Effect of Moisture on Impact Toughness of Sugar-Coated Tablets Manufactured by the Dusting Method

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The purpose of this study was to clarify the effect of moisture on the impact toughness of sugar-coated tablets manufactured by the dusting method. We demonstrated that moisture plays an important role in the impact toughness of sugar-coated tablets. Moisturizing the sugar-coating layer resulted in enhancement of impact toughness of sugar-coated tablets, while reducing moisture in the sugar-coating layer resulted in weakening of the impact toughness. This was due to the characteristics of sucrose, the main ingredient of the sugar-coating layer, which is a soft and non-fragile material at high moisture levels, but hard and fragile at low moisture levels. We also demonstrated that friability as an indicator of impact toughness changed with time, and friability should be measured at 14 d after manufacture. This is due to moisture movement from outer sugar-coating layer into the inner sugar-coated tablets. Incorporating microcrystalline cellulose (MCC) in the subcoating layer resulted in sugar-coating layers with high resistance against impact even though moisture content of sugar-coated tablets was low. We confirmed the high impact toughness of the sugar-coated tablets with MCC whose moisture content was low from the results of both free fall and friability tests. We suggest that the dusting method using dusting powder containing MCC is a useful method for the production of sugar-coated tablets containing moisture sensitive drugs.

Key words sugar-coated tablets; moisture; impact toughness; equilibrium relative humidity; sucrose; microcrystalline cellulose

Moisture is one of the most important factors for clarifying the characteristics of solid dosage forms in the pharmaceutical field. There have been a number of reports regarding the effects of moisture on physicochemical properties such as stability of drugs,[1] compactibility of drugs and excipients,[2,3] friability of tablets,[4] and amorphous-to-crystalline transformation[5,6] in solid dosage forms. Moisture in solid dosage forms has attracted much interest over the last decade. Much research is currently in progress.

Moisture in solid dosage forms is generally classified into mobile and immobile water.[1,7—9] The measurement of mobile water is expressed by water activity or equilibrium relative humidity (ERH). The water activity of a substance is defined as the ratio of the vapor pressure of water due to the substance to the vapor pressure of pure water at the same temperature. ERH is water activity expressed as a percentage.[9] Since the amount of mobile water is critical to physicochemical properties on tablets and ERH is easy to measure, we used ERH as a parameter of moisture content in tablets in this study.

In our previous work,[10] we proposed a new dusting method for improvement of impact toughness of sugar-coated tablets. The new dusting method uses a dusting powder containing microcrystalline cellulose (MCC). There have been a number of reports regarding the effect of moisture on MCC properties and the moisture sorption and desorption of MCC.[11—14] Fielden *et al.* reported that MCC was capable of physically retaining a high percentage of water within itself, while also allowing easy removal by evaporation.[11] Suzuki *et al.* reported that the physical structure of MCC changed during the wet granulation process, and the interaction between MCC and water was gradually strengthened.[12] Moisture thus affects the physical properties of MCC.

Although there have been several reports regarding the relationship between moisture and color change on sugar-coated tablets,[15—17] the effect of moisture on impact toughness of sugar-coated tablets has not been sufficiently clarified. Above all, the effect of moisture on impact toughness of sugar-coated tablets with MCC has not been sufficiently clarified. Therefore, the purpose of this study was to clarify the effect of moisture on the impact toughness of sugar-coated tablets manufactured by the dusting method.

Furthermore, we conducted a free fall test for evaluation of impact toughness of sugar-coated tablets with low moisture content manufactured by the dusting method using dusting powder with or without MCC. We also investigated the relationship between the friability test and the free fall test.

Experimental

Materials Core tablets containing fursultiamine hydrochloride, vitamin B_6, vitamin B_{12}. vitamin E were used. The weight, diameter, radius of curvature and thickness of core tablets were 180 mg, 8 mm, 6.5 mm, 4.25 mm, respectively. Sucrose (Ensuiko Sugar Refining Co.), talc (Matsumura Sangyo Co.), precipitated calcium carbonate (Nitto Funka Kougyo Co.), titanium dioxide (Ishihara Sangyo), powdered acacia (San-ei Yakuhin Boueki Co.), and microcrystalline cellulose (MCC) (Avicel PH-F20, Asahi Kasei Co.) were used for sugar coating.

