Granulation of Core Particles Suitable for Film Coating by Agitation Fluidized Bed I. Optimum Formulation for Core Particles and Development of a Novel Friability Test Method

Tomohiro HAMASHITA,*[,a] Yasuo NAKAGAWA,[a] Takao AKETO,[a] and Satoru WATANO[b]

[a] *Oral Solid Formulation Laboratory, Self Medication Laboratories, Taisho Pharmaceutical Co., Ltd.; 1–403 Yoshino-cho, Kita-ku, Saitama, Saitama 331–9530, Japan: and* [b] *Department of Chemical Engineering, Osaka Prefecture University; 1–1 Gakuen-cho, Naka-ku, Sakai, Osaka 599–8531, Japan.*

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To prepare powdered medicines without bitter taste, film coating is required to cover the surface of core particles. In this study, effect of formulation and operating conditions of agitation fluidized bed on the core particle properties was investigated. In order to prevent breakage of the core particles during coating process, which sometimes causes variation of drug dissolution rate, addition of maltose syrup powder during the formulation process of the core particles was investigated. Also, a method for friability test in which the core particles were subjected to strong impact was proposed to evaluate strength of the core particles. The friability of the core particles determined by this test method correlated well with the actual friability of the particles during the coating process. Based on this result, we confirmed this novel friability test method could predict the core particle endurance during the coating process.

Key words masking bitter taste; core particle; agitation fluidized bed granulation; friability test method

Adequate patient compliance is an important element of successful medical treatment, and one of the effective methods to improve the patient compliance is to improve the ingest ability of the medicine. Recently, selection of the pharmaceutical dosage forms and improvement of the ingest ability of medicines have begun to be taken into consideration during the design and development of solid medicinal forms for oral intake, from the viewpoint of improvement of the patients treatment compliance. Masking of the bitter taste of drugs is very important from the point of marketing view as well as improvement of the treatment compliance by the patients.[1,2] Powder form is one of the useful dosing forms of medicines for patients who cannot swallow tablets.[3]

Ibuprofen [(*RS*)-2-(4-isobutylphenyl) propanoic acid], a nonsteroidal anti-inflammatory drug, is widely used in the treatment of moderate pain and fever, because of its high efficacy and safety. However, it is necessary to mask the bitter taste since it has a strong bitter taste. Although several masking methods are available to mask the bitter taste for different formulations of ibuprofen, such as adjustment of pH for suspensions,[1] compression into chewable tablets with polymer coating of the granules for taste-masking,[1] and addition of flavors and sweeteners,[2] few methods have been reported to mask the bitter taste of ibuprofen in the powder form. Physical masking methods are widely applied to mask the bitter taste of drugs.[1—6] The film coating method, which is one of the physical masking methods, is considered to be suitable for masking bitter taste, because of its ability to control the dissolution rate of drugs in the mouth.

Several equipments with various features have been used for the film coating, especially a spouted bed with draft tube[7—11] for masking bitter taste of drugs. The spouted bed with draft tube has an advantage of good coating efficiency without causing agglomerations, because the jet of air prevents cohesion of the particles. However, it also has the disadvantage of breaking weak particles because of the vigorous jet of air. Therefore, it is necessary to prepare core particles that are not broken when they are subjected to the coating process by the spouted bed with draft tube. To manufacture drug containing core particles by fluidized bed granulation, lactose granules[12] or sugar beads[13] are used and they are layered with drugs. However, it requires long operation time to manufacture the core particles with containing high content of drug and those particles become large. When the size grows, it becomes uncomfortable for patients to ingest powder form medicine.

In this background, agitation fluidized bed granulation[14,15] has gathered a special interest as a suitable manufacturing method of core particles with a high content of drugs. In the manufacture of core particles, attention must be paid to several physical properties of particles for coating process, such as adequate mass median diameter, narrow size distribution, large apparent density, spherical shape, and low friability to allow the particles to endure the coating process. Since agitation fluidized bed granulation can impart compression and shear forces to particles, it is possible to produce core particles containing high content of drug with suitable physical properties for the coating process. In order to determine the optimal operating conditions and the optimal formulation of the core particles, the effects of the various operating conditions and several kinds of excipients with varying water solubility levels were investigated. As mentioned above, care must be taken to prevent breakage of the core particles during the coating process. It is thus important to evaluate the strength of the core particles. So far, several methods have been used to evaluate the strength of the core particles, such as the rotation test[14,15] and the compression test,[16] however these methods are complicated and time-consuming, and it would appear that there are few simple-and-easy-to-use test methods that can be used to evaluate and predict the friability of core particles during the coating process.

