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Characteristics of erythritol and formulation of a novel coating with erythritol termed thin-layer sugarless coating

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Abstract

The purpose of this study was to clarify the characteristics of erythritol and to develop the optimum basic formulation of a novel coating with erythritol termed thin-layer sugarless coating. Characteristics of erythritol were investigated compared with maltitol, mannitol, sorbitol, xylitol, and sucrose. Furthermore, the optimum basic formulation of thin-layer sugarless coating with erythritol was determined by coating glass beads. We selected a continuous spray mist method for thin-layer sugarless coating due to the formation of a thin sugarless coating layer by a simple method. We demonstrated that erythritol is a suitable coating material for thin-layer sugarless coating compared with maltitol, mannitol, sorbitol, xylitol, and sucrose because of its high water solubility, low hygroscopicity, instant crystallization, and low tackiness. We also demonstrated that thin-layer sugarless coating with erythritol can reduce coating time compared with the coating with maltitol or sucrose due to its characteristics. We developed the optimum basic formulation of thin-layer sugarless coating consists of erythritol, powdered acacia, and talc. We confirmed that a smooth coating layer and high coating efficiency were achieved using the formulation.

Keywords: Erythritol; Sugarless coating; Crystallization; Tackiness; Powdered acacia; Talc

1. Introduction

Sugars and sugar alcohols have attracted considerable interest in the pharmaceutical industry. According to the increase in the number of the listed sugars and sugar alcohols in the official compendia, a variety of sugars and sugar alcohols are now available for excipients in the pharmaceutical field. One of the most interesting sugar alcohols as a pharmaceutical excipient is erythritol (Munro et al., 1998). Noda et al. (1994) reported that erythritol did not affect serum levels of glucose, insulin or other serum constituents and more than 90% of ingested erythritol was readily absorbed and excreted in urine without degradation in healthy subjects. Therefore, erythritol is extremely low calorie, 0 kcal/g. In addition, erythritol is heat-stable and compatible with drugs and pharmaceutical excipients. Erythritol has thus been recently used as a pharmaceutical excipient of a solid dosage form such as fast-dissolving tablets (Bi et al., 1999; Ohmori et al., 2003). However, very little is known about coating formulations with erythritol in the pharmaceutical field.

Tablet coating is one of the most significant processes for improving the physical and chemical

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properties of drugs in tablets (Bauer et al., 1998). Tablet coating can improve stability, appearance, easiness to swallow, and mask unpleasant taste and odor of drugs. Tablet coating can generally be divided into two types. One is film coating and the other is sugar-coating. A number of film coating studies have been carried out and a variety of polymers can be applied for tablet coating (Bauer et al., 1998; Felton and McGinity, 1999; Petereit and Weisbrod, 1999; Thoma and Bechtold, 1999). On the contrary, only sucrose can be applied for sugar-coating in the pharmaceutical field. There have been few or no alternatives to sucrose for sugar-coating in the pharmaceutical field.

In this study, we clarified the characteristics of erythritol and developed an optimum basic formulation of a novel coating with erythritol termed thin-layer sugarless coating. Characteristics of erythritol, maltitol, mannitol, sorbitol, xylitol, and sucrose such as water solubility, hygroscopicity, moisture evaporation, crystallization, and tackiness were investigated to clarify the characteristics of coating materials. Furthermore, the optimum basic formulation of thin-layer sugarless coating was determined using glass beads. The glass beads are round hydrophilic water insoluble compounds and show extremely low water absorption. The characteristics were suitable for the coating materials on formulation study from the viewpoint of isolation of effect of the coating formulation from other complicating factors such as shape, swelling, and disintegration of core materials. Moreover, the diameter of the glass beads we used was 6.5 mm, which is the size range of conventional plain tablets. In addition, glass beads have been sometimes used as the model materials in the pharmaceutical filed (Cutt et al., 1986; Iida et al., 1992; Mosharraf and Nyström, 1999; Mattsson et al., 2000).

2. Materials and method

2.1. Materials

Erythritol (Nikken Chemicals Co.), maltitol (Towa Chemical Ind. Co.), mannitol (Merck), sorbitol (Towa Chemical Ind. Co.), xylitol (Eisai Co.), sucrose (Ensuiko Sugar Refining Co.), hydroxypropylcellulose (HPC) (HPC-L, Nippon Soda Co.), hydroxypropylmethylcellulose (HPMC) (TC-5MW, Shin-Etsu Chemical Co.), talc (Matsumura Sangyo Co.) and powdered acacia (San-ei Yakuhin Boeki Co.) were used in this study. Glass beads (1/4 in. (diameter ca. 6.5 mm), Wako Pure Chemical Ind.) were used to test the coatings.

2.2. Solubility

Solubilities of erythritol, maltitol, mannitol, sorbitol, xylitol, and sucrose were quoted from reference materials (Nikken Chemicals, Hayashibara Co.)[1,2].