Manufacturing of Sugar-Coated Tablets by the Dusting Method Sugar coating was performed manually in a 12-inch onion pan (Kikusui Seisakusyo). Five thousand tablets were loaded in the pan. A dusting method can be divided into 4 steps: (1) Subcoating, (2) Smoothing, (3) Coloring, (4) Polishing. The subcoating is applied to round the edges to build up the tablet size. The susbcoating step consists of alternately applying a sugar-coating suspension to the tablets followed by dusting with the powders and then drying. Firstly, the sugar-coating suspension is added to the core tablets. Secondly, the tablets are stirred by hand to distribute the suspension. Thirdly, the dusting powder is dusted onto the tablets until no wet tablets show and the tablets again tumble freely. Finally, the tablets are dried by the hot air at 55 °C and the exhaust. The excess dusting powder is removed by the exhaust. The subcoating step was repeated 13 times. The weight of final subcoated tablet was 298 mg. The smoothing step is to smooth out the tablet surface further prior to application of the coloring. The smoothing step consists of alternately applying a sugar-coating suspension to the tablets and then drying. The drying temperature was 55 °C. The weight of final smoothed tablet was 345 mg. The coloring step is to impart the desired color to the tablets. The coloring step consists of alternately applying a coloring syrup to the tablets and then drying. The drying temperature was initially

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Table 1. Sugar-Coating Suspension Formulation (w/w%)

	Suspension A
Sucrose	41.8
Talc	11.5
Precipitated calcium carbonate	18.9
Titanium dioxide	1.7
Powdered acacia	4.9
Purified water	21.2

Table 2. Dusting Powder Formulations (w/w%)

	Dusting powder A	Dusting powder D
Talc	98	78
Powdered acacia	2	2
MCC	—	20

50 °C, and was gradually reduced to 25 °C. The weight of final colored tablet was 370 mg. The polishing step is to achieve a final gloss. Polishing was achieved by applying a mixture of waxes (carnauba wax and white beeswax) to the tablets in a polishing pan.

Formulations of the sugar-coating suspension, suspension A, and the dusting powders, dusting powder A and dusting powder D, are shown in Tables 1 and 2, respectively. Dusting powder A listed in Table 2 is a standard dusting powder. Dusting powder D listed in Table 2 is a new dusting powder.[10]

Evaluation of Impact Toughness of Sugar-Coated Tablets Friability of sugar-coated tablets was measured in order to evaluate impact toughness.[10] The tester consists of a drum and a motor. The diameter of the drum was 50 cm. A stainless steel sheet where tablets were dropped in the test was attached to the inner side of the drum. The friability test was conducted at 30 rpm for 10 min. Twenty tablets were used for the test. Weight loss percentage was calculated as friability. Lower friability means stronger impact toughness. In addition, the free fall test was conducted to measure impact toughness of sugar-coated tablets and we compared the free fall test with the friability test in this study. The free fall test was conducted as follows: One hundred sugar-coated tablets were placed into a glass bottle (PS-10K, Daiichi glass Co.). The glass bottle was closed with a metal cap. The glass bottle containing the sugar-coated tablets was put into a paper box. The paper box was dropped from 110 cm height. After the test, cracked sugar-coated tablets, whose cracks were more than 3 mm long, were counted. The free fall was conducted from 1 to 3 times. Unless otherwise specified, impact toughness of sugar-coated tablets was measured at 14 d after manufacture.

Equilibrium Relative Humidity of Tablets Equilibrium relative humidity (ERH) of tablets was measured using a water activity analyzer (Hygroskop DT, Rotronic). In the measurement of ERH of sugar-coated tablets, 6 roughly crushed sugar-coated tablets were used unless otherwise specified.

