Preparation of Rapidly Disintegrating Tablets Containing Itraconazole Solid Dispersions

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The disintegratability of tablets prepared from two types of solid dispersions containing the water-soluble polymer TC-5 and the enteric polymer HP-55 as an excipient were compared. The disintegratability was better in the tablets of solid dispersions containing non-water-soluble HP-55 than those containing TC-5. In consideration of the dissolubility of solid dispersions containing HP-55, the mean diameter of the solid dispersion (coating powder) must be controlled to 120 μm or less, but as this markedly increases the adhesion/aggregation tendency of the particles (angle of repose: 47°), control of the adhesion/aggregation tendency emerged as another problem. Therefore, surface-modification was performed in a high-speed agitating granulator using 0.1% light anhydrous silicic acid as a surface modifier, and marked improvement in the flowability was observed. This made continuous tableting using a rotary tablet machine possible even with the poorly flowable solid dispersions. Also, in tableting of the solid dispersions, no recrystallization of amorphous itraconazole by the tableting pressure was observed, and the tablets maintained satisfactory dissolubility. Moreover, it was possible to obtain the rapidly disintegrating tablets with very satisfactory properties, *i.e.*, a tablet hardness of 30 N or higher and a disintegration time of 30 s or less, by the addition of croscarmellose as a disintegrant at 2% to the surface-modified solid dispersion and selection of the tableting pressure at 4.5 kN.

Key words rapidly disintegrating tablet; surface-modifying; solid dispersion; enteric polymer

Itraconazole, a triazole antifungal agent, is a capsule preparation sold as Itrizole Capsule 50 by Janssen Pharmaceutical K.K. It is presently in wide clinical use for the treatment of dermatomycosis, visceral mycosis, and tinea unguium.[1—4] In the treatment of tinea unguium using this itoraconazole preparation, a very high dose of 200 mg (4 capsules) at a time and a daily dose of 400 mg (8 capsules) is administered.[1,5] Therefore, the preparation of dosage forms that may improve the ease of compliance are considered to be needed.

However, itraconazole is a poorly water-soluble agent with solubility in water of 1 μg/ml or less, so that measures to improve the solubility are necessary in the pharmaceutical processes to ensure an effective plasma concentration by oral administration.[6—12] In addition, as it is a basic drug at pK_a 3.7, it would not dissolve unless the solvent is a low-pH solution such as gastric juice even with pharmaceutical approaches.[13—15] For this reason, there have been a number of reports concerning methods to improve its solubility by preparing solid dispersions using a water-soluble polymer that dissolves even in a low-pH solution as an excipient,[6—9] but there has been no report on solid dispersions using enteric polymers. Recently, however, it has been reported that Itraconazole preparations containing water-soluble polymers as excipients may obstruct the tube in tube administration of simple suspensions, which is attracting attention as an administration method for patients with dysphagia, as the particle surface of solid dispersions become viscous due to partial dissolution of the excipient.[16] Previously,[17] we evaluated Itraconazole solid dispersions using an enteric polymer as an excipient, selected the fluidized bed coating method, and found that their solubility in the Japanese Pharmacopoeia (JP) 1st fluid can be improved by controlling the mean particle size.

In the present report, to improve the ease of taking itraconazole preparations, which are difficult to take because of the large dose, we evaluated the preparation of rapidly disintegrating tablets using the above solid dispersions as additional pharmaceutical modification. Using the itraconazole solid dispersions, a manufacturing method established in a previous study,[17] we devised a method to prepare tablets with dissolubility (dissolution profile) equivalent to that of its predecessor Itrizole Capsule 50 as well as rapid disintegratability and sufficient strength. The results of evaluation of the tablets are presented.

