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Development and evaluation of the tablets coated with the novel formulation termed thin-layer sugarless coated tablets

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Abstract

The purpose of this study was to develop and evaluate the thin-layer sugarless coated tablets containing Vitamin C, Vitamin E, Vitamin B_2, calcium pantothenate, and L-cysteine. As a result of the formulation study, three coating layers, 2% under coating (UC), 38% build-up coating (BC), and 5% syrup coating (SC) were necessary for sufficient impact toughness, elegant appearance, and improvement of appearance stability after storage at 25 °C/75% RH for 6 months under open conditions. We demonstrated that the thin-layer sugarless coated tablets are superior to the sugar-coated tablets in terms of small tablet size and stability of calcium pantothenate. It was due to the coating method, the continuous spray mist method, which can minimize the thicknesses of coating layers and the moisture content in the tablets. We also demonstrated that the thin-layer sugarless coated tablets are superior to the film-coated tablets in terms of masking ability of the unpleasant odor and the appearance, stability of the appearance, and low hygroscopicity. It was due to the dense, opaque, and stable coating layers mainly consist of erythritol. We revealed that thin-layer sugarless coated tablets have both advantages of film-coated tablets and sugar-coated tablets.

Keywords: Erythritol; Thin-layer sugarless coated tablets; Masking; Stability

1. Introduction

Quality of life is one of the most important key words in the healthcare field. Freckles on faces lead to decreased quality of life. Tablets containing Vitamin C, Vitamin E, L-cysteine, Vitamin B_2, and calcium pantothenate are effective for the treatment of freckles. Fujiwara et al. (2003) reported that oral administration of Vitamin C, Vitamin E, and L-cysteine was effective in inhibiting the melanogenesis induced by UV-B exposure.

Odor and taste masking is important from the viewpoint of patient acceptance, preference, and compliance. In the development of tablets containing Vitamin C, Vitamin E, Vitamin B_2, calcium pantothenate and L-cysteine, tablet coating is necessary in order to mask the unpleasant odor and taste of L-cysteine and bitter taste of calcium pantothenate. There are two main tablet coating in the pharmaceutical field. One is film coating and the other is sugar coating (Bauer et al., 1998). Film-coated tablets have excellent properties such as masking of bitter taste, slight size increase, low calorie due to a polymer, and low moisture content. However, film-coated tablets are inferior to sugar-coated tablets in terms of easiness of swallowing, elegant appearance and

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masking of unpleasant odor. In contrast, sugar-coated tablets are a dosage form having excellent properties such as easiness of swallowing, elegant appearance, and masking of unpleasant taste and odor. However, sugar-coated tablets still have problems of remarkable size increase, high calorie due to sucrose, and relatively high moisture content.

In the development of tablets containing vitamins, interactions between some of vitamins must be considered. Therefore, incorporation of vitamins into the coating layer has been sometimes used for reduction of the interactions and stabilization of vitamins on sugar-coated tablets in the pharmaceutical field (DeRitter, 1982). However, incorporation of vitamins into the coating layer is a complicated and disadvantageous method from the viewpoint of process validation and content uniformity. Another method to stabilize vitamins is reducing the moisture content in the tablets because some vitamins are moisture sensitive (DeRitter et al., 1970; DeRitter, 1982; Maekawa et al., 1977; Takeda Chemical Ind., 1997). Especially, calcium pantothenate content is easily decreased when tablets have a high moisture content. Furthermore, Vitamin C is easily discolored when tablets have a high moisture content. Therefore, the moisture content of the tablets should be low in order to stabilize the calcium pantothenate content and tablet appearance. Moreover, hygroscopicty of the tablets should be low from the viewpoint of stability of the unpacked tablets under high humidity conditions.

Sugarless tablets may be requested by patients. Diabetics are eager to take sugarless tablets. In addition, some patients prefer to take sugarless tablets rather than sugar-coated tablets. However, there have been no practical coating techniques using sugarless materials such as sugar alcohols in the pharmaceutical fields, and no sugarless coated tablets on the market.

In the previous study (Ohmori et al., 2004c), we demonstrated that eyrthritol has high water solubility, low hygroscopicity, instant crystallization, and low tackiness. The characteristics are suitable for coating from the viewpoint of easiness of spraying and uniform formation of coating layer with low hygroscopicity. Therefore, we developed a novel coating with erythritol termed thin-layer sugarless coating. The coating method is a continuous spray mist method, which is a simple method requiring a simple coating machine and skills. In this study, we applied this thin-layer sugarless coating to the tablets containing Vitamin C, Vitamin E, Vitamin B_2, calcium pantothenate and L-cysteine. We studied the thin-layer sugarless coating formulation on the tablets and developed the thin-layer sugarless coated tablets. In addition, we evaluated the characteristics of the thin-layer sugarless coated tablets, such as masking of the unpleasant odor from L-cysteine, masking of appearance, stability of appearance, and stability of calcium pantothenate content. Especially, in order to determine the masking degree of the unpleasant odor in the tablets, we carried out both a sensory evaluation and an evaluation using an electronic nose system (Chauvet et al., 2000a,b).