The Sucrose Tablets Prepared by Wet Compression Method and Evaluation of the Tablets Sucrose, whose mean particle diameter measured by a laser particle analyzer (Helos & Rodes, Sympatec) was 16.5 μm, was used for this experiment. Sucrose was placed in a mortar and 5 w/w% amount of purified water was added. Sucrose was granulated using a pestle in the mortar. The wet masses of sucrose (367.5 mg) were directly compacted with a compression instrument (Autograph AG-5000B, Shimadzu Co.) using a 10 mm diameter flat-faced punch. The compression speed was 10 mm/min. The compression pressure was 20 MPa. After compression, the tablets were dried in a vacuum dryer (VS-40, Irie Seisakusho) at 40°C. The tablet crushing force was measured by diametrical compression using a tablet hardness tester (TH-303MP, Toyama Sangyo Co.). Tensile strength (T) was calculated using the following Eq. 1[18]:

$$T=2F/\pi DL \qquad (1)$$

where F is the crushing force, D is the tablet diameter, and L is the tablet thickness. In addition, the friability was measured. Five tablets were used for the friability test. Five tablets were used for the measurement of ERH.

Moisturizing and Drying After the storage of sugar-coated tablets in a glass bottle for 14 d at room temperature, the sugar-coated tablets were moisturized at 25 °C/63% RH or 25 °C/75% RH or 25 °C/84% RH for 14 d. After moisturizing, the friability of sugar-coated tablets was measured.

Four kinds of powders were used for the study of moisturizing and drying behaviors of the sugar-coating layers: (1) powder consisted of 60% solid of suspension A and 40% of dusting powder A, (2) powder consisted of 60% solid of suspension A and 40% of dusting powder D, (3) powder consisted of solid of suspension A, and (4) powder consisted of sucrose. The powders 1, 2, 3, and 4 corresponded to the standard subcoating layer, the new subcoating layer, the smoothing layer, and the syrup coating layer, respectively. The powders in weighing bottles were moisturized during storage at 25 °C/93% RH for 14 d and then either dried at 60 °C for 5 h or dried at 25 °C/11% RH for more than 20 d. Loss on drying of each powder (1 g, 60 °C, 5 h, 0.53±0.13 kPa) was measured before the experiment. In this experiment, it was preferable to determine the moisture content gravimetrically at various times instead of the measurement of ERH in terms of the measurement of moisture content on moisturizing and drying process.

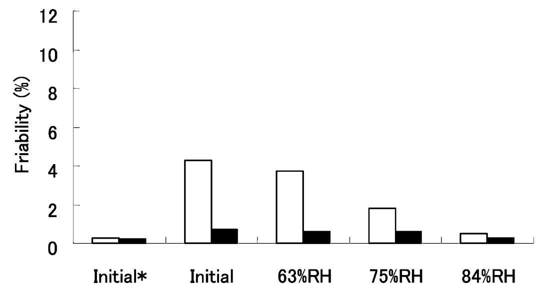

Fig. 1. Friability of Sugar-Coated Tablets Stored in a Closed Glass Bottle and Stored under Various RH Conditions for 14 d

□, dusting powder A (ERH 53%); ■, dusting powder D (ERH 47%). Initial*, sugar-coated tablets immediately after manufacture. Initial, sugar-coated tablets stored in a glass bottle for 14 d at room temperature.

Results and Discussion

Effect of Moisturizing on Impact Toughness of Sugar-Coated Tablets Figure 1 shows the friability of sugar-coated tablets stored in a closed glass bottle or moisturized at 25 °C/various RH for 14 d. Although the friability of sugar-coated tablets immediately after manufacture was low, the friability was high after storage in the closed glass bottle for 14 d at room temperature, especially in the case of sugar-coated tablets manufactured using dusting powder A. We found that friability changed with time. After moisturizing, friability of sugar-coated tablets decreased, especially in the case of sugar-coated tablets manufactured using dusting powder A. The higher humidity condition resulted in lower friability of sugar-coated tablets. Friability of sugar-coated tablets stored at 25 °C/84% RH for 14 d was almost the same as friability of sugar-coated tablets immediately after manufacture. These results suggested that moisture plays an important role in the impact toughness of sugar-coated tablets. Moisture in the sugar-coating layer might play the role of a binder for increasing impact toughness of the sugar-coating layer.