Experimental

Materials The drug was itraconazole (Hanmi Pharm. Co., Ltd.), a poorly soluble compound. Solid dispersions of itroconazole were prepared using hypromellose (HPMC, TC-5RW®, Shin-etsu Chemical; TC-5) or hypromellose phthalate (HPMCP, HP-55®, Shin-etsu Chemical; HP-55) as an excipient. A mixed powder of erythritol (Erythritol (fine powder), NIKKEN Fine Chemical Co., Ltd.) and crystalline cellulose·carmellose sodium (CEOLUS RC-A591NF®, Asahi Kasei Chemicals) was used as seed particles. In the granulation process, TC-5 was used as a binder. Polysorbate 80 (Nihon Surfactant Kogyo), light anhydrous silicic acid (200FAD®, Nippon Aerosil Co., Ltd.), croscarmellose sodium (Ac-di-sol®, FMC Corporation), and magnesium stearate (Nitto Kasei Co., Ltd.) were used as other additives.

Method of Preparation Preparation of Solid Dispersions: Solid dispersions of itraconazole were prepared by the fluidized bed coating method.[17] Itraconazole 167 g, HP-55 60 g, and Polysorbate 80 1.2 g were dissolved with 2 l of a mixture of methylene chloride/ethanol (7 : 3). Using a fluidized bed coating machine (SFC-MINI®, Freund), 525 g of seed particles were coated with the drug solution, and solid dispersions were obtained. Coating conditions (air supply temperature, air flow rate, and solution feeding rate) were adjusted to obtain a spray pressure of 0.18 MPa and product temperature of about 40 °C. Thereafter, granulation was performed using a TC-5 solution to efficiently recover microparticles adhering to the interior of fluidized bed coating machine.

In part of the evaluations (Effects of Excipients in Solid Dispersions on the Tablet Disintegratability), itraconazole solid dispersions were prepared by the hot extrusion method.[17] Mixture of itraconazole 16.7 g, HP-55 6 g, and Polysorbate 80 0.12 g were extruded in a single screw extruder machine (Diaspora, Imoto Machinery Co., Ltd.) at 30 rpm, and the die temperature

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set to 160 °C. The extrudate was milled and passed through 200 mesh sieve, and added various additive to milled extrudate (solid dispersion) above composition.

Surface-Modification: The granules obtained were surface-modified by using light anhydrous silicic acid in a high-speed agitating granulator (LMA-10, Nara Machinery Co., Ltd.) by the method of Kato *et al.*[18,19] (material quantity 500 g, amount of light anhydrous silicic acid added 0—2.5 g, blade rotation rate 200/min, chopper rotation rate 1500/min, agitating time 1.5 min), and improvement in the flowability was evaluated.

Mixing and Tableting: To the surface-modified granules, croscarmellose sodium was added at 0—2% as a disintegrant, magnesium stearate at 0.25% as a lubricant, they were mixed for 5 min in a V-shaped mixer (V-10, Tokuju Corporation), and a mixed tableting powder was obtained.

The mixed tableting powder was tableted with a rotary type full-automatic tablet press (HT-AP15SSII, Hata Iron Works Co., Ltd.) at a tableting pressure of 4—8 kN and a rotation speed of 20/min, and flat-faced tablets 8.5 mm in diameter containing 50 mg itraconazole/tablet were prepared. Table 1 shows the prescription of the tablets evaluated.

Product Analysis and Assessment Thermal Analysis: Using a differential scanning calorimeter (DSC, MAC Science Co., Ltd.), thermal behavior of the tablets in a temperature range of 25—190 °C was examined at a temperature increase rate of 2 °C/min, using alumina as a standard, and in a nitrogen atmosphere (50 ml/min).

Angle of Repose and Loose Bulk Density: The angle of repose and loose bulk density were measured using a powder tester (Hosokawa Micron).

Pharmaceutical Uniformity Test (Content Uniformity Test): The pharmaceutical uniformity test (content uniformity test) was performed according to the JP XV. The content was measured by high-performance liquid chromatography. The analytical conditions were: Column, CAPCELL PAK C18MG (4.6×150 mm, particle size 3 μm, Shiseido); mobile phase, a mixture of diisopropylamine in methanol (1→500)/ammonium acetate in water (1→200) (17 : 3); internal standard solution, a solution of pyrene in a mixture of methanol/tetrahydrofuran (1 : 1) (1→5000); flow rate, adjusted to make the retention time of Itraconazole about 7 min; and measurement wavelength, 263 nm.