2. Materials and methods

2.1. Materials

Core tablets containing Vitamin C (Takeda Chemical Ind.), Vitamin E (Eisai Co.), Vitamin B_2 (Takeda Chemical Ind.), calcium pantothenate type S (BASF Takeda Vitamins), and L-cysteine (Kyowa Hakko Kogyo Co.) were used. The weight, diameter, radius of curvature and thickness of core tablets were 300 mg, 8.8, 7.0, 5.16 mm, respectively. Erythritol (Nikken Chemicals Co.), sucrose (Ensuiko Sugar Refining Co.), talc (Matsumura Sangyo Co.), titanium dioxide (TiO_2) (Ishihara Sangyo Co.), powdered acacia (San-ei Yakuhin Boeki Co.), microcrystalline cellulose (MCC)(Avicel PH-F20, Asahi Kasei Co.), polyethylene glycol 6000 (PEG 6000) (Sanyo Chemical Ind.), and hydroxypropylmethylcellulose (HPMC) (TC-5MW, Shin-Etsu Chemical Co.) were used for the coating. Lactose (Granulac 200, Meggle GmbH) was used for the compatibility study. All other chemicals were of reagent grade.

2.2. Thin-layer sugarless coating

Thin-layer sugarless coating was performed by the continuous spray mist method, which is often used in film coating. A coating machine (Dria Coater (DRC-500), Powrex Co.) was used as the thin-layer sugarless coating machine. Three thousand two hundred and forty grams of core tablets were loaded in the coating machine. The thin-layer sugarless coating can be divided into four steps: (1) under coating (UC), (2) build-up coating (BC), (3) syrup coating (SC),

(4) polishing (PO). The thin-layer sugarless coating formulation was as follows: the UC formulation was HPMC 10.0% and purified water 90.0%, the BC formulation was erythritol 18.2–22.0%, talc 10.6%, TiO_2 0.8%, MCC 0–3.8% (0–10% (solid)), powdered acacia 4.6% and purified water 62.0%, the SC formulation was erythritol 34.2%, PEG 6000 3.8% and purified water 62.0%. The coating conditions of UC were as follows: inlet air temperature 70 °C; outlet air temperature 45–49 °C; spray feed rate 10 g/min; spray air pressure 0.35 MPa; spray air volume 5000 Nl/h; pan revolution 10 rpm. Weight increase of UC was 6 mg per tablet. The coating conditions of BC were as follows: inlet air temperature 60 °C; outlet air temperature 42–46 °C; spray feed rate 20 g/min; spray air pressure 0.35 MPa; spray air volume 5000 Nl/h; pan revolution 10 rpm. Weight increase of BC was 15–114 mg per tablet. The coating conditions of SC were as follows: inlet air temperature 55 °C; outlet air temperature 37–40 °C; spray feed rate 10 g/min; spray air pressure 0.35 MPa; spray air volume 5000 Nl/h; pan revolution 10 rpm. Weight increase of SC was 15 mg per tablet. PO was achieved by applying a mixture of waxes (carnauba wax and white beeswax) to the tablets in a polishing pan.

2.3. Film coating

A coating machine (HCT-MINI, Freund Ind. Co.) was used as the film-coating machine. Three hundred grams of core tablets were loaded in the coating machine. The film-coating suspension formulation was HPMC 5.5–7.5%, TiO_2 1.0–3.0% (10–30% (solid)), PEG 6000 1.5%, purified water 90.0%. The coating conditions were as follows: inlet air temperature 75 °C; outlet air temperature 38–45 °C; spray feed rate 1 g/min; spray air pressure 0.15 MPa; pan revolution 30 rpm. Weight increase of film coating was 12 mg per tablet.

2.4. Sugar coating

Sugar coating was performed manually in a 12 in. onion pan (Kikusui Seisakusyo). Nine hundred grams of core tablets were loaded in the pan. A sugar-coating suspension (sucrose 41.8%, talc 30.4%, TiO_2 1.7%, powdered acacia 4.9%, purified water 21.2%), dusting powder (talc 78%, powdered acacia 2%, MCC 20%) and syrup (sucrose 66.6%, purified water 33.4%) were used for sugar coating. The dusting method was carried out. The dusting method can be divided into four steps: (1) subcoating, (2) smoothing, (3) syrup coating, (4) polishing. The subcoating was applied to round the edges and build up the tablets size. The subcoating step consisted of alternately applying the sugar-coating suspension to the tablets followed by dusting with the powders and then drying at 55 °C. Weight increase of subcoating was 180 mg per tablet. The smoothing step was to smooth out the tablet surface further prior to application of the syrup coating. The smoothing step consisted of alternately applying the sugar-coating suspension to the tablets and then drying at 55 °C. Weight increase of smoothing was 75 mg per tablet. The syrup coating step was to impart an elegant appearance to the tablets. The syrup coating consisted of alternately applying the syrup to the tablets and then drying at 50 °C. The drying temperature in the syrup coating step was gradually reduced to 25 °C. Weight increase of syrup coating was 45 mg per tablet. Polishing was achieved by applying a mixture of waxes (carnauba wax and white beeswax) to the tablets in a polishing pan.

2.5. Impact toughness

Impact toughness of thin-layer sugarless coated tablets was evaluated by the friability test; an easy method to measure impact toughness (Ohmori et al., 2004a). The friability tester consists of a drum and a motor. The diameter of the drum was 50 cm. A stainless steel sheet onto which 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.