Effect of Storage Time in the Closed Glass Bottle on Impact Toughness of Sugar-Coated Tablets Figure 2 shows the relationship between storage time in a closed glass bottle at room temperature and friability of sugar-coated tablets. Irrespective of the dusting powder, friability of sugar-coated tablets increased with time. Friability of sugar-coated tablets manufactured using dusting powder A was below 1% when measured immediately after manufacture. However, the friability increased significantly with time even though sugar-coated tablets were stored in a closed glass bottle, and leveled off at 14 d after manufacture. In contrast, the friability of sugar-coated tablets manufactured using dusting powder D increased slightly with time, and also leveled off at 14 d after

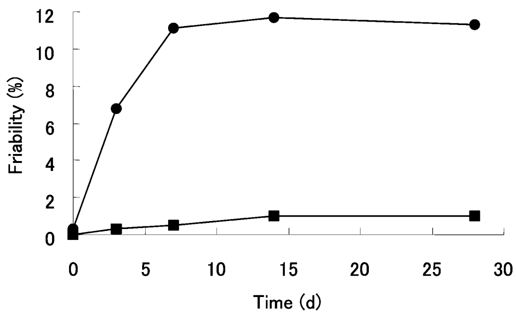

Fig. 2. Relationship between Storage Time in a Closed Glass Bottle and Friability of Sugar-Coated Tablets

●, dusting powder A (ERH 42%); ■, dusting powder D (ERH 44%).

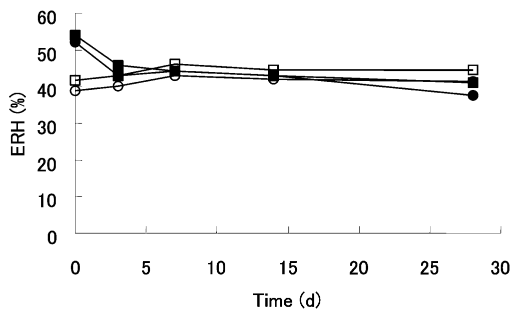

Fig. 3. Relationship between Storage Time in a Closed Glass Bottle and ERH of Sugar-Coated Tablets

●, ○, dusting powder A; ■, □, dusting powder D. Closed symbols are ERH of intact sugar-coated tablets and open symbols are ERH of crushed sugar-coated tablets.

manufacture. The friability 14 d after manufacture was low, at approximately 1%. We found that measurement time was important for the evaluation of impact toughness of sugar-coated tablets and the best time to measure friability as an indicator of impact toughness was at 14 d after manufacture.

Since moisture affected the impact toughness of sugar-coated tablets as shown in Fig. 1, ERH of sugar-coated tablets was measured with time in order to consider the mechanism of change of friability with time as shown in Fig. 2. ERH of intact sugar-coated tablets shows ERH of the surface of the sugar-coating layer. ERH of crushed sugar-coated tablets shows ERH of the inside of sugar-coated tablets. This is shown in Fig. 3. Irrespective of the dusting powder, the ERH behaviors of sugar-coated tablets were almost the same. ERH of intact sugar-coated tablets immediately after manufacture was higher than that of crushed sugar-coated tablets. With the passage of time, ERH of intact sugar-coated tablets decreased and that of crushed sugar-coated tablets increased. This finding suggests that moisture content in the sugar-coating layer changes with time and moisture would move from the outer sugar-coating layer to the core tablet during storage for approximately 14 d after manufacture.

This moisture change should depend on the manufacturing method of sugar-coated tablets whose drying temperature in the coloring step is gradually decreased to 25 °C in order to gloss the coloring layer. Sugar-coated tablets, especially the coloring layer, should not dry completely immediately after manufacture. Therefore, there may be a sufficient amount of moisture in the coloring layer, which can move into the core tablet, immediately after manufacture. The moisture movement from the coloring layer to the core tablet may result in a decrease in ERH in the sugar-coating layer. The decrease in ERH in the sugar-coating layer may result in an increase in friability of the sugar-coated tablets.