Table 1. Formulation of Tablets (mg)

Process	Component	Formulation No. 1	2	3	4
Preparation of solid dispersion (Coating)	Seed Particles	← 157.6 →			
	Itraconazol	← 50.0 →			
	Excipient (TC-5 or HP-55)	← 18.0 →			
	Polysorbate 80	← 0.4 →			
Granulation	Binder	← 3.6 →			
	Plasticizer	← 2.0 →			
Surface-modification	Light anhydrous silicic acid (0.1%)	← 0.2 →			
Mixing	Croscarmellose sodium	0 (0%)	2.3 (1%)	4.6 (2%)	11.6 (5%)
	Magnesium stearate	← 0.6 →			
	Total	232.4	234.7	237.0	244.0

Dissolution Test: The dissolution test was performed by Dissolution Test method 2 (paddle method) of the JP XV. The test fluid was the JP 1st fluid, and the paddle rotation speed was 100/min. The sampled dissolution fluid was assayed by high-performance liquid chromatography. The analytical conditions were: Column, CAPCELL PAK C18MG (4.6×150 mm, particle size 3 μm, Shiseido); mobile phase, a mixture of diisopropylamine in methanol (1→500)/ammonium acetate in water (1→200) (17 : 3); flow rate, adjusted to make the retention time of itraconazole about 7 min; and measurement wavelength, 263 nm. To evaluate the equivalence of dissolution behavior of the test preparation with that of the innovator product, the value of f2 function was calculated by the method described in the "Guidelines for Bioequivalence Studies of Generic Products".[20] The approximate time when the dissolution rate of the innovator product reaches 85% (Ta) was set at 120 min, the value of f2 function was calculated at 4 points, *i.e.*, Ta/4, 2Ta/4, 3Ta/4, and Ta, and the test preparation was judged to be equivalent when the value of f2 function was 42 or higher.

Disintegration Test: The disintegration time was measured using a tablet disintegration tester (T-4H, Toyama Sangyo) by the disintegration test method of the JP XV. The test was performed using water at 37 °C as the test fluid without auxiliary discs.

Results and Discussion

Effects of Excipients in Solid Dispersions on the Tablet Disintegratability In our previous study,[17] we prepared solid dispersions by the hot extrusion method using water-soluble polymer hypromellose (TC-5) or enteric polymer hypromellose phthalate (HP-55) as an excipient.

Tablets were prepared by adding each additive to these two types of solid dispersions (Formulation No. 3) and their physical properties were compared (Table 2). The disintegratability was better in the tablets containing HP-55 than those containing TC-5 as an excipient. Since TC-5 is a water-soluble polymer, it is considered to increase the viscosity of water that has penetrated into the tablets to reduce its penetration rate[21] and, thus, to have prolonged the disintegration time of the tablets prepared with TC-5. To shorten the disintegration time of tablets containing itraconazole solid dispersions, the selection of solid dispersions containing HP-55, which is insoluble to water, as an excipient was important. Therefore, solid dispersions containing HP-55 as an excipient were found to be useful for the preparation of rapidly disintegrating tablets.

Control of Dissolution Rate of Solid Dispersions To examine whether the dissolution rate (dissolution profile) can be freely controlled by the use of solid dispersions containing HP-55 as an excipient, which were found above to be useful for the preparation of rapidly disintegrating tablets, the mean diameter of solid dispersions (coated particles) was evaluated.

Figure 1 shows dissolution profiles of 4 types of solid dispersions different in mean diameter (70.9, 107.4, 122.9, 242.5 μm) in the JP 1st fluid. A dissolution profile of Itrizole capsule 50, an innovator product, is also shown as a reference. The mean diameter of solid dispersion particles and dissolution rate were correlated, with the dissolution rate in-

Table 2. Physical Properties of Tablets Contained Solid Dispersions Based on TC-5 or HP-55

Excipient	Weight (mg) (n=6)	Thickness (mm) (n=6)	Hardness (N) (n=3)	Disintegration time (min) (n=3)
HP-55	238.8±0.5	3.77±0.04	37.9±2.5	1.01±0.10
TC-5	237.7±1.0	3.58±0.04	43.0±4.7	3.24±0.08

Each value represents the mean±S.D.

creasing with decreases in the mean diameter. Therefore, this manufacturing method was shown to be excellent in that it allowed free control of the dissolution profile by adjusting the mean diameter, *i.e.*, specific surface area, of solid dispersions in the coating process.