2.6. Evaluation of masking of unpleasant odor

In order to quantify the unpleasant odor originated from L-cysteine, a sensory evaluation and an evaluation using an electronic nose system were conducted. The thin-layer sugarless coated tablets, sugar-coated tablets, film-coated tablets, and plain tablets were used for this experiment. Ten volunteers were participated in the sensory evaluation. The tablets were placed into a glass bottle. The glass bottle was capped with

a metal cap. The volunteers opened each glass bottle containing the tablets, smelled the odor, and gave each bottle a score. The scores were five ranks. 0, no unpleasant odor; 1, slight unpleasant odor; 2, unpleasant odor; 3, strong unpleasant odor; 4, remarkably strong unpleasant odor. From 0 to 1, the unpleasant odor was sufficiently masked in the tablets. From 2 to 4, the unpleasant odor was insufficiently masked in the tablets.

The electronic nose system (αPrometheus, Alpha M.O.S.) is composed of three main elements, which are a sensor array system (αFox 2000, Alpha M.O.S.), a fingerprint mass spectrometer (αKronos, Alpha M.O.S.), and a headspace autosampler (HS100, Alpha M.O.S.). The sensor array contains six metal oxide gas sensors (T30/1, P10/1, P10/2, P40/1, T70/2, PA2). The principle of the detection on the sensor array is based on conductivity measurements. The fingerprint mass spectrometer is based on an electron impact quadrupole mass spectrometer and allows direct headspace injection in a MS detector. The headspace autosampler allows automation of the headspace generation, extraction, and injection in both the sensor array and the fingerprint mass spectrometer. The evaluation using the electronic nose system was performed in triplicate for each sample. The measurement conditions were as follows: sample three tablets; vial volume 10 ml; incubation temperature 100 °C; incubation time 15 min; agitation speed 500 rpm; injection volume 500 μl (αFox2000), 4500 μl (αKronos). In this study, the sensors (P10/2, P40/1) and *m*/*z* (48, 53, 64) were used for the evaluation of masking of the unpleasant odor. The data were analyzed with Alpha Soft Version 8.0 software. Principal component analysis (PCA) was used to remove the redundancy of variables and to give a representative map of the different olfactive areas.

2.7. Equilibrium relative humidity of tablets

Equilibrium relative humidity (ERH) of tablets was measured using a water activity analyzer (Hygroskop DT, Rotronic). Six roughly crushed coated tablets were used for the measurement. We used ERH as a measure of moisture content in tablets.

2.8. Calcium pantothenate content

Measurements of calcium pantothenate content were performed by high-performance liquid chromatography (HPLC) (model 2690, Waters) with UV detection at 210 nm (model 2487, Waters). The mobile phase used was 0.05 mol/l ammonium dihydrogenphosphate aqueous solution (pH 3.5):methanol (19:1) at flow rate of 1.0 ml/min through a column (YMC-Pack ODS AM-302) at 25 °C.

2.9. Appearance

Scanning electron micrographs of cross-sections of thin-layer sugarless coated tablets were obtained using a scanning electron microscope (S-2300, Hitachi). The appearances of thin-layer sugarless coated tablets and sugar-coated tablets were obtained using a digital microscope (VH8000, Keyence). Yellowness (YI) and color difference (ΔE) were determined using a color computer (SM-5, Suga Test Instruments). Yellowness (YI) and color difference (ΔE) were calculated using the following equations:

$$\text{yellowness (YI)} = 100 \times \frac{1.28X - 1.06Z}{Y} \quad (1)$$

$$\text{color difference } (\Delta E) = ((\Delta L)^2 + (\Delta a)^2 + (\Delta b)^2)^{1/2} \quad (2)$$

The masking criteria was yellowness 7 because we can see tablets whose yellowness below 7 as white tablets.

2.10. Compatibility of Vitamin C and titanium oxide

Compatibility test of Vitamin C and titanium oxide (TiO_2) was carried out. Vitamin C/TiO_2 (10/1) was placed into the glass bottles and stored at 60 °C for 2 weeks under closed conditions and at 40 °C/75% RH for 2 weeks under open conditions. Color difference (ΔE) was determined using the color computer. Compatibility tests of Vitamin C, lactose, and Vitamin C/lactose (10/1) were also carried out as the references.

2.11. Hygroscopicity

Hygroscopicity of the tablets was determined by measurements of calcium pantothenate content. The thin-layer sugarless coated tablets were stored at 40 °C/75% for 1 month under open conditions and measurement of calcium pantothenate content was

carried out by the HPLC method described above. Plain tablets, film-coated tablets, and sugar-coated tablets were also stored at 40 °C/75% for 1 month under open conditions and measurements of calcium pantothenate content were carried out as references.

3. Results and discussion

3.1. Thin-layer sugarless coating formulation

Tablet size is one of the most important factors in patient acceptance, preference, and compliance. We reduced the thickness of the sugarless coating layer in order to minimize tablet size. In general, reduction of the thickness of the coating layer leads to weakened impact toughness of the coating layer. However, strong impact toughness is indispensable for sugarless coated tablets. If the impact toughness of sugarless coated tablets is weak, cracking or removal of the sugarless-coating layer will occur and these will cause deterioration of the characteristics of the tablets.