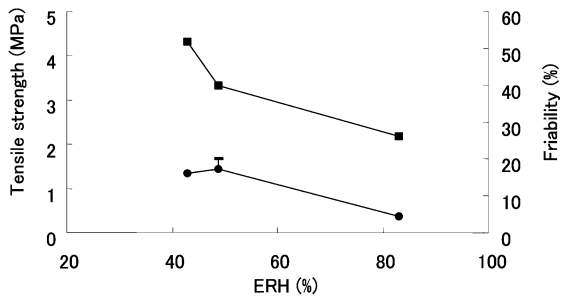

Fig. 4. Relationship between ERH, Tensile Strength, and Friability of Sucrose Tablets Prepared by the Wet Compression Method

●, tensile strength (mean ± S.D.; $n=5$); ■, friability.

Effect of Moisture on Tensile Strength and Impact Toughness of Sucrose Tablets Prepared by the Wet Compression Method Since the sugar-coating layer mainly consisted of sucrose, the relationship between ERH and impact toughness of sucrose tablets was investigated in order to clarify the effect of moisture on impact toughness of sugar-coated tablets. Sugar coating was mainly performed by crystallization of dissolved sucrose during the coating process. A wet compression method may be relatively similar to sugar coating. Therefore, we investigated tensile strength and friability of sucrose tablets prepared by the wet compression method at various ERH. The results are shown in Fig. 4. Tensile strength of sucrose tablets leveled off below ERH 50%. Tensile strength and friability of sucrose tablets increased with decreasing ERH. These findings indicated that sucrose is a soft and non-fragile material at high ERH, but hard and fragile at low ERH. The characteristics of sucrose would reflect the characteristics of sugar-coated tablets; the impact toughness of sugar-coated tablets with high ERH is strong and that with low ERH is weak.

Moisturizing and Drying Behaviors of Sugar-Coating Layers We demonstrated above that moisture in the sugar-coated tablets affects the impact toughness of the sugar-coated tablets. In addition, moisturizing and drying behaviors are significant for the physical properties of solid dosage forms in the pharmaceutical field.[19] These results and information prompted us to investigate the moisturizing and drying behaviors of the sugar-coating layers.

Sugar coating was performed as an alternative process of wetting and drying. This process was performed by the intermittent spray process. It was difficult to measure the drying behaviors of subcoating layers, smoothing layers and syrup coating layers separately and directly in the sugar-coated tablets. Therefore, the measurement of moisturizing and drying behaviors of the solid of the suspension, the dusting powders and sucrose was carried out instead of the measurement of moisturizing and drying behaviors of the subcoating layers, the smoothing layer and the syrup coating layer.

Figure 5A shows the moisturizing profiles of powders. Figures 5B and C show the drying profiles of powders. All the powders were easily moisturized. All the moisturizing profiles were linear, but all the drying profiles were non-linear. The drying behavior of 60% solid of suspension A and 40% of dusting powder A was almost equal to the drying be-