2.3. Hygroscopicity

Hygroscopicity of erythritol, maltitol, mannitol, sorbitol, xylitol, and sucrose were measured by a microbalance system (MB-300G, VTI). Samples (ca. 10 mg) were placed on the microbalance pan, surrounded by a thermal jacket used for controlled isothermal scanning. The measurement conditions were as follows: drying temperature 60 °C; heating rate (drying) 5 °C/min; maximum drying time 60 min; equilibrium criteria (drying) 0.01 wt.%; experimental temperature 25 °C; maximum equilibrium time (experimental) 180 min; equilibrium criteria (experimental) 0.01 wt.%; start %RH 0%; maximum %RH 95%; steps 5%.

2.4. Moisture evaporation

Erythritol, maltitol, and sucrose were dissolved in purified water at various concentrations. Ten grams of each aqueous solution were put in the balance dish ($W \times D \times H = 138\text{mm} \times 138\,\text{mm} \times 25\,\text{mm}$, Ina Optika) and dried in a tray drying oven (Perfect oven PV-330, Tabai Espec) at 70 °C. At various times, the weight losses were determined gravimetrically as moisture evaporation. We measured moisture evaporation of 10 g purified water as the reference. Moisture evaporation percentages were calculated using the following equation.

$$\text{Moisture evaporation}(\%) = \frac{(W_c - W_t) \times 100}{(W_c - W_o) \times (1 - C)} \quad (1)$$

[1] Nikken Chemicals Co. Erythritol Technical Information

[2] Hayashibara Co. Pharmaceutical Excipients Technical Information

where W_o is weight of the balance dish, W_c the initial weight of the balance dish and solution, W_t the weight of balance dish and solution at time t, and C is the concentration of the solute in the solution.

2.5. Crystallization

After drying at 70 °C for 2 h in the tray drying oven, the crystals in the balance dish were picked up. Then, the crystals were dried in a vacuum dryer (VS-40, Irie Seisakusho) at 40 °C for 16 h in order to remove adhesive moisture. The crystals after the drying were weighed. Crystallization percentages were calculated using the following equation.

$$\text{Crystallization}(\%) = \frac{W_{ct} \times 100}{(W_c - W_o) \times C} \quad (2)$$

where W_o is weight of the balance dish, W_c the initial weight of the balance dish and solution, W_{ct} the weight of crystals, and C is the concentration of the solute in the solution.

2.6. Tackiness

Tackiness was measured using a compression instrument (Autograph AG-I 50 kN, Shimadzu) at 24 ± 2 °C/45 ± 5% RH. The clear slide glass was fixed on the table of the compression instrument. Another clear slide glass was fixed on the crosshead of the compression instrument. One hundred milligrams of either erythritol, maltitol, sucrose, HPC, or HPMC aqueous solution was put on the slide glass on the table of the compression instrument. The clear slide glass on the crosshead moved down. It followed that the solution was between the slide glasses. After 10 N was loaded on the solution between the slide glasses, the slide glass on the cross head moved up. The test speed of the crosshead was 1 mm/min. We calculated the areas of force–distance curves in the experiments and determined the areas as tackiness. We measured the tackiness of purified water as a reference value. The tackiness changes of erythritol, maltitol, and sucrose aqueous solutions after drying at 70 °C were also measured.

2.7. Coating

A coating machine (HCT-MINI, Freund Ind. Co.) was used for coating. One thousand glass beads (358 g) and 36% erythritol or maltitol or sucrose aqueous solutions were used for coating. One hundred and eighty grams of each aqueous solution was sprayed for coating. The coating conditions were as follows: inlet air temperature 70 °C; outlet air temperature 35–42 °C; spray feed rate 1–7 g/min; spray air pressure 0.2 MPa; pan revolution 30 rpm.

2.8. Beads adhered to the coating pan

After coating, the number of glass beads adhered to the pan was measured and the percentage of glass beads adhered to the pan was calculated. A large percentage of beads adherent to the coating pan indicated a large percentage of defective coatings.

2.9. Appearance

Appearances of coated beads were photographed using a digital microscope (VH-8000, Keyence).

2.10. Coating efficiency

The coating machine (HCT-MINI, Freund Ind. Co.) was used for the coating. One thousand glass beads (358 g) were coated. One hundred and eighty grams of each coating solution was sprayed for coating. The coating formulations are shown in Table 1. The coating conditions were as follows: inlet air temperature 70 °C; outlet air temperature 35–42 °C; spray feed rate

Table 1
Coating formulations (w/w, %)

	Rp.1	Rp.2	Rp.3	Rp.4	Rp.5	Rp.6	Rp.7
Erythritol	36.0	32.4	32.4	28.8	25.2	21.6	21.6
Powdered acacia	–	3.6	–	–	–	–	3.6
Talc	–	–	3.6	7.2	10.8	14.4	10.8
Purified water	64.0	64.0	64.0	64.0	64.0	64.0	64.0

5 g/min; spray air pressure 0.2 MPa; pan revolution 30 rpm.The total weights of glass beads before and after coating were measured. Coating efficiency was evaluated as a yield, which was calculated using the following equation.

$$\text{Yield}(\%) = \frac{(W_c - W_o) \times 100}{0.36 \times 180} \quad (3)$$

where W_o is the total weight of glass beads before coating, and W_c the total weight of glass beads after coating.