Fig. 1 shows the relationship between coating level and friability of coating layer. When the thin-layer sugarless coating formulation (a BC formulation, i.e. erythritol, talc, titanium oxide, powdered acacia) was applied to the tablets whose coating level was 35%, the coating layer was smooth and uniform, but the thin-layer sugarless coated tablets were remarkably weak against impact. This would be due to the weakness of erythritol against impact. Erythritol has poor bonding ability. Incorporating a binder, powdered acacia, into the formulation was insufficient for improvement of impact toughness of the coating layer. Therefore, MCC was formulated into the thin-layer sugarless coating formulation in order to improve its impact toughness. We previously demonstrated that MCC is a suitable material for the improvement of impact toughness (Ohmori et al., 2004a,b). An increase of MCC level resulted in a decrease of friability of the sugarless coating layer. However, in the case of 10% MCC level, the thin-layer sugarless coated tablets were cracked after storage at 25 °C/75% RH for 6 months under open conditions. This could be due to swelling of MCC in the coating layer under high humidity conditions. Therefore, the MCC level was decreased 10% to 5% and the coating level was increased 35 to 40%. Thin-layer sugarless coated tablets, whose MCC level was 5% and coating level was 40%, have acceptable impact toughness and did not crack after storage at 25 °C/75% RH for 6 months under open conditions.

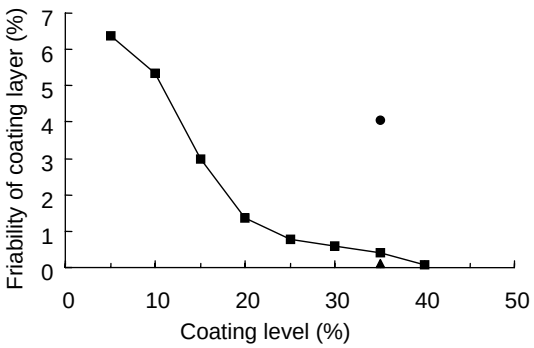

Fig. 1. Relationship between coating level and friability of coating layer. Key: (●) MCC 0%; (■) MCC 5%; (▲) MCC 10%.

Syrup coating was performed in order to add gloss, elegant appearance, and low hygroscopicity into the thin-layer sugarless coated tablets. Since the coating layer consisted of only erythritol was weak against impact (Ohmori et al., 2004c), PEG 6000 was incorporated into the syrup coating layer. PEG 6000 has been often used as a binder (Shah et al., 1977; Haramiishi et al., 1991), a plasticizer (Takeuchi et al., 1989; Nakagami et al., 1991), and a lubricant (Makino et al., 1994) and PEG 6000 is well known as a binder with low hygroscopicity compared to other binders such as powdered acacia, hydroxypropylcellulose (HPC), and HPMC. Therefore, the thin-layer sugarless coated tablets with syrup coating (5%), whose formulation is 90% erythritol and 10% PEG 6000, had sufficient impact toughness, elegant appearance, and low hygroscopicity.

When the thin-layer sugarless coated tablets, whose coating layers were BC and SC layers, were stored at 40 °C/75% RH for 6 months under closed conditions, the appearance of the thin-layer sugarless coated tablets did not change remarkably. However, when the thin-layer sugarless coated tablets were stored at 40 °C/75% RH for 1 month or at 25 °C/75% RH for 6 months under open conditions, the appearance of the thin-layer sugarless coated tablets changed. This is shown in Table 1. It could have been due to the migration of drugs from the core tablets to the coating layer by the medium of moisture under high humidity conditions because vitamins and L-cysteine are highly water

Table 1
Color differences (ΔE) of thin-layer sugarless coated tablets with or without under coating (UC)

	Thin-layer sugarless coated tablets without UC	Thin-layer sugarless coated tablets with UC
40 °C 75% RH 6 months closed condition	1.5	1.5
40 °C 75% RH 1 month open condition	8.6	4.1
25 °C 75% RH 6 months open condition	4.8	2.5