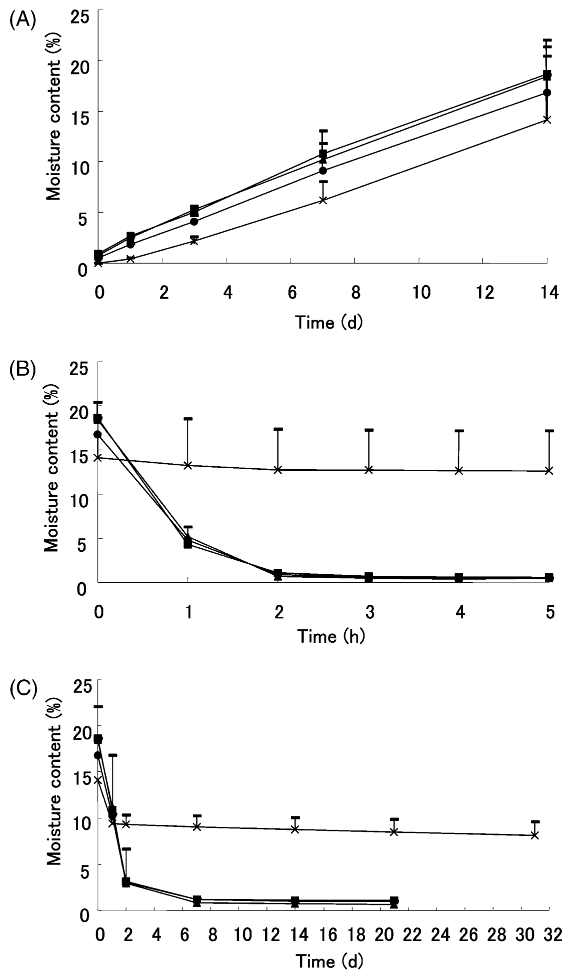

Fig. 5. Moisturizing and Drying Profiles

(A) Moisturizing profiles at 25 °C/93% RH (mean±S.D.; n=9), (B) drying profiles at 60 °C (mean±S.D.; n=3), (C) drying profiles at 25 °C/11% RH (mean±S.D.; n=3). ●, 60% solid of suspension A and 40% of dusting powder A; ■, 60% solid of suspension A and 40% of dusting powder D; ▲, solid of suspension A; ×, sucrose.

havior of 60% solid of suspension A and 40% of dusting powder D. They were easy to dry. In addition, the solid of suspension A was also easy to dry.

We confirmed that the moisturizing and drying behaviors of the subcoating layer with MCC are almost equal to those without MCC. In this study, MCC did not significantly affect the moisturizing and drying behaviors of solid of suspension A and the dusting powders. This might be due to the relatively low level of MCC in the subcoating layer in this study.

Sucrose was hard to dry under all conditions. In other words, the syrup coating layer was hard to dry under all conditions. We confirmed that sucrose is hard to dry when it is wetted. The hardness of drying under all conditions is supposed that sucrose would release its moisture reluctantly since the molecular structure of sucrose is relatively similar to that of water. Drying at 60 °C (Fig. 5B) was more hard to dry than drying at 25 °C/11% RH (Fig. 5C). The reason why is that sucrose on the surface crystallized under the drying at 60 °C and the crystallized sucrose made a dense crystal layer which prevented further moisture evaporation.

We confirmed that the subcoating layer and the smoothing layer are easy to dry and do not hold moisture easily. On the other hand, the coloring layer is hard to dry and holds moisture readily. These findings suggest that the moisture content in the core tablet would be low and that in the subcoating layer and the smoothing layer may be relatively low while that in the coloring layer may be relatively high immediately after manufacture. These characteristics of moisturizing and drying behaviors in the sugar-coating layers would result in moisture movement within the sugar-coated tablets as mentioned in Fig. 3.

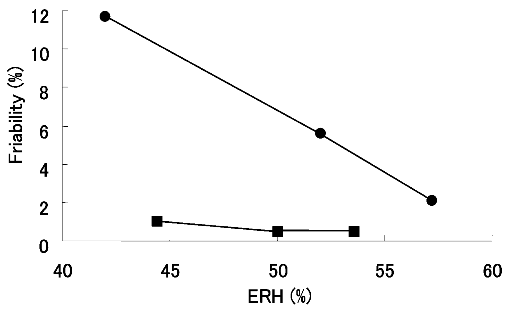

Fig. 6. Relationship between ERH and Friability of Sugar-Coated Tablets

●, dusting powder A; ■, dusting powder D.

Effect of ERH on Impact Toughness of Sugar-Coated Tablets The stability of vitamins is susceptible to moisture.[20] In the development of sugar-coated tablets containing vitamins, we investigate the relationship between ERH and the stability of vitamins. In this study, ERH of sugar-coated tablets must be lower than 55% for the achievement of stabilized vitamins. Reduction of ERH results in both enhancement of the stability of vitamins and weakening of the impact toughness of conventional sugar-coated tablets. Figure 6 shows the relationship between ERH of sugar-coated tablets and friability. Friability of sugar-coated tablets manufactured by the dusting method using dusting powder D was less susceptible to ERH. Its friability was low even at low ERH.

When moisture content was low in sugar-coated tablets, the impact toughness depended on the impact toughness of the subcoating layer and the smoothing layer because the coloring layer of sucrose is hard and fragile at low moisture content. Strong bonding between the subcoating layer and the smoothing layer is necessary for the enhancement of impact toughness of sugar-coated tablets whose moisture content is low because we demonstrated that the bond between the two layers is critical to the impact toughness of the sugar-coated tablets in our previous paper.[10] We also demonstrated in the previous paper that MCC is a suitable material for the enhancement of the bond between the subcoating layer and the smoothing layer in sugar-coated tablets.[10] In this study, we confirmed that MCC enhances the impact toughness of the sugar-coated tablets even when the moisture content of the sugar-coated tablets is low. Therefore, the dusting method using dusting powder containing MCC is available for the production of sugar-coated tablets containing moisture sensitive drugs such as vitamins.