In this paper, the optimal operating conditions of the agitation fluidized bed granulation method and optimal formulation for the preparation of core particles that can be success-

* To whom correspondence should be addressed. e-mail: tomohiro.hamashita@po.rd.taisho.co.jp

Table 1. Formulation of Core Particles

	No. 1	No. 2	No. 3	No. 4	No. 5
Ibuprofen	0.393	0.399	0.399	0.399	0.399
Riboflavin	0.003	0.004	0.004	0.004	0.004
Light anhydrous silicic acid	0.044	0.044	0.044	0.044	0.044
Microcrystalline cellulose	0.175	0.177	0.177	0.177	0.177
Dibasic calcium phosphate		0.310			
Maltose syrup powder	0.306		0.310		
D-Mannitol				0.310	
Powdered sucrose					0.310
Hydroxypropylcellulose	0.079	0.066	0.066	0.066	0.066
Total	1.000	1.000	1.000	1.000	1.000

No. 1: HPC-L 7% solution, No. 2—No. 5: HPC-L 5% solution.

Table 2. Formulation of Coating Film

Materials	Weight ratio [—]
Hydroxypropylmethylcellulose	0.034
Talc	0.040
Ethylcellulose	0.026
Water	0.408
Ethyl alcohol	0.492
Total	1.000

fully subjected to the coating process has been reported. A novel friability testing method is also proposed to simply evaluate the strength of core particles.

Experimental

Samples Table 1 lists the formulation of core particles in case of determination of the optimal operating conditions and for investigation of the influence of excipients. Ibuprofen and riboflavin were used as the model drugs. Light anhydrous silicic acid (Nippon Aerosil Co., Ltd.) and microcrystalline cellulose (Asahi Kasei Chemicals Co., Ltd.) were used as common excipients, and dibasic calcium phosphate (Kyowa Chemical Industry Co., Ltd.), maltose syrup powder (Hayashibara Co., Ltd.), D-mannitol (Towa Chemical Industry Co., Ltd.) and powdered sucrose (Tokukura Co., Ltd.) were adopted as other excipients. Those powders were mixed and milled to about 20 μm diameter by a mill (Yariya Kikai Seisakusyo Co., Ltd.) before they were used for the granulation process. Aqueous hydroxypropylcellulose (HPC-L, Nippon Soda Co., Ltd.) solution was used as a binder. Table 2 shows the coating film formulation. During the coating process, talc (Asada milling Co., Ltd.) was added as a filler to the solution after ethyl cellulose (Ethocel standard 20 premium, The Dow Chemical Co., Ltd.) and hydroxypropylmethylcellulose (TC5-R, Shin-Etsu Chemical Co., Ltd.) was dissolved in water and ethyl alcohol solution, dispersed well in it, and used as a 10% solution.

Equipment and Conditions Figure 1 illustrates an experimental set-up. For wet granulation of core particles, an agitation fluidized bed (MP-01, Powrex Co., Ltd.) was used. Binder solution was sprayed through a binary nozzle located at the top of the vessel. The powder samples listed in Table 1 were granulated, and then dried under the conditions listed in Table 3. Obtained granules were sieved to have the size range under 850 μm.

For the film coating, a spouted bed with draft tube (GPCG-1, Powrex Co., Ltd.) was used. The coating film solution was sprayed through a binary nozzle located at the bottom of the vessel. The core particles that had made by agitation fluidized under the condition of agitator rotational speed at 5.0 rps and air flow velocity at 2.5 m/s. The large size particles over 500 μm diameter had coated thickly because of small surface area. Therefore for the detail investigation of the influences of excipients, granules had been sieved to have the size range under 500 μm were fed into the coater. The coating film listed in Table 2 were coated and dried under the conditions shown in Table 4. After being dried, the coated particles were again sieved to have the size range under 500 μm.

Size Distribution Based on the weight of granules on each sieve, mass median diameter and geometric standard deviation of granules were measured by using a sieve analysis (Robot shifter RPS-85, Seishin Enterprise Co., Ltd.).