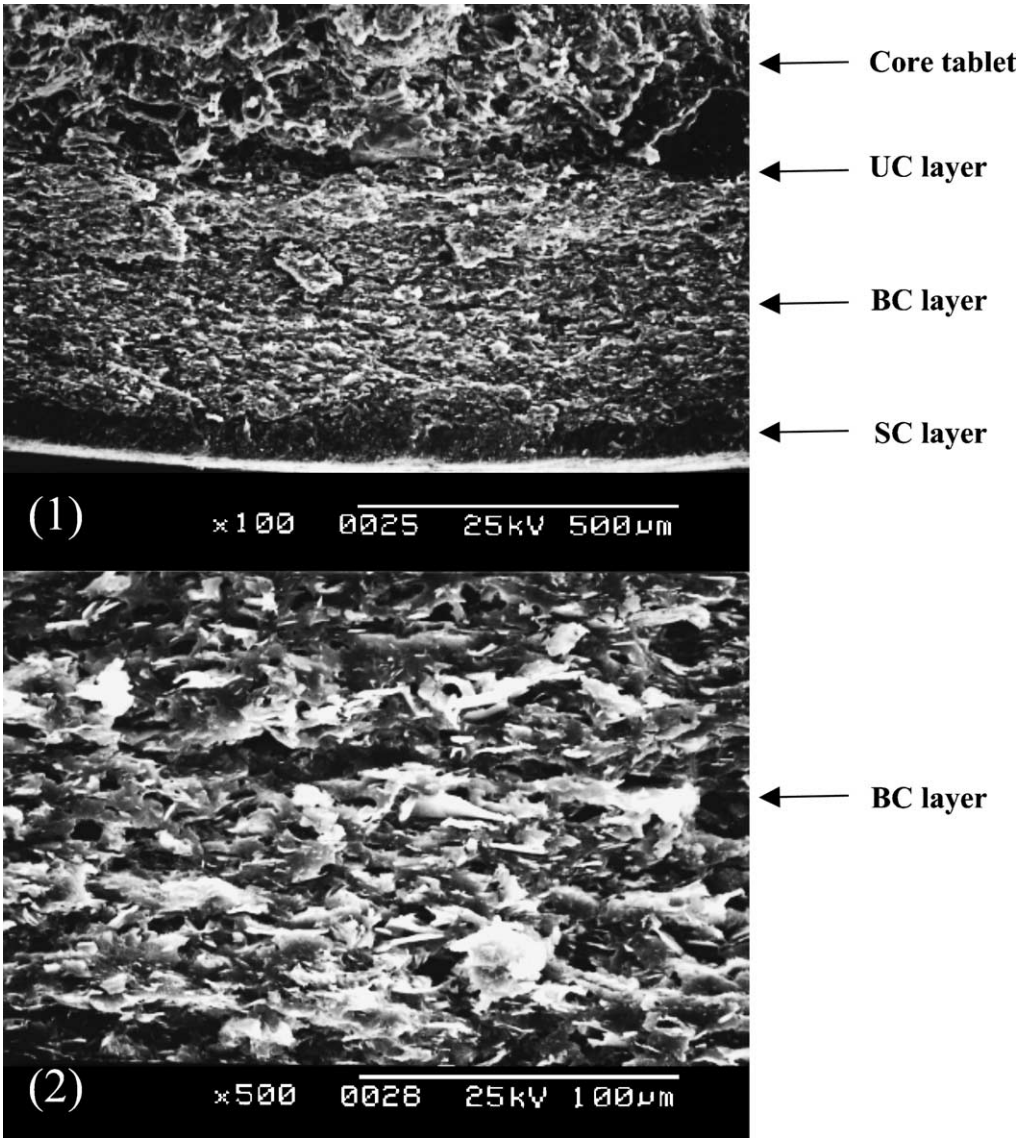

Fig. 2. Scanning electron micrographs of cross-sections of thin-layer sugarless coated tablets. (1) Cross-section of coating layers; (2) cross-section of build-up coating (BC) layer.

soluble. This consideration was reported by Nakamura et al. (1987) in the case of sugar-coated tablets. They reported that a higher water soluble ingredient resulted in a faster migration into the sugar coating layer under high humidity conditions. They also suggested that a moisture protective undercoat was necessary for the prevention of migration of highly water soluble ingredients in the sugar-coated tablets stored in high humidity conditions. In addition, a viscous material prevents the migration of drugs (Warren and Price, 1977) and under coating prevents the migration (Bauer et al., 1998). Therefore, an under coating of HPMC would be effective for this color change. When the thin-layer sugarless coated tablets having 2% HPMC undercoat were stored at 40 °C/75% RH for 1 month or at 25 °C/75% RH for 6 months under open conditions, the appearance of the thin-layer sugarless coated tablets was stable. It was confirmed that undercoat is an effective way to improve appearance stability of the tablets under high humidity conditions.

Fig. 2 shows scanning electron micrographs of cross-sections of the thin-layer sugarless coated tablets. The sugarless-coating layers were thin compared with the sugar-coating layers and dense compared with the film-coating layer. The SC layer was denser than the BC layer on the thin-layer sugarless coated tablets, as with sugar coating. In sugar coating, a SC layer consists of sucrose is dense and leads to sugar-coated tablets with low hygroscopicity (Maekawa et al., 1975). Incorporation of a binder and a glident into the SC layer leads to the loose SC layer and sugar-coated tablets with relatively high hygroscopicity. In the thin-layer sugarless coating, the ninety percent of erythritol in the SC layer could lead to the dense coating layer and thin-layer sugarless coated tablets with low hygroscopicity.

3.2. Evaluation of the thin-layer sugarless coated tablets

We evaluated the characteristics of the thin-layer sugarless coated tablets. Fig. 3 shows the appearances of thin-layer sugarless coated tablets and sugar-coated tablets. We confirmed that the thin-layer sugarless