3. Results and discussion

3.1. Solubility and hygroscopicity

A sugarless coating base requires high solubility and low hygroscopicity. High solubility is essential for uniform coating and easiness of spraying, and low hygroscopicity is essential for the low hygroscopicity of coated dosage forms. Solubilities of erythritol, maltitol, mannitol, sorbitol, xylitol, and sucrose in water are shown in Fig. 1. Solubility of mannitol was relatively low compared with other sugar alcohols. Solubilities of erythritol, maltitol, sorbitol, xylitol, and sucrose were high. Hygroscopicity of erythritol, maltitol, mannitol, sorbitol, xylitol, and sucrose are shown in Fig. 2. The critical relative humidity (CRH) of erythritol, maltitol, mannitol, sorbitol, xylitol, and sucrose were 90, 85, more than 95, 70, 75, and 80% RH, respectively. Although the hygroscopicity of sorbitol and xylitol were relatively high, the hygroscopicity of erythritol, maltitol, mannitol, and sucrose were low. Therefore, erythritol and malititol were candidates for a sugarless coating base because of their high solubility and low hygroscopicity. We examined other characteristics such as moisture evaporation, crystallization, and tackiness of erythritol and malititol aqueous solutions compared with sucrose aqueous solution.

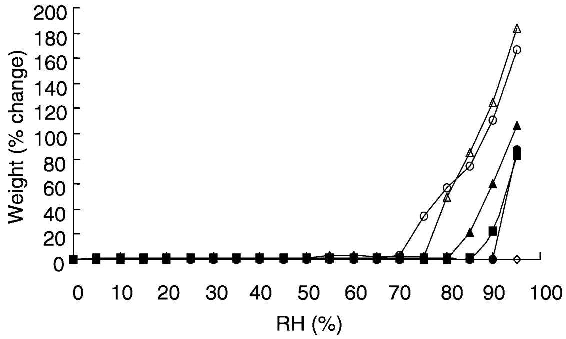


Fig. 2. Hygroscopicity. Key: (●) erythritol; (■) maltitol; (◇) mannitol; (○) sorbitol; (△) xylitol; (▲) sucrose.

3.2. Moisture evaporation and crystallization

Crystallization is one of the most important characteristics of the coating solution, because low crystallization makes coating layer formation difficult. In general, moisture evaporation is related to crystallization of aqueous solutions containing solutes. Therefore, moisture evaporation of 20% erythritol, maltitol, and sucrose aqueous solution were investigated. The results are shown in Fig. 3. Moisture

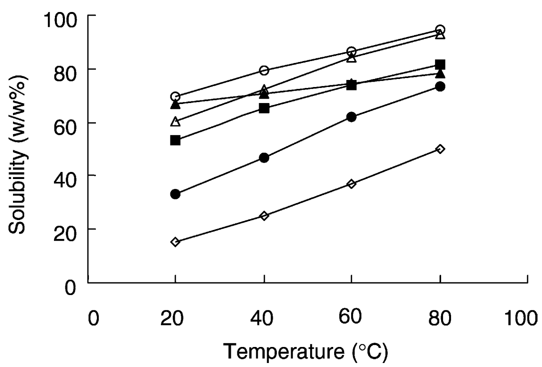


Fig. 1. Solubility in water. Key: (●) erythritol; (■) maltitol; (◇) mannitol; (○) sorbitol; (△) xylitol; (▲) sucrose.

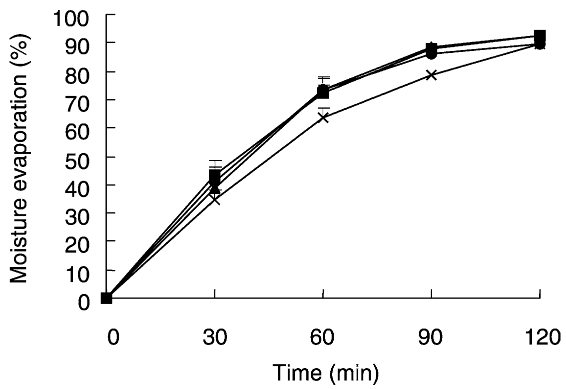


Fig. 3. Moisture evaporation (mean ± S.D.; $n = 3$). Key: (●) 20% erythritol; (■) 20% maltitol; (▲) 20% sucrose; (×) purified water.