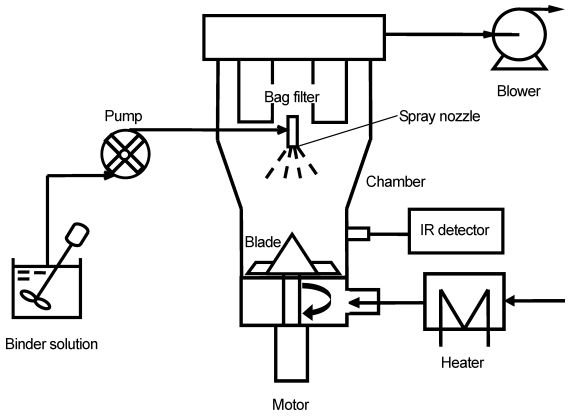

Fig. 1. Schematic Diagram of Experimental Set-Up

Table 3. Operating Conditions of Agitation Fluidized Bed

Vessel diameter [m]	0.16
Powder feed weight [kg]	0.4—0.5
Agitator rotational speed [rps]	3.3—6.7
Air flow velocity [m/s]	2.5—7.5
Air temperature [°C]	60
Binder solution feed rate [g/min]	10
Spray nozzle insert [i.d., mm]	1.0
Spray air flow quantity [Nl/min]	35
Spray air pressure [Pa]	1.5×10^5

Table 4. Operating Conditions of Spouted Bed with Draft Tube

Vessel diameter [m]	0.14
Powder feed weight [kg]	0.50
Air flow velocity [m/s]	0.75
Air temperature [°C]	60
Coating film solution feed rate [g/min]	10
Spray nozzle insert [i.d., mm]	1.0
Spray air flow quantity [Nl/min]	150
Spray air pressure [Pa]	5.0×10^5

Apparent Density The apparent density of granules was measured using a 100 ml volume cylinder (Tsutsui Rikagaku Kikai Co., Ltd.).

Shape Factor To evaluate granules shape, a shape factor ϕ was measured by means of an image analysis system.[17] Images of about 500 particles were obtained by using a digital microscope (Keyence Co., Ltd.) under ×25 magnification, and ϕ was calculated according to the following Eq. 1, using an image analysis software WinROOF (Mitani Co., Ltd.):

$$\phi=\frac{4\pi\Sigma S}{L^2} \quad (1)$$

Here, S and L indicate the projected core particle area and perimeter, respectively. The mean value of ϕ was used for the analysis.

Dissolution Test The dissolution pattern of ibuprofen from the core particles was investigated using a dissolution apparatus, RT-3 (Dainippon Seiki Co., Ltd.), according to a paddle method described in the Japanese Pharmacopoeia, Fifteenth Edition (JPXV) at 50 rpm and 37 °C.[18] Ibuprofen dissolves better in high pH medium because of its chemical property. To investigate the detail dissolution pattern of ibuprofen from the particles, JPXV dissolution medium No. 2 (pH 6.8) containing 0.01 w/v% polysorbate 80 was used. The sample weight is 0.45 g. Core particles include 0.18 g of ibuprofen and coated particles include 0.15 g of ibuprofen that is the maximum dosage of ibuprofen in the OTC drug in Japan now. At the appropriate time intervals, the test mediums were filtered through a membrane filter (F-25; pore size 50 μm, Dainippon Seiki Co., Ltd.). The concentration of the dissolved ibuprofen was determined spectrophotometrically at 225 nm by a HPLC (Separation Module; 2695, Dual Absorbance Detector; 2487 and Personal Computer, Waters Corporation). The column type is TSK-GEL ODS-80Ts (TOSOH CORPORATION, Column size is 4.6 mm×150 mm). Mobile phase consists of acetonitrile (0.629), water (0.32), methanol (0.05) and phosphoric acid (0.001). The speed of a moving fluid was about 1.0 ml/min.

Surface Observation The surface of the core particle was observed by a scanning electron microscopy (SEM; Hitachi High-Technologies Co., Ltd.).