Also, to evaluate the equivalence with the innovator product, the f2 function value was calculated by the method described in the "Guideline of Bioequivalence Studies of Generic Products".[20] The f2 function value was 42 or higher in the solid dispersions with mean particle sizes of 70.9, 107.9 and 122.9 μm, and their dissolution behavior was judged to be equivalent to that of Itrizole Capsule 50 (Table 3). From these results, the dissolution profiles of solid dispersions in which the mean diameter was adjusted to 120 μm or less were found to be equivalent to that of Itrizole Capsule 50.

In solid dispersions containing HP-55, which does not dissolve in the JP 1st fluid, as an excipient, the drug-release rate from inside the matrix is considered to decrease with increases in the thickness of the coating layer, which is the matrix of the drug and HP-55. Therefore, in solid dispersions prepared by this method, it is considered important to increase the specific surface area and to reduce the coating thickness of the drug/HP-55 matrix by controlling the mean diameter below 120 μm to ensure satisfactory dissolubility.

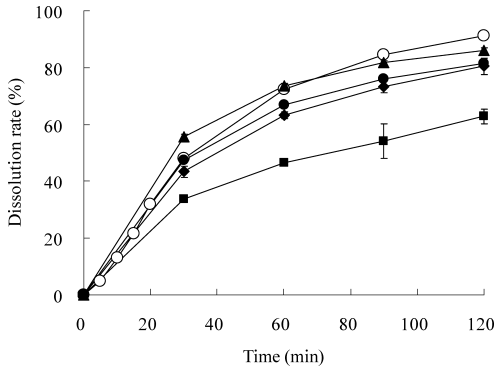


Fig. 1. Dissolution Profiles of Solid Dispersions Different in Mean Diameter in the JP 1st Fluid

Mean diameter; 70.9 μm (▲), 107.4 μm (●), 122.9 μm (◆), 242.5 μm (■). A dissolution profile of Itrizole capsule 50, an innovator product, is also shown as a reference (○). Each point represents the mean±S.D. (n=3). The mean diameter of solid dispersion particles and dissolution rate were correlated, with the dissolution rate increasing with decreases in the mean diameter. Therefore, this manufacturing method was shown to be excellent in that it allowed free control of the dissolution profile by adjusting the mean diameter, *i.e.*, specific surface area, of solid dispersions in the coating process. In addition, in solid dispersions in which the mean diameter was adjusted to 120 μm or less (70.9, 107.4, 122.9 μm), the dissolution profile was found to be equivalent to that of Itrizole Capsule 50.

Table 3. Equivalence in Dissolution to Itrizole Capsule 50

Criteria of equivalence in dissolution	D50 (μm)	f2 value	Judgment
f2 value is equal or more than 42	70.9	65.1	Equivalent
	107.4	53.5	Equivalent
	122.9	51.3	Equivalent
	242.5	29.6	Not equivalent

Surface-Modification Experiment As observed above, dissolubility equivalent to an innovator product was found to be obtained in solid dispersions containing HP-55 as an excipient by controlling the mean particle size of the coated preparation to 120 μm or less.[22] However, in solid dispersions with a mean diameter of 120 μm or less, obstruction of the tablet machine hopper was observed due to their high adhesion-aggregation tendency and poor flowability, and continuous tableting with a rotary tablet machine was difficult. Therefore, for continuous tableting of solid dispersions showing a dissolution profile equivalent to that of an innovator product, we noted a surface-modification method reported to be effective for improving the flowability of poorly flowable bulk drugs[18,19] and applied it to our solid dispersions.

Surface-modification was performed in a high-speed agitating granulator by adding light anhydrous silicic acid at 0.025 to 0.5%. Table 4 shows the results of measurement of the angle of repose and loose bulk density as indices of flowability, and Fig. 2 shows the results of measurement of the angle of repose. Without surface-modification, the angle of repose of solid dispersions was very large at 47°, but it was reduced to 36° by the addition of light anhydrous silicic acid to 0.1%. However, no further decrease in the angle of repose was noted even when light anhydrous silicic acid was added at more than 0.1%.