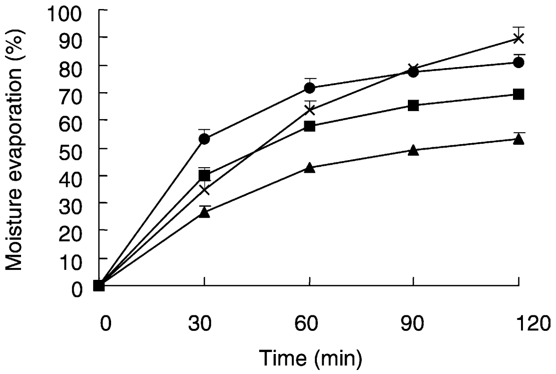


Fig. 4. Moisture evaporation(mean ± S.D.; $n = 3$). Key: (●) 36% erythritol; (■) 59% maltitol; (▲) 68% sucrose; (×) purified water.

evaporation percentages of all solutions increased with time. Moisture evaporation profiles of 20% erythritol, maltitol, and sucrose aqueous solutions were similar. Furthermore, moisture evaporation of 36% erythritol, 59% maltitol, and 68% sucrose solution saturated at 25 °C, were investigated. The results are shown in Fig. 4. Moisture evaporation percentages of all solutions also increased with time. Moisture evaporation speeds in Fig. 4 tended to decrease with the increase in concentration of solutes in the solutions irrespective of the solute.

Fig. 5 shows crystallization of 20% erythritol, maltitol, and sucrose aqueous solution. Fig. 6 also shows crystallization of 36% erythritol, 59% maltitol, and 68% sucrose solution. In the case of erythritol, both 20 and 36% solutions crystallized completely because the moisture evaporated and the solutions were concentrated after drying at 70 °C for 2 h. The crystallized erythritol was confirmed as crystals using the differential scanning calorimeter (DSC) and the powder X-ray diffractometer (PXRD) (data not shown). On the other hand, in the case of maltitol, both 20

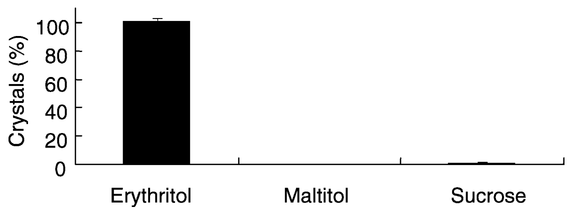


Fig. 5. Crystallization (mean ± S.D.; $n = 3$). Solution: 20% erythritol; 20% maltitol; 20% sucrose.

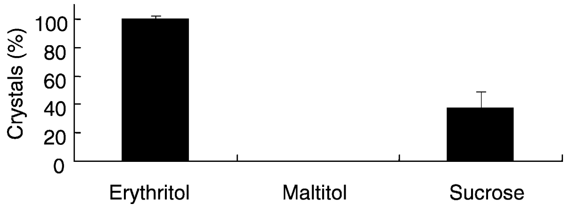


Fig. 6. Crystallization (mean ± S.D.; $n = 3$). Solution: 36% erythritol; 59% maltitol; 68% sucrose.

and 59% solutions did not crystallize even though the moisture evaporated and the solutions were concentrated. Maltitol solutions can maintain supersaturation. In the case of sucrose, the increase of concentration in the solution resulted in the increase of crystallization. We revealed that erythritol aqueous solutions readily crystallized, maltitol aqueous solutions hardly crystallized and crystallization of sucrose aqueous solutions depended on the concentration. In other words, the readiness of crystallization from the aqueous solution was in the order erythritol > sucrose > maltitol.

3.3. Tackiness

Tackiness (Heng et al., 1996; Kokubo et al., 1998; Wesseling et al., 1999) is one of the most important characteristics of coating solution, because high tackiness causes difficulty of coating. Fig. 7 shows tackiness of the solutions at (24 ± 2) °C/(45 ± 5)% RH. Tackiness values of erythritol, maltitol and sucrose aqueous solutions were lower than those of HPC and HPMC aqueous solutions even though their concentrations were high. Tackiness values of 36% erythritol, maltitol and sucrose aqueous solutions were similar and their tackiness values were similar to that of purified water. In general, coating has been carried out by spraying and drying simultaneously. Investigation of the tackiness change of solutions after drying is important in order to clarify the characteristics of solutions in the process of coating. Fig. 8 shows the tackiness changes of 36% erythritol, maltitol and sucrose aqueous solutions after drying at 70 °C. The tackiness of erythritol solution after drying at 70 °C for 5 min reduced readily because of its crystallization. On the other hand, the tackiness of maltitol solution after drying at 70 °C increased with drying time because of its lack of crystallization. The tackiness of