Free Fall Test of Sugar-Coated Tablets Several methods have been used to measure the impact toughness of tablets. The free fall test is a well known method for evaluation of impact toughness of sugar-coated tablets. We conducted the free fall test. The results are shown in Fig. 7. The percentage of cracked tablets in the sugar-coated tablets made with MCC was zero even though the free fall test was

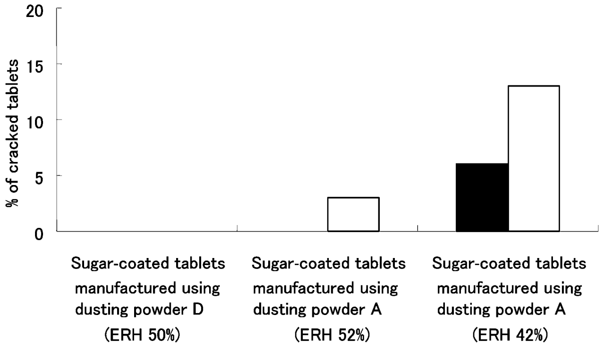

Fig. 7. Percentage of Cracked Tablets after the Free Fall Test on Sugar-Coated Tablets

■,1 time; □, 3 times.

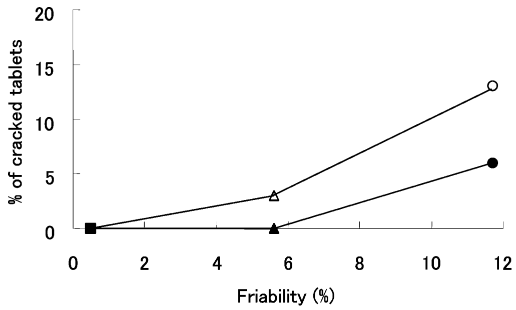

Fig. 8. Relationship between Friability and Percentage of Cracked Tablets after the Free Fall Test on Sugar-Coated Tablets

●, ○, dusting powder A (ERH 42%); ▲, △, dusting powder A (ERH 52%); ■, □, dusting powder D (ERH 50%). Closed symbols are 1 time and open symbols are 3 times on the free fall test.

conducted three times. The sugar-coated tablets made with MCC showed high impact toughness in the free fall test.

In addition, we compared the free fall test and the friability test. Figure 8 shows the relationship between the free fall test and the friability test. In the case of one 110 cm drop, there was no difference between the sugar-coated tablets manufactured by the dusting method using dusting powder A (ERH 52%) and dusting powder D (ERH 50%). In the case of three 110 cm drops, there was a difference between the two sugar-coated tablets. The friability was related to the results from three 110 cm drops. This revealed that the friability test tests severe impact and friability conditions for sugar-coated tablets.

The free fall test is an adequate method for the measurement of effects of weight and shape of sugar-coated tablets on their impact toughness. However, the data of free fall test were scattered because of the inconsistent point of impact. The friability test is superior to the free fall test from the practical point of view. The friability test is also an adequate method for measurement of effects of weight and shape of sugar-coated tablets on their impact toughness because the tablets undergo free fall; the tablets fall from 50 cm height 300 times during the test. The differences in point of impact on sugar-coated tablets are minimized in the friability test. In addition, the friability test is easy to conduct.

A further method for evaluation of impact toughness of sugar-coated tablets is a falling weight test. The test is an adequate method for measurement of impact toughness of sugar-coating layer. However, the impact toughness of sugar-coated tablets is related to not only the impact toughness of sugar-coating layer but also the weight and shape of the tablets. Lighter and rounder sugar-coated tablets have higher impact toughness. In other words, the falling weight test is an inadequate method for measurement of the effects of weight and shape of sugar-coated tablets on impact toughness of sugar-coated tablets.