Figure 3 shows the SEM PHOTO of the surface of surface-modified solid dispersions. Light anhydrous silicic acid adhered evenly to the surface of solid dispersions, and this change in the surface condition is considered to have markedly improved the flowability.[23]

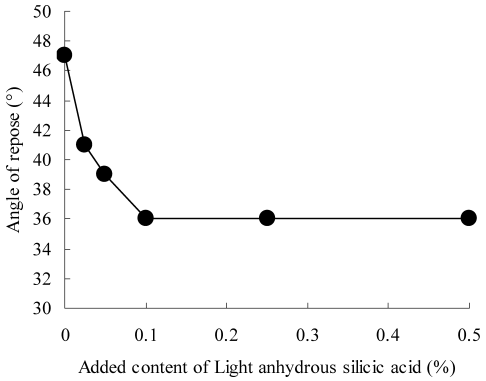
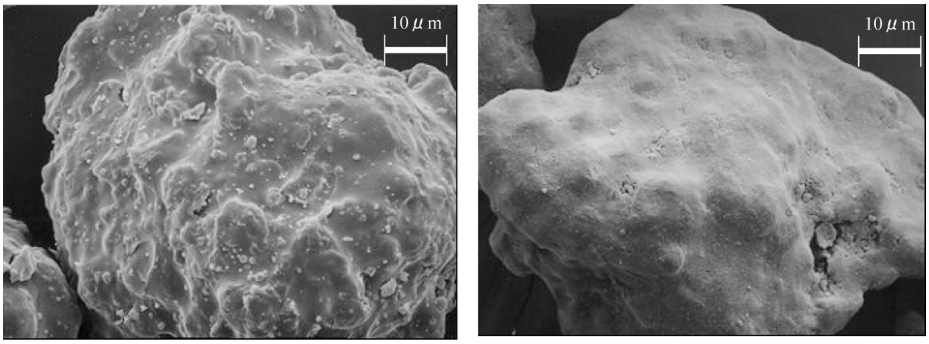


Fig. 2. Angle of Repose of Surface-Modified Solid Dispersion with a Mean Diameter of 70.9 μm

The flowability can be markedly improved by surface-modification using light anhydrous silicic acid even in solid dispersions with a mean diameter of 120 μm or less, which could not be continuously tableted due to a strong adhesion/aggregation tendency. Since the angle of repose decreased from 47° to 36° after surface-modification, continuous tableting using a rotary tablet machine is considered to be possible with the solid dispersions having dissolution characteristics equivalent to those of an innovator product.

Table 4. Flowability of Surface-Modified Solid Dispersions

Added content of light anhydrous silicic acid (%)	0	0.025	0.05	0.1	0.25	0.5
Angle of repose (°)	47	41	39	36	36	36
Loose bulk density (g/ml)	0.52	0.56	0.56	0.58	0.58	0.58



Pre-modified Surface-modified (0.1%)

Fig. 3. SEM Photos of the Surface of Surface-Modified Solid Dispersions

Table 5. Tablet Weight and Content Uniformity

Tableting time (min)	Weight (mg) (n=10)	Content (%) (n=10)	Acceptance value
0	238.8±1.6 (0.67)	99.9±0.8	1.8
15	237.3±1.0 (0.40)	99.6±0.6	1.8
30	237.6±1.1 (0.68)	99.6±0.7	1.9

Each value represents the mean±S.D. and (relative standard deviation).

These results suggest that the flowability can be markedly improved by surface-modification using light anhydrous silicic acid even in solid dispersions with a mean diameter of 120 μm or less, which could not be continuously tableted due to a strong adhesion/aggregation tendency. Since the angle of repose decreased from 47° to 36° after surface-modification, continuous tableting using a rotary tablet machine is considered to be possible with the solid dispersions having dissolution characteristics equivalent to those of an innovator product.