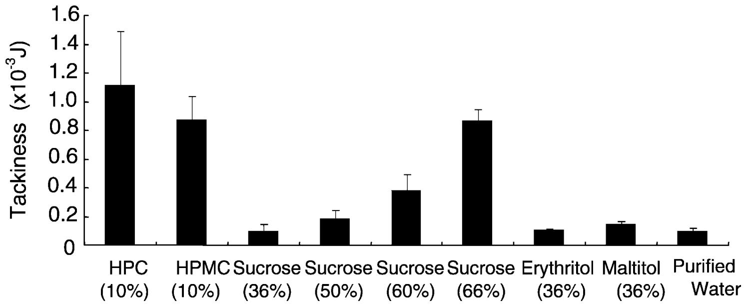


Fig. 7. Tackiness (mean ± S.D.; $n = 3$). Solution: 10% HPC; 10% HPMC; 36–66% sucrose; 36% erythritol; 36% maltitol; purified water.

maltitol solution after drying at 70 °C for 15 min was higher than those of HPC and HPMC solutions. After drying of the malitol solution, its solution temperature increased and its solubility increased as shown in Fig. 1. Therefore, no crystallization occurred in the early stage during drying. In the latter stage during drying, maltitol solution maintained supersaturation even though the concentration exceeded the saturation concentration at 70 °C. Therefore, no crystallization occurred and tackiness continuously increased with drying time in this study. In the case of sucrose, tackiness increased until 5 min and then decreased because of its crystallization. After drying of the sucrose solution, its solution temperature increased and its solubility increased as shown in Fig. 1. Therefore, no crystallization occurred in the early stage during drying. After the solution was concentrated at a certain level, crystallization of sucrose occurred and its tackiness decreased with drying time in this study.

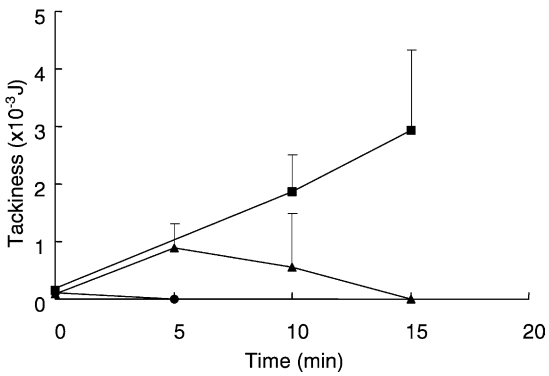


Fig. 8. Relationship between drying time and tackiness (mean ± S.D.; $n = 3$). Key: (●) 36% erythritol; (■) 36% maltitol; (▲) 36% sucrose.

We revealed that the tackiness change behaviors were different. Measurements of tackinesses of coating solutions would be useful to predict the characteristics of solutions in the process of coating.

3.4. Continuous spray mist method

In general, a sugar-coating suspension has a high solid concentration more than 60%. The suspension is viscous and difficult to spray as mist. Therefore, sugar-coating is performed by a intermittent spray method, which is a complex method requires a sophisticated machine and expert skills. The sugar-coating layer is generally 100% weight against the core tablets weight because it is difficult to form thin coating layer due to the intermittent spray method. Therefore, the tablet size significantly increases. In addition, the moisture content of the tablets becomes high due to the intermittent spray method. On the other hand, a film-coating suspension has a low solid concentration less than 30%. The suspension is less viscous and easy to spray as mist. Therefore, film coating is performed by a continuous spray mist method, which is a simple and requires a simple coating machine and skills. The coating layer is thin and the tablet size slightly increases. The continuous spray mist method involves simultaneous spraying and drying in the coating machine. Therefore, the moisture content of the tablets is low. In addition, the continuous spray mist method can be easily outsourced, because the required coating machine is a conventional coating machine and the required coating skills are also conventional coating skills. According to the above idea, we performed a formulation study for thin-layer sugarless coating using the continuous spray mist method.

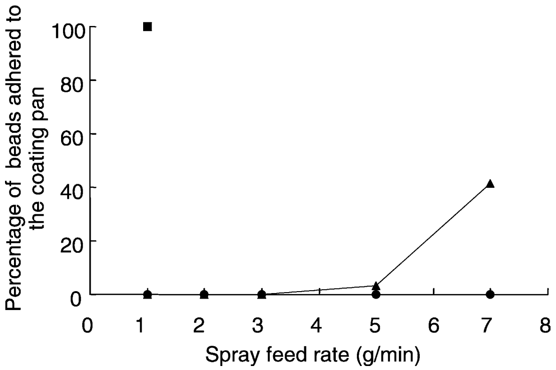


Fig. 9. Relationship between spray feed rate and percentage of beads adhered to the coating pan. Key: (●) erythritol; (■) maltitol; (▲) sucrose.

3.5. Coating time

Short coating time is desirable. We investigated the maximum spray feed rate in order to evaluate coating time to spray the certain amount of the solution. Fig. 9 shows the relationship between spray feed rate and percentages of beads adhered to the coating pan. In the case of erythritol, a high spray feed rate, 7 g/min, could be applied for coating. This was due to instant crystallization and low tackiness of erythritol aqueous solution. On the other hand, in the case of maltitol, 1 g/min could not be applied for coating due to slow crystallization and high tackiness of maltitol aqueous solution. In the case of sucrose, coating was successful until 3 g/min. However, coating was not successful over 5 g/min. This was due to medium crystallization and tackiness of sucrose aqueous solution. In this study, the maximum spray feed rates were 7 g/min for erythritol, less than 1 g/min for maltitol, and 3 g/min for sucrose. The same proportion of maximum spray feed rate between erythritol, maltitol, and sucrose on this study scale would apply on plant scale. We demonstrated that using erythritol as a coating material can reduce the coating time compared with maltitol and sucrose for the continuous spray mist method.