Friability Test Method The friability of core particles was evaluated by two friability test methods. The core particles were sieved to have the size range of under 850 μm before the test method #1. Sieved core particles (5 g) were fed into a stainless steel cylindrical container (32 mm in diameter and 88 mm in height) with 2 stainless steel balls (20 mm in diameter, the density is 7930 kg/m^3), and the container was shaken 1500 times for 1 min. A mill (Mitsubishi Chemical Engineering Co., Ltd.) was used for this method. The friability of the core particles was calculated based on the increased fraction of fine particles smaller than 75 μm. The core particles were sieved to have the size range between 355 and 850 μm before the test method #2. Sieved core particles (5 g) were fed into an acrylic resin friabilator (300 mm in diameter and 50 mm in height) with 20 stainless steel balls (3 mm in diameter, the density is 7930 kg/m^3), and then rotated at 25 rpm for 60 min. A tablet friabilator (Kayagaki Irika Kogyo Co., Ltd.) was used for this method. The friability of the core particles was calculated based on the increased fraction of fine particles smaller than 180 μm.

Results and Discussion

Effect of the Operating Conditions of the Agitation Fluidized Bed on the Core Particle Properties Figures 2, 3 and 4 show the effect of the agitator rotational speed on granule mass median diameter, apparent density and shape factor, respectively. As seen in Figs. 2, 3 and 4, granule mass median diameter decreased, and apparent density and shape factor increased with an increase in agitator rotational speed. Granules are rolled and compressed and sheared by the agitator rotation. Therefore granules size became small and structure densified and shape became spherical. Especially under the condition of high agitator rotational speed, apparent density was increased greatly because granules received large energy from the agitator blade.

Figures 5, 6 and 7 show the effect of air flow velocity on granule mass median diameter, apparent density and shape factor, respectively. As seen in these figures, granule mass median diameter increased and apparent density and shape factor decreased with an increase in air flow velocity. Granules receive less effect from the agitator rotation when the air flow velocity increases. It was observed that granule movement in agitation fluidized bed looked like the one in a conventional fluidized bed when the agitator rotational speed was small and the air flow velocity was large. In these conditions, the agitator didn't affect well and granules were similar to the one of the conventional fluidized bed granulation. The effect specifically influenced granules apparent density. Even

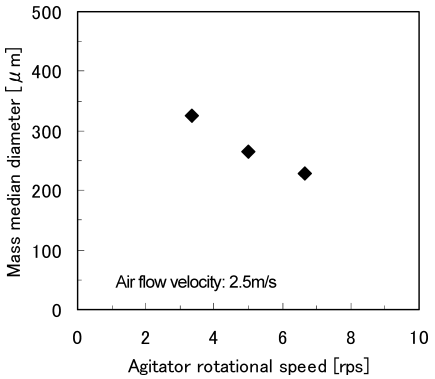

Fig. 2. Effect of Agitator Rotational Speed on Granule Mass Median Diameter

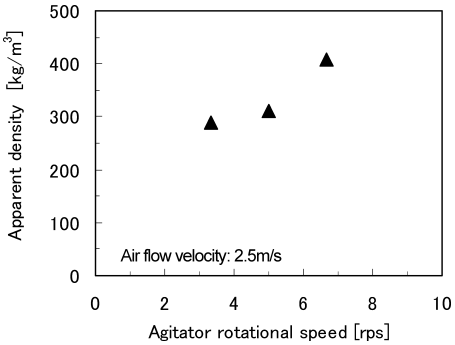

Fig. 3. Effect of Agitator Rotational Speed on Granule Apparent Density

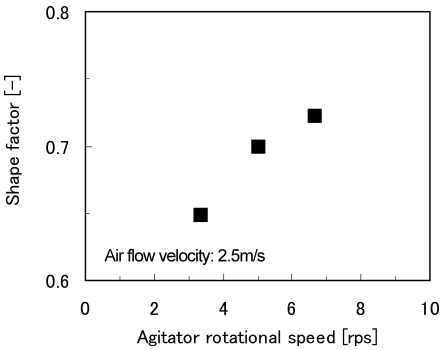

Fig. 4. Effect of Agitator Rotational Speed on Granule Shape Factor

in the middle of air flow velocity, apparent density quite decreased. For the coating process, conventional fluidized bed granules couldn't be coated well because these granules had small apparent density, rough shape, and high friability easy to be broken during the coating process. Core particles weren't broken under these operating conditions by agitator because of rich moisture in agirtator fluidized bed. Therefore, it is important for the core particles to receive effect from the agitator rotation.