From the results of the free fall test and the friability test, we demonstrated that the dusting method using dusting powder D was available for sugar-coated tablets containing moisture sensitive drugs such as vitamins, from a practical point of view.

Conclusions

We demonstrated that moisture played an important role in the impact toughness of sugar-coated tablets, due to the characteristics of sucrose. Sucrose, which is the main ingredient of the sugar-coating layer, is a soft and non-fragile material at high ERH, but hard and fragile at low ERH. We found that moisturizing resulted in a decrease in friability as an indicator of impact toughness, while reduction of moisture resulted in an increase in friability.

In the sugar coating, the drying temperature in the coloring step is low in order to gloss the sugar-coating layer. In addition, sucrose is hard to dry. Therefore, there remains a sufficient amount of moisture in the coloring layer immediately after manufacture, which can move into the core of the tablets. Moisture in the sugar-coating layer reduced during the storage time. Therefore, friability changed with time and friability should be measured at 14 d after manufacture.

We conducted both the free fall test and the friability test for evaluation of impact toughness of sugar-coated tablets, and analyzed the relationship between the free fall test and the friability test. The friability test was useful for evaluation of impact toughness of sugar-coated tablets because it was easy to conduct and offered severe impact and friability conditions. In both tests, the sugar-coated tablets manufactured by the dusting method using dusting powder containing MCC were strong against impact even though the ERH was low. It suggested that the dusting method using dusting powder containing MCC is available for the production of sugar-coated tablets containing moisture sensitive drugs such as vitamins.

References

1) Carstensen J. T., *Drug Dev. Ind. Pharm.*, **14**, 1927—1969 (1988).
2) Bangudu A. B., Pilpel N., *J. Pharm. Pharmacol.*, **37**, 289—293 (1985).
3) Kawashima Y., Takeuchi H., Hino T., Niwa T., Lin T. L., Sekigawa F., Ohya M., *S.T.P. Pharma Sci.*, **3**, 170—177 (1993).
4) Wollish E. G., Mlodozeniec A. R., *Pharm. Technol.*, **6**, 49—64 (1982).
5) Carstensen J. T., Scoik K. V., *Pharm. Res.*, **7**, 1278—1281 (1990).
6) Takeuchi H., Yasuji T., Yamamoto H., Kawashima Y., *Pharm. Dev. Technol.*, **5**, 355—363 (2000).
7) Zografi G., Kontny M. J., *Pharm. Res.*, **3**, 187—194 (1986).
8) Zografi G., *Drug Dev. Ind. Pharm.*, **14**, 1905—1926 (1988).
9) Heidemann D. R., Jarosz P. J., *Pharm. Res.*, **8**, 292—297 (1991).
10) Ohmori S., Ohno Y., Makino T., Kashihara T., *Chem. Pharm. Bull.*, **52**, 322—328 (2004).
11) Fielden K. E., Newton J. M., O'Brien P., Rowe R. C., *J. Pharm. Pharmacol.*, **40**, 674—678 (1988).
12) Suzuki T., Kikuchi H., Yonemochi E., Terada K., Yamamoto K., *Chem. Pharm. Bull.*, **49**, 373—378 (2001).
13) Suzuki T., Kikuchi H., Yamamura S., Terada K., Yamamoto K., *J. Pharm. Pharmacol.*, **53**, 609—616 (2001).

14) Kleinebudde P., *Pharm. Res.*, **14**, 804—809 (1997).
15) Nakabayashi K., Shimamoto T., Mima H., *Chem. Pharm. Bull.*, **28**, 1099—1106 (1980).
16) Nakabayashi K., Shimamoto T., Mima H., *Chem. Pharm. Bull.*, **28**, 1107—1111 (1980).
17) Tomida Y., Makino T., *Drug Dev. Ind. Pharm.*, **25**, 445—452 (1999).
18) Fell J. T., Newton J. M., *J. Pharm. Sci.*, **59**, 688—691 (1970).
19) Berggren J., Alderborn G., *Int. J. Pharmaceut.*, **219**, 113—126 (2001).
20) DeRitter E., *J. Pharm. Sci.*, **71**, 1073—1096 (1982).