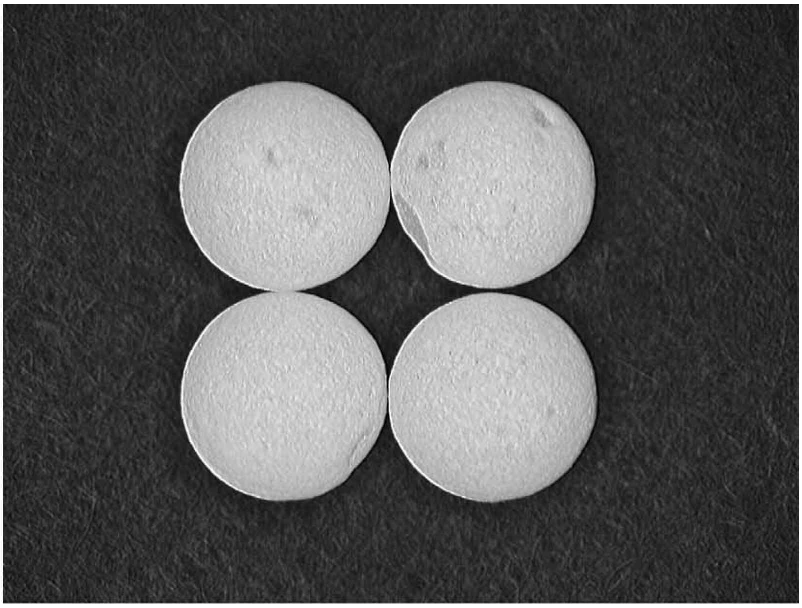
3.6. Basic thin-layer sugarless coating formulation

Fig. 10 shows photographs of coated glass beads. When the erythritol aqueous solution was used as the coating solution, the beads collided and some areas of the coating layer were removed from the coated beads during coating. Therefore, less uniform coating, with some areas being insufficiently coated, was found when using the erythritol aqueous solution as the coating solution (Fig. 10(a)). It was due to the characteristics of erythritol, which is weak against impact because its binding ability is low.

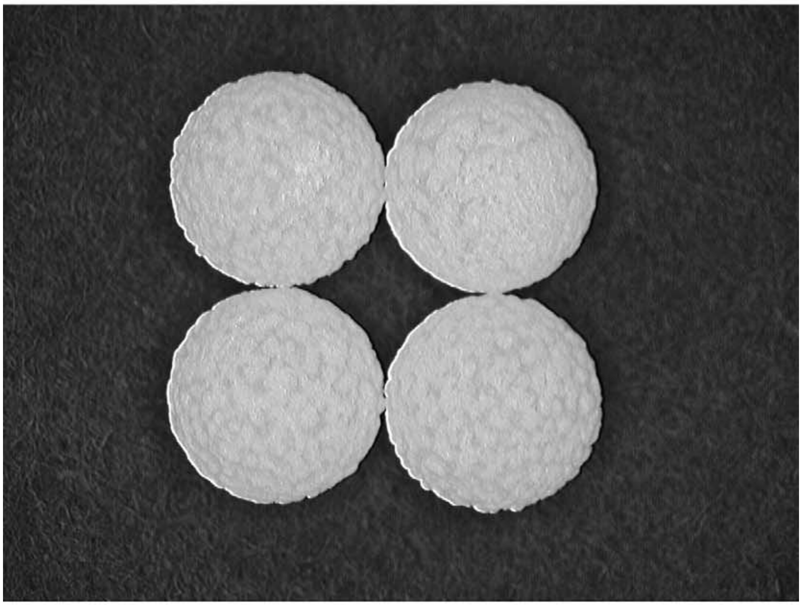
The addition of a binder to the erythritol aqueous solution would contribute to the reduction of removal of the coating layer from the coated beads during the coating because of an increase of hardness of the coating layer. Therefore, powdered acacia was incorporated into the erythritol aqueous solution. However, less uniform coating was achieved (Fig. 10(b)). This might have been due to insufficient spreading of the coating solution during the coating.