Effects of Excipients on the Core Particle Properties To coat the core particles uniformly with a high efficiency of taste masking, the mass median diameter and size distribution were both important. Especially, a diameter of larger than 100 μm was the most suitable to prevent cohesion during the coating process and reduce the coating time, because the smaller particles have larger surface area. On the other hand, a diameter of under 500 μm was the most suitable to

improve the ingest ability of powdered medicines because large particles sometimes enter between teeth. Especially for senior, it is painful when large granules enter between artificial teeth.[19] Also, a narrow size distribution was suitable to achieve a high coating efficiency. Therefore, the mass median diameter criterion of 300 μm was adopted. In regard to the size distribution, the geometric standard deviation criterion of less than 2.0 was adopted.

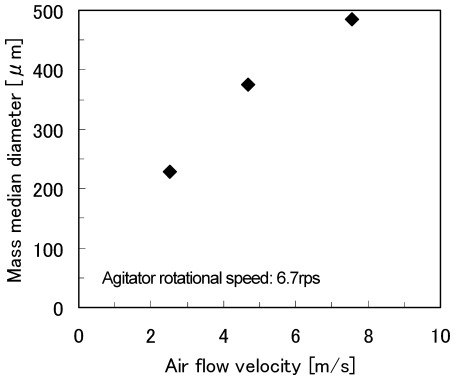

Fig. 5. Effect of Air Flow Velocity on Granule Mass Median Diameter

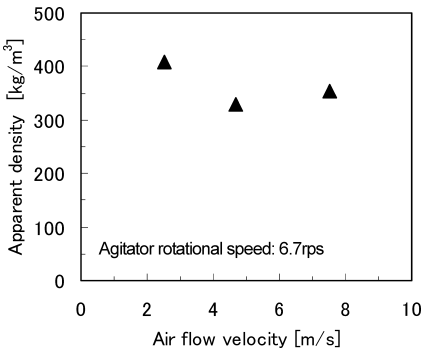

Fig. 6. Effect of Air Flow Velocity on Granule Apparent Density

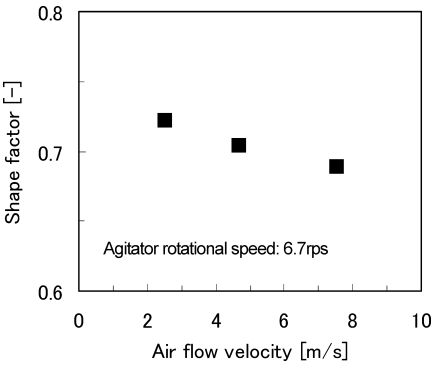

Fig. 7. Effect of Air Flow Velocity on Granule Shape Factor

Table 5 shows the mass median diameter of granules, geometric standard deviation of granules, ratio of coarse granules (larger than 850 μm), yield of the granules, apparent density of granules and shape factor of the granules, respectively. As mentioned above, the yield was determined as the percentage of particles having diameter between 106 and 500 μm. As seen in this table, the mass median diameter of granules were almost the same around 300 μm. There were no significant differences in this parameter among the four formulations. However, the yields of the four formulations were different; yields of the powdered sucrose formulation and D-mannitol formulation were lower than those of the other two formulations. Figure 8 illustrates the solubility of the four excipients in water at 20 °C.[20] In the powdered sucrose formulation, powdered sucrose was dissolved well because of its high solubility in water; leading to generate large granules and decreased yield. In the D-mannitol formulation, the fine particles in the agitation fluidized bed were attrited, which caused small particles and smaller yield because of the crystalline property of D-mannitol. As seen in this table, the apparent density and the shape factor of the granules were the highest when powdered sucrose was used as the excipient. The higher water solubility of the excipient caused greater dissolution, resulting in higher density and a spherical shape.

As mentioned above, the core particle properties differed among the four formulations. To investigate the dissolution rate of the drugs from these particles, all of them were coated with the same film material using a spouted bed with draft tube.

Figure 9 shows the dissolution rate of ibuprofen from the particles. As seen in this figure, the dissolution rates of the ibuprofen varied among the four formulations, even though