Tableting Experiment Content Uniformity Test of Tablets: To examine the possibility of continuous tableting using a rotary tablet machine (open feeder), tablets were punched continuously using surface-modified solid dispersions with improved flowability (formulation No. 3). The tablets were serially sampled, and the tablet mass and content were examined (Table 5). When solid dispersions were tableted without surface-modification, the hopper was obstructed due to lumping, and continuous tableting was impossible. When surface-modified solid dispersions were used, however, the relative standard deviation of the tablet mass was 1.0% or less at all sampling points until 30 min after the beginning of tableting, and that of the content (%) was also very satisfactory at 1.0% or less. The criterion of the JP XV pharmaceutical uniformity test (content uniformity test) is "not exceeding 15.0%", and the value obtained in this experiment was much better than this criterion, indicating excellent flowability of the tested surface-modified solid dispersions.

These results confirmed that the flowability of our solid dispersions with a mean diameter of 120 μm or less can be improved by surface-modification and that tablets with dissolution characteristics equivalent to those of an innovator product can be prepared using these solid dispersions. In addition, as the results of a pharmaceutical uniformity test (content uniformity test) of the prepared tablets were 2% or less, tablets with excellent content uniformity are considered to be prepared by adopting this surface-modification method.

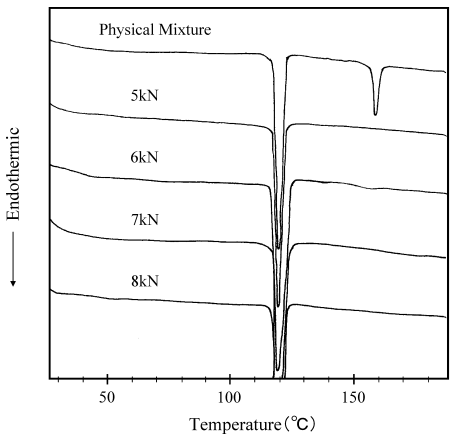


Fig. 4. DSC Curves of Tableted Solid Dispersion at a Tableting Pressure of 5—8 kN (4 Levels)

Effects of the Tableting Pressure on the Dissolution Rate: Since amorphous drugs are theremodynamically unstable, they may be recrystallized by the tableting pressure, causing a decrease in the dissolubility.[24,25] Therefore, the tablets prepared from solid dispersions containing HP-55 as an excipient at a tableting pressure of 5—8 kN (4 levels) were examined by thermal analysis (DSC) and the dissolution test to evaluate whether recrystallization would occur in these tablets. Figure 4 shows the results of DSC of the tableted solid dispersions and physical mixtures. The heat absorption peak observed in all DSC charts at about 120 °C is the one associated with melting of erythritol used as seed particles. The physical mixtures showed a heat absorption peak at 160 °C due to melting of crystalline itraconazole, but none of the tableted solid dispersions showed a heat absorption peak at 160 °C at any tableting pressure, indicating that they maintained an amorphous state. Also, as shown in Fig. 5, no change in the dissolution profile associated with changes in the tableting pressure was noted. Therefore, no crystallization of amorphous itraconazole or decrease in the dissolution rate was noted in the solid dispersions after tableting at a tableting pressure of 5—8 kN. These results confirmed that

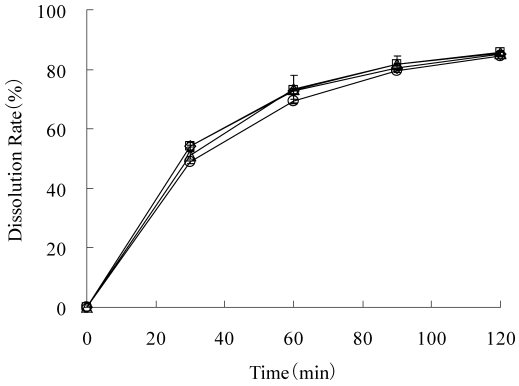


Fig. 5. Dissolution Profiles of Tablets Prepared from Solid Dispersions at a Tableting Pressure of 5—8 kN (4 Levels)

Tableting pressure; 5 kN (◇), 6 kN (□), 7 kN (△), 8 kN (○). Each point represents the mean±S.D. (n=3). No difference was observed in the dissolution profile among the 4 preparations. Therefore, the dissolubility of itraconazole was confirmed not to be reduced by its recrystallization during tableting of the solid dispersions contained amorphous itraconazole at a tableting pressure of 5—8 kN.