Felton and McGinity (2002) reported that the addition of insoluble excipients to film-coating formulations can improve the appearance of the film, enhance the stability of photolytic medicines, and aid in processing. Insoluble excipients are often incorporated in sugar or film-coating formulations in order to achieve uniform coating without coating troubles such as twinning, in which tablets stick permanently together. Talc, a hydrophobic water insoluble compound, a very common insoluble excipient that is used as both an antiadherent and a glident in order to reduce impact of collisions and aggregation during the coating. We incorporated talc into the erythritol aqueous solution as the coating suspension. Ten percentage addition of talc into the solution improved its appearance compared with that using the erythritol aqueous solution (Fig. 10(c)). However, 10% amount of talc was not enough for smoothed appearance. Thus, we increased it to 30%. The appearance of beads was smoothed and uniform coating was achieved when 30% talc was incorporated into the erythritol aqueous solution (Fig. 10(d)). This amount of talc reduced the impact of collisions during the coating and enhanced the spreading of the coating solution. In addition, when both powdered acacia and talc were used in the coating suspension, uniform coating was achieved and the coating layer was smoothed (Fig. 10(e)).

Fig. 11 shows the relationship between coating formulations and coating yield. When erythritol aqueous solution was used as the coating solution, the coating yield was extremely low, 57.4%. This would be due to insufficient bonding ability to the beads. Erythritol aqueous solution has a low adhesive ability to beads. The erythritol coating layer would thus be weak against impact and the coating layer would be removed from the coated beads. With incorporation of powdered acacia into the erythritol aqueous solution, the coating yield increased to 87.8%. Powdered acacia enhanced both the adhesion of the coating solution

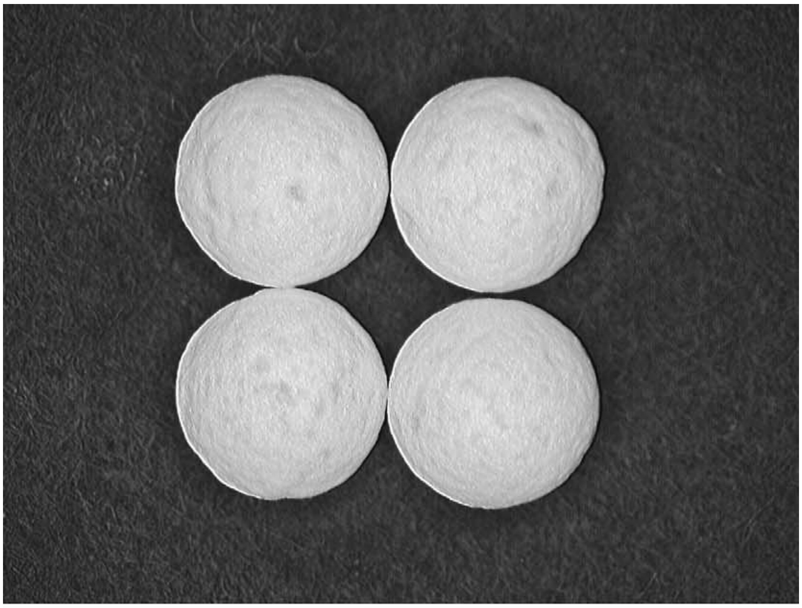


(a)

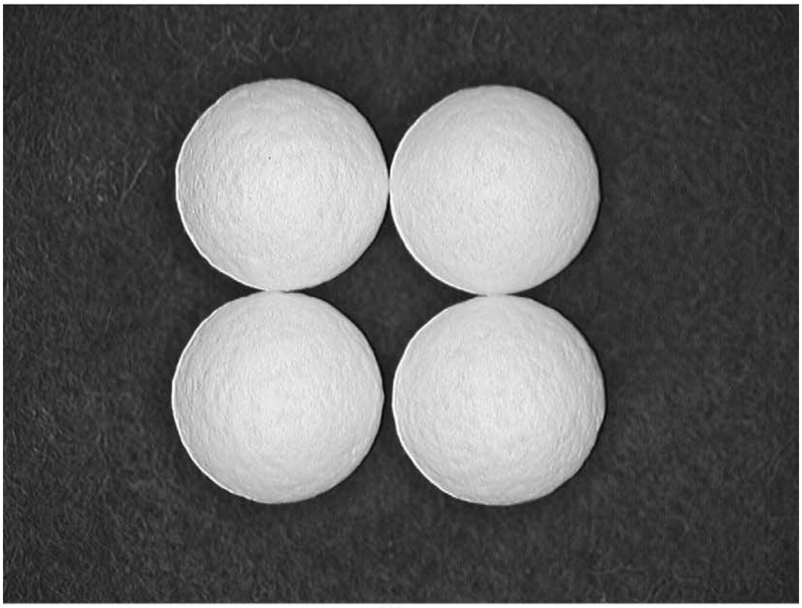


(b)

Fig. 10. Photographs. (a) Rp.1; (b) Rp.2; (c)Rp.3; (d) Rp.5; (e) Rp.7.