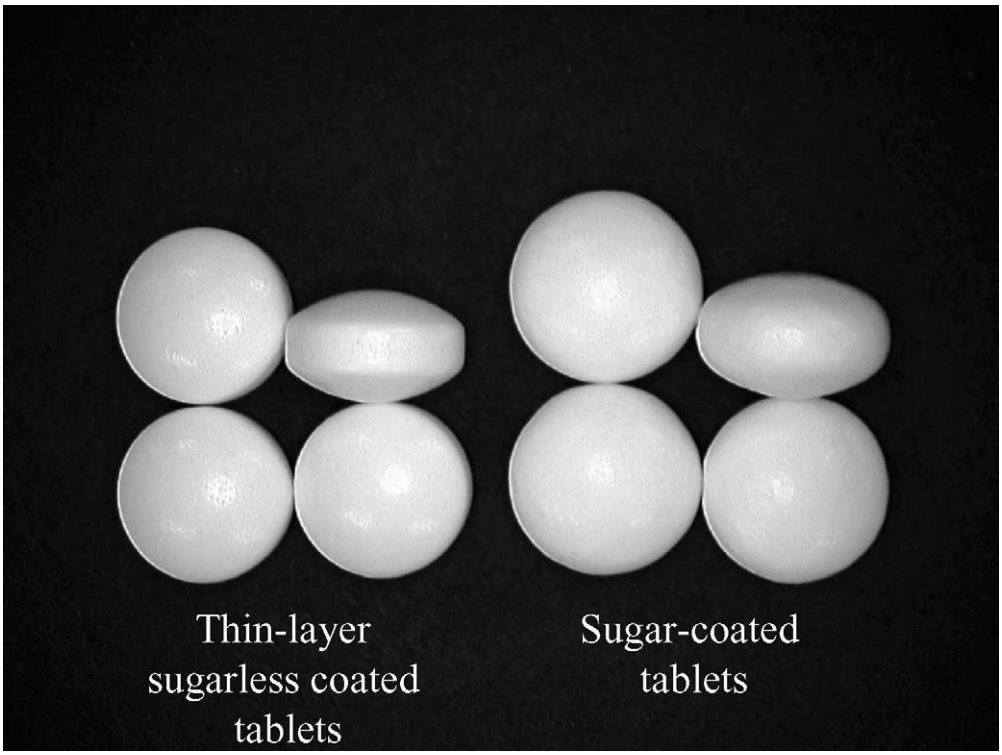

Fig. 3. Appearances of thin-layer sugarless coated tablets and sugar-coated tablets.

coated tablets have the same gloss and elegant appearance as the sugar-coated tablets. The appearance differences between the two tablets were the size and roundness of tablets. The thin-layer sugarless coated tablets were smaller than the sugar-coated tablets. The diameter of the thin-layer sugarless coated tablets was 9.6 mm and that of sugar-coated tablets was 10.4 mm. The thin-layer sugarless coated tablets were less round than the sugar-coated tablets. The roundness of the thin-layer sugarless coated tablets was between those of the sugar-coated tablets and the film-coated tablets. It was due to the coating method, the continuous spray mist method.

L-Cysteine is the active ingredient in the thin-layer sugarless coated tablets and it has an unpleasant odor. We evaluated the degree of unpleasant odor between four kinds of tablets; thin-layer sugarless coated tablets, sugar-coated tablets, film-coated tablets, and plain tablets. Fig. 4 shows the sensory evaluation. The unpleasant odor was sufficiently masked in the thin-layer sugarless coated tablets and the sugar-coated tablets whereas the unpleasant odor was insufficiently masked in the plain tablets and the film-coated tablets. The masking ability of the thin-layer sugarless coating was superior to that of the film-coating and the same as that of the sugar-coating.

Although sensory evaluation is subjective, evaluation using an electronic nose can be objective. We evaluated the masking ability of the thin-layer sugarless coating using the electronic nose system. Fig. 5 shows the electronic nose system evaluation. In Fig. 5(a) and (b), the thin-layer sugarless coated tablets were located near the sugar-coated tablets whereas the film-coated tablets were located near the plain tablets. This suggested that the odor of the thin-layer sugarless coated tablets was relatively similar to that of the sugar-coated tablets whereas the odor of the film tablets was relatively similar to that of the plain tablets. Therefore, the odor masking degree of the thin-layer sugarless coated tablets was relatively similar to that of the sugar-coated tablets whereas the odor masking degree of the film-coated tablets was relatively similar to that of the plain tablets. This revealed that the thin-layer sugarless coating has the same masking ability as the sugar coating. It would be due to the dense coating layers shown in Fig. 2, as with sugar coating.

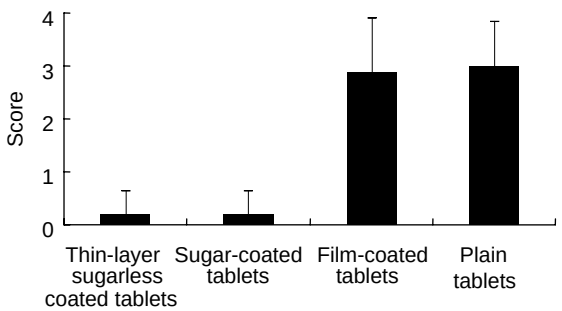

Fig. 4. Sensory evaluation. Score: 0, no unpleasant odor; 1, slight unpleasant odor; 2, unpleasant odor; 3, strong unpleasant odor; 4, remarkably strong unpleasant odor.