Table 6. Effect of Disintegrant Content on Physical Properties of Tablets

Disintegrant content (%)	Weight (mg) (n=10)	Thickness (mm) (n=10)	Hardness (N) (n=5)	Disintegration time (min′ s″) (n=6)
0	232.4±0.1	3.69±0.01	51.0±2.7	1′ 32″
1.0	234.6±0.2	3.70±0.01	56.0±2.1	0′ 56″
2.0	235.3±0.2	3.72±0.01	41.5±2.2	0′ 49″
5.0	243.6±0.1	3.75±0.01	55.0±1.8	0′ 51″

Each value represents the mean±S.D.

these solid dispersions can be tableted while retaining their improved solubility.

Selection of the Disintegrant Addition Rate: The effects of croscarmellose sodium, which had been reported to improve the disintegratability by the addition at a small percent,[26] on the tablet disintegratability was examined by changing its addition rate. Croscarmellose sodium was added at 0—5% to the surface-modified solid dispersions prepared as above, tableting was performed at a tableting pressure of 4.75 kN, and physical properties were examined (Table 6). The disintegration time was 1.5 min or longer in the tablets not containing the disintegrant, but it could be shortened to less than 1 min by the addition of the disintegrant at 1% or more. No effect of the addition of croscarmellose sodium on the tablet hardness was noted. In addition, as no further shortening of the dissolution time was noted by the addition of the disintegrant at 2% or more, 2% is considered to be its appropriate addition rate.

Effects of the Tableting Pressure on Mechanical Properties of Tablets: Tablets containing croscarmellose sodium at 2% were prepared at a tableting pressure of 4.0—4.75 kN, and their physical properties were examined (Table 7). The tablet hardness increased, and the disintegration time prolonged, with the tableting pressure, but the tablet hardness was 30 N or higher, and the disintegration time was 30 s or less, both being very satisfactory, at a tableting pressure of 4.5 kN.

As observed above, the preparation of rapidly disintegrating tablets containing itraconazole solid dispersions is considered to be made possible by improving the flowability of solid dispersions by surface-modification and optimizing the disintegrant content and tableting pressure.

Table 7. Physical Properties of Tablets

Compression force (kN)	Weight (mg) (n=10)	Thickness (mm) (n=10)	Hardness (N) (n=5)	Disintegration time (min′ s″) (n=6)
4.0	235.6±0.3 (0.12)	3.90±0.01	24.8±2.1	0′ 22″
4.5	235.7±0.3 (0.13)	3.79±0.01	37.2±1.5	0′ 30″
4.75	235.3±0.2 (0.07)	3.72±0.01	41.5±2.2	0′ 49″

Each value represents the mean±S.D. and (relative standard deviation).

Conclusions

Two types of solid dispersions containing the water-soluble polymer TC-5 and the enteric polymer HP-55 as an excipient were prepared by the hot extrusion method, and the disintegratability of tablets prepared from these solid dispersions was compared. The disintegratability was better in the tablets of solid dispersions containing non-water-soluble HP-55 than those containing TC-5. Therefore, solid dispersions containing HP-55 were found to be useful for the preparation of rapidly disintegrating tablets. However, in consideration of the dissolubility of solid dispersions containing HP-55, the mean diameter of solid dispersion (coating powder) must be controlled to 120 μm or less , but as this markedly increases the adhesion/aggregation tendency of the particles (angle of repose: 47°), control of the adhesion/aggregation tendency emerged as another problem. Therefore, surface-modification was performed in a high-speed agitating granulator using 0.1% light anhydrous silicic acid as a surface modifier, and marked improvement in the flowability was observed. This made continuous tableting using a rotary tablet machine (open feeder) possible even with the poorly flowable solid dispersions.

Also, in tableting of the solid dispersions, no recrystallization of amorphous itraconazole by the tableting pressure was observed, and the tablets maintained satisfactory dissolubility. In addition, rapidly disintegrating tablets with very satisfactory properties, *i.e.*, a tablet hardness of 30 N or higher and a disintegration time of 30 s or less, were shown to be prepared by the addition of a disintegrant and optimization of the tableting pressure.

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