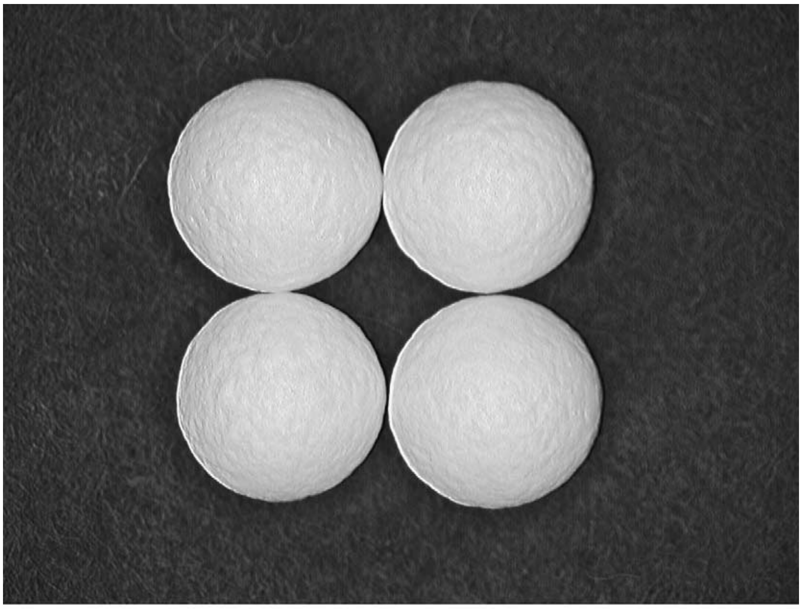
(c)



(d)

Fig. 10. (*Continued*).

to the beads and hardness of the coating layer during the coating. With incorporation of talc into the erythritol aqueous solution, the coating yield increased at the level of 20% talc and leveled off beyond the level of 20% talc. Talc reduced the impact of collisions and prevented the removal of the coating layer during the coating. However, this had a limited effect on the coating yield, which was below 80%. Incorporation of



(e)

Fig. 10. (*Continued*).

both powdered acacia and talc into the erythritol aqueous solution caused the coating yield to increase to 90.1%.

The thin-layer sugarless coating formulation should have both the binder, powdered acacia, and the glident, talc, besides erythritol because of the synergism among the binder, increasing adhesion and bonding of the coating suspension to the beads, and the glident, reducing the impact of collisions during the coating, in order to achieve high coating efficiency.

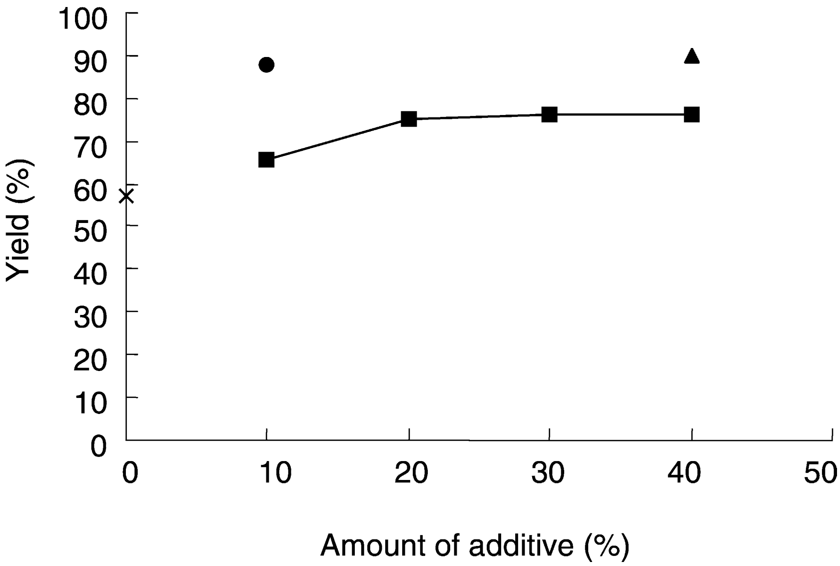


Fig. 11. Relationship between coating formulation and coating yield. (×) Rp.1; (●) Rp.2; (■) Rp.3–6; (▲) Rp.7.

4. Conclusions

We clarified the characteristics of erythritol compared with maltitol, mannitol, sorbitol, xylitol, and sucrose. Erythritol showed high water solubility, low hygroscopicity, instant crystallization, and low tackiness characteristics. We suggested that erythritol is a suitable coating material for a novel coating termed thin-layer sugarless coating compared with maltitol and sucrose because of its characteristics. We selected a continuous spray mist method for thin-layer sugarless coating due to formation of a thin sugarless coating layer and a simple method compared to conventional sugar-coating, which is performed with an intermittent spray method, a complex method requiring a sophisticated machine and expert skills. We demonstrated that erythritol reduced the coating time compared with maltitol and sucrose in the continuous spray mist method. The optimum basic thin-layer sugarless coating formulation was a combination of the binder, powdered acacia and the glident, talc, besides erythritol. We demonstrated that a uniform and smoothed coating layer could be achieved with high coating efficiency using the coating formulation. In the next study, we applied the thin-layer sugarless coating to the plain tablets containing drugs.

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