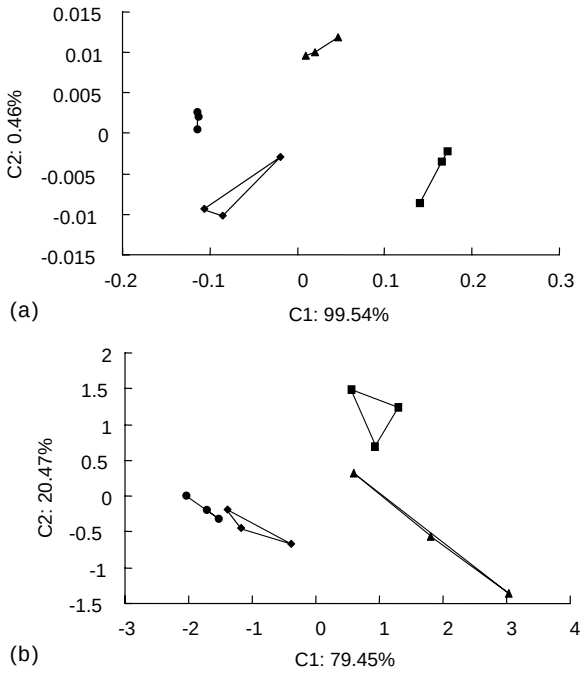

Fig. 5. Electronic nose system evaluation. Principal component analysis (PCA) map of the tablets. (a) Sensor array, (b) fingerprint mass spectrometry. Key: (●) thin-layer sugarless coated tablets; (◆) sugar-coated tablets; (■) film-coated tablets; (▲) plain tablets.

The thin-layer sugarless coating was conducted by the continuous spray mist method. The moisture content of thin-layer sugarless coated tablets can thus be reduced compared with sugar-coated tablets whose method is an intermittent spray method. Fig. 6(a) and (b) shows ERH of the tablets under the coating processes of thin-layer sugarless coating and sugar coating. ERH of the thin-layer sugarless coated tablets

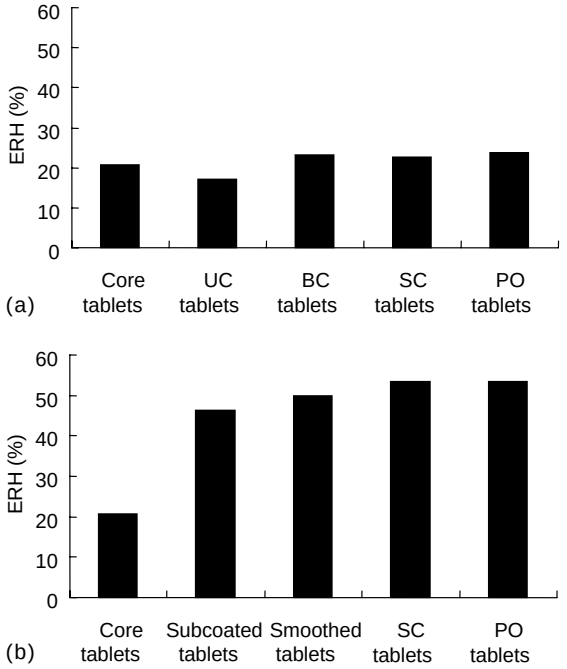

Fig. 6. ERH of tablets under the processes of thin-layer sugarless coating and sugar coating (a) thin-layer sugarless coating, (b) sugar coating.

was remarkably low and below 30%. ERH of the thin-layer sugarless coated tablets was similar to that of the core tablets whereas ERH of the sugar-coated tablets increased remarkably compared with the core tablets. Fig. 7 shows the relationship between ERH and calcium pantothenate content after storage at

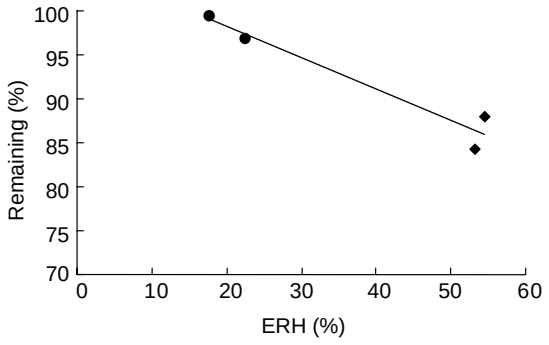

Fig. 7. Relationship between ERH and remaining percentage of calcium pantothenate content after storage at 40 °C for 6 months under closed condition. Key: (●) thin-layer sugarless coated tablets; (◆) sugar-coated tablets.

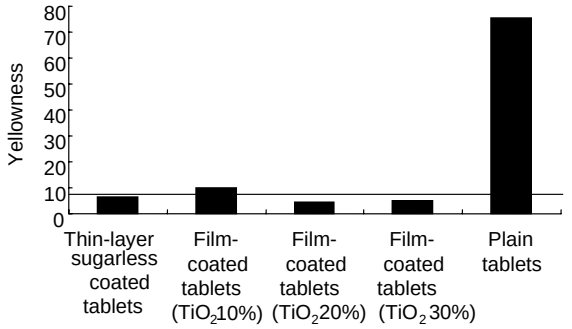

Fig. 8. Yellowness of plain tablets, film-coated tablets, and thin-layer sugarless coated tablets.

40 °C for 6 months under closed conditions. The calcium pantothenate content in the thin-layer sugarless coated tablets was relatively high and stable. In contrast, the calcium pantothenate content in the sugar-coated tablets was relatively low, below 90%, and unstable because of relatively high moisture content. The thin-layer sugarless coating was effective for stabilization of moisture sensitive drugs, such as calcium pantothenate, because of its coating method, the continuous spray mist method, which was able to coat the tablets without remarkable moisture increase.