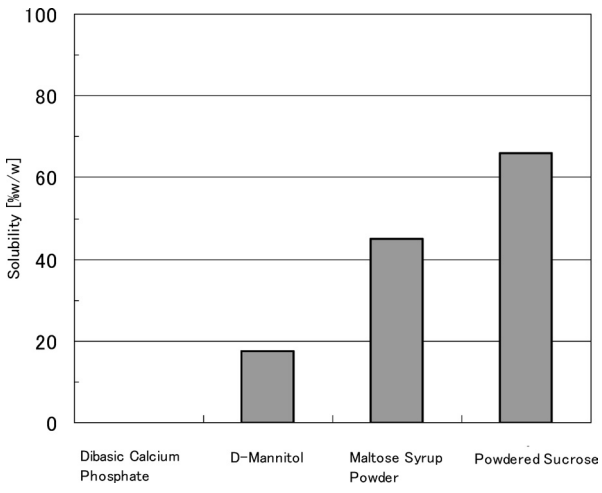

Fig. 8. Water Solubility of Four Excipients

Table 5. Granules Properties

	Dibasic calcium phosphate	D-Mannitol	Maltose syrup powder	Powdered sucrose
Mass median diameter of granules [μm]	273	295	305	298
Geometric standard deviation of granules [—]	1.71	1.90	1.72	1.70
Ratio of coarse granules [%]	0.10	1.02	0.84	14.85
Yield of granules [%]	98	73	93	75
Apparent density of granules [kg/m^3]	384	440	474	518
Shape factor of granules [—]	0.7139	0.7629	0.7807	0.7784

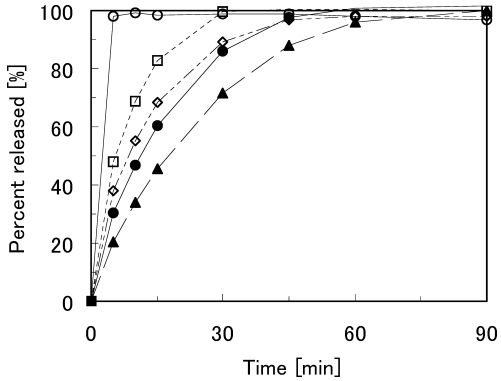

Fig. 9. Dissolution Rate of Ibuprofen from Core Particles

—●—, maltose syrup powder; —□—, dibasic calcium phosphate; —◇—, D-mannitol; —▲—, powdered sucrose; —○—, maltose syrup powder uncoated.

they were coated with the same film material. However, it appeared that masking of the bitter taste of the drug was unsatisfactory when the dissolution rate of the ibuprofen was too fast. By contrast, it seemed that the bioavailability of the drug was low when the dissolution rate of the drug was too slow. It is important to mask the bitter taste of medicines in the powder-form without lowering their bioavailability. Thus, it seemed that differences of the dissolution rate of a drug depended on the core particle structure. To investigate the differences in the core particle structure, the surfaces of the core particles were examined by a SEM analysis (Fig. 10). As seen in Figs. 10a and c, the surfaces of the core particles containing dibasic calcium phosphate and D-mannitol were rough, as dibasic calcium phosphate and D-mannitol did not dissolve well because of its low solubility. By contrast, as seen in Figs. 10e and g, the surfaces of the core particles containing maltose syrup powder and powdered sucrose were smooth, as both of these excipients are highly soluble in water and dissolved well. However, as seen in Figs. 10b, d, f and h, the surface seemed to become smooth due to the film coating. Ideally, all of the core particles should be coated uniformly for masking the bitter taste of the drug. As mentioned above, the surfaces of the coated particles were almost the same in all the formulations, however, fine particles were sometimes generated during the coating process. Uniform coating of fine particles is very difficult because of the large surface area and easy to be agglomerated. The thickness of the coated film decreased when fine particles were coated, because of the tremendous increase of the surface area of the particles. It also seemed that the amount of fine particles influenced the dissolution rate of the drug from the particles. Core particles that were easily broken into fine during the coating process were not sutiable for the satifactory masking, because it was difficult to control the dissolution rate of the drugs from the particles. It is thus important to evaluate the strengh of the core particles before they are subjected to the coating process. It would be useful to establish a friability test method for evaluating and predicting the endurance level of the core particles for the coating process. Therefore, a friability test method to evaluate the strength of the core particles is proposed.

