degradation of the tablet in the disintegration test. In this study, SSE with an HLB of 16 (S-1670) was used because it exhibited good wettability. However, as there are other kinds of sucrose fatty acid esters,[25,26] their possibility as a disintegration-accelerating agent might have to be studied in the future. Furthermore, automatic compression with a single stroke press or rotary press will have to be examined for practical use in the future.

Conclusion

In this study, direct compression methods using SSE as an additive were examined to produce fast-disintegrating tablets of FS. Hardness of more than 30 N and disintegration time of less than 20 s were selected as criteria for evaluation of the tablets. XL (20% (w/w) or more) was required to improve the FS taste, and FS (20 mg), MC (134 mg), CC (6 mg) and XL (40 mg) were chosen as the control formulation. Tablets were produced by direct compression 1) with the simple addition of SSE, 2) using a lyophilized mixture of FS and SSE and 3) using a FS/SSE mixture obtained by evaporation of their ethanol solution. Tablets produced using the FS/SSE mixture obtained by ethanol evaporation could satisfy both the hardness and disintegration time, required for fast-disintegrating tablets. In this method, good FS/SSE mixing and finer particles resulted in tablets of appropriate hardness and disintegration rate.

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