The core tablets were yellow because of incorporation of Vitamin B_2 as the active ingredient. The appearance masking ability of the thin-layer sugarless coating was compared with that of film coating. Fig. 8 shows a comparison of yellowness of the tablets. The film-coated tablets, whose titanium oxide level in the

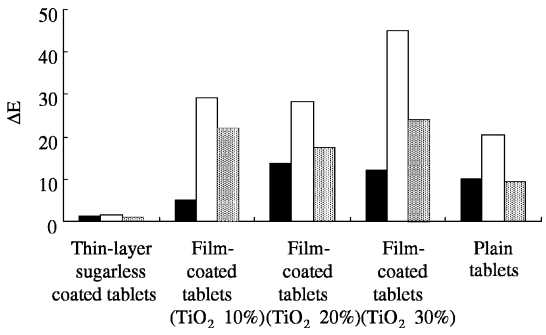

Fig. 9. Color differences (ΔE) of plain tablets, film-coated tablets, and thin-layer sugarless coated tablets. Key: (■) 60 °C 2 weeks closed condition; (□) 40 °C/75% RH 1 month open condition; (▨) 25 °C 75% RH 6 months open condition.

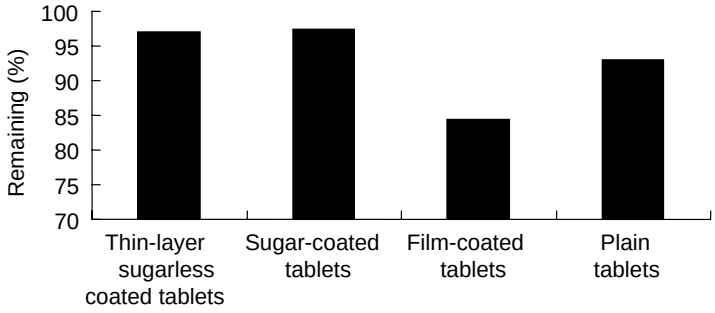

Fig. 10. Remaining percentage of calcium pantothenate content in the tablets after stored at 40 °C/75% RH for 1 months under open condition.

coating layer was 10%, insufficiently masked the appearance. The film-coated tablets having 20% or more titanium oxide level in the coating layer sufficiently masked the appearance. A certain level of titanium oxide was thus necessary for masking the appearance of the core tablets in the film-coated tablets because the film-coating polymer, HPMC, is transparence. On the other hand, the thin-layer sugarless coated tablets were sufficiently masked the appearance of the core tablets because erythritol, which is the main ingredient in the coating layers, is relatively fine crystals and shows a certain level of opacity. Fig. 9 shows the appearance stability of plain tablets, film-coated tablets, and thin-layer sugarless coated tablets. The appearances of the plain tablets and the film-coated tablets after storage at 60 °C for 2 weeks under closed conditions or at 40 °C/75% RH for 1 month or at 25 °C/75% RH for 6 months under open conditions changed. This would be due to appearance stability of Vitamin C and compatibility between Vitamin C and titanium oxide. The color of Vitamin C after storage under high humidity conditions remarkably changes. Vitamin C is incompatible with titanium oxide. This is shown in Table 2. There was a sufficient amount of titanium oxide in the film layer to cause a color change of Vitamin C. On the other hand, erythritol is stable and low hygroscopicity. The thin sugarless coating layers have a small amount of titanium oxide. Therefore, the appearance stability of the thin-layer sugarless coating with erythritol was excellent, even after storage under severe conditions such as 60 °C closed conditions or 40 °C/75% RH open conditions.

Table 2
Color differences (ΔE) in the compatibility study between Vitamin C and excipients

	VC	VC/TiO_2 10/1	Lactose	VC/lactose 10/1
60 °C 2 weeks closed condition	1.3	4.4	0.8	2.8
40 °C 75% RH 2 weeks open condition	3	5.4	1.3	1.7

We confirmed low hygroscopicity of the thin-layer sugarless coated tablets by the measurement of stability of calcium pantothenate after storage at 40 °C/75% RH for 1 month under open conditions. The results are shown in Fig. 10. The stability of calcium pantothenate in the thin-layer sugarless coated tablets was superior to that in the plain tablets, the film-coated tablets, and almost the same as that in the sugar-coated tablets and thus the hygroscopicity of the thin-layer sugarless coated tablets was lower than that of the plain tablets, the film-coated tablets, and almost the same as that of the sugar-coated tablets.

4. Conclusions

We developed the thin-layer sugarless coated tablets, which have three coating layers, 2% under coating (UC) (HPMC), 38% build-up coating (BC) (erythritol, talc, TiO_2, MCC, and powdered acacia), and 5% syrup coating (SC) (erythritol and PEG 6000). Incorporation of MCC into the BC layer was an effective way to improve impact toughness of the thin-layer sugarless coated tablets. The continuous spray mist method leads to the coated tablets with thin coating layers and low moisture content. Therefore, the thin-layer sugarless coated tablets are superior to

the sugar-coated tablets in terms of small tablet size and stability of calcium pantothenate. In addition, erythritol, which is the main ingredient in the coating layers, leads to the glossy, dense, opaque, and stable coating layers. Therefore, the thin-layer sugarless coated tablets are superior to film-coated tablets in terms of elegant appearance, masking ability of the unpleasant odor and the appearance, stability of the appearance, and low hygroscopicity.

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