Friability of Core Particles Figure 11 shows relationship between the friability of the core particles during the coating process and the friability of the particles as deter-

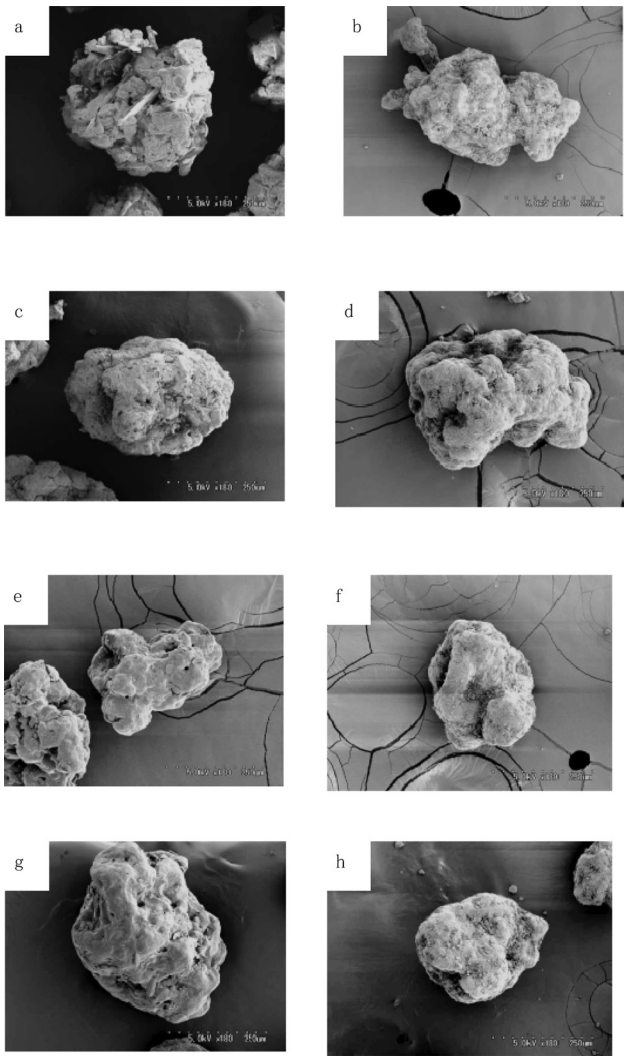

Fig. 10. Photographs of Particles

(a) Dibasic calcium phosphate uncoated, (b) dibasic calcium phosphate coated, (c) D-mannitol uncoated, (d) D-mannitol coated, (e) maltose syrup powder uncoated, (f) maltose syrup powder coated, (g) powdered sucrose uncoated, (h) powdered sucrose coated.

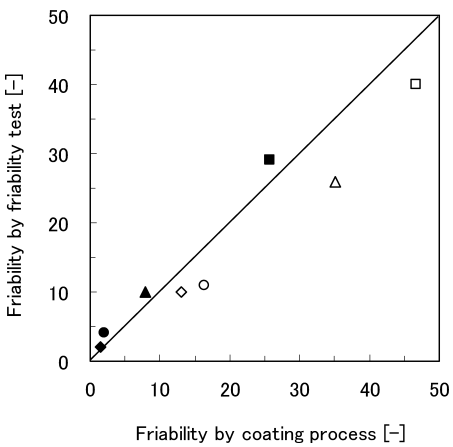

Fig. 11. Relationship between Core Particle Endurance during Coating Process and Particle Friability as Determined by Friability Test Methods #1, #2

■, dibasic calcium phosphate at method #1; ▲, D-mannitol at method #1; ●, maltose syrup powder at method #1; ◆, powdered sucrose at method #1; □, dibasic calcium phosphate at method #2; △, D-mannitol at method #2; ○, maltose syrup powder at method #2; ◇, powdered sucrose at method #2.

mined by the friability test methods #1, #2. The friability of the core particles during the coating process was calculated based on the increased fraction of fine particles smaller than 75 μm. As seen in this figure, the core particle friability as determined by the test methods #1 and #2 corresponded to the core particle endurance during the coating process. Comparison with conventional test method like #2, test method #1 is convenience to know the strength of the granules not only quickly but also extensively because the method needs only 1 min and uses the granules size range of under 850 μm. In addition, the friability as determined by the test method #1 was consistent with the endurance of the core particles during the coating process. As a result, by using maltose syrup powder or powdered sucrose, it is possible to manufacture the core particles that are not easily broken during the coating process. Moreover, the core particle endurance during the coating process could be predicted reliably by using our novel friability test.

Conclusions

Manufacturing of core particles containing bitter taste drugs by agitation fluidized bed granulation was studied. A novel friability test method was proposed in order to predict the endurance of core particles during the coating process. By using maltose syrup powder, core particles that were not broken down during the coating process could be produced. The friability as determined by our proposed method agreed well with the endurance of the core particles during the coating process. Based on these results, a novel friability test method that can predict the endurance of the core particles during the coating process is established.

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