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Manufacture of fine spherical granules by an extrusion/spheronization method

Hideyoshi Kanbe [a,b,*], Tetsuo Hayashi [a], Yoichi Onuki [a], Takashi Sonobe [b]

[a] *Central Research Laboratories, SSP Co., Ltd., Nanpeidai 1143, Narita-shi, Chiba 286-1511, Japan*
[b] *School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Shizuoka-shi, Shizuoka 422-8526, Japan*

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Abstract

Fine spherical granules of uniform particle size less than 500 μm are desired for easy handling in dispensing pharmacy. These fine particles have been produced by layering an active ingredient and excipients on a core; however, several technical problems have been difficult to overcome, e.g., the amount of layered ingredients is limited and often granules themselves agglomerate during the layering process and affect the quality of the finished product.

Here, we studied the feasibility of the manufacture of fine spherical granules by an extrusion/spheronization method. A screen with a pore size of 0.4 mm or smaller was used for extrusion, and reduction of the extrusion pressure at the screen was necessary to prevent the screen from breaking. In light of the reduction of the screen pressure, we found low substituted hydroxypropylcellulose (L-HPC), croscarmellose sodium (Ac-Di-Sol) and carmellose calcium (ECG®-505), markedly decreased the screen pressure. It is suggested that the high swelling property of these excipients is closely related to screen pressure reduction.

In the spheronization process, it was found that L-HPC gave the highest sphericity, while Ac-Di-Sol and ECG-505 were unsatisfactory.

It is concluded that L-HPC is the most appropriate excipient for the manufacture of fine spherical granules of less than 500 μm diameter by the extrusion/spheronization method.

Keywords: Extrusion/spheronization; Fine spherical granules; Pressure sensor; Extrusion pressure; Swelling property; Low substituted hydroxypropylcellulose (L-HPC)

1. Introduction

Film coating is one of the most frequently used methods for the controlled release of an active ingredient fabricated in a solid dosage form of large particle size, such as tablets and granules (Shimizu et al., 2003; Fukumoto, 1994; Nakayama, 1992; Yamada et al., 2002) on which it is relatively easy to form uniform film at the surface. It is difficult to prepare spherical granules of less than 500 μm with a smooth surface and uniform particle size distribution by conventional granulation. The objective of this study was to prepare spherical granules with uniform particle size distribution by extrusion/spheronization methods.

The small core of 100–300 μm has been developed, and there is a report to manufacture of fine spherical granules by the powder coating of a drug on a small core by the tumbling granulation method using a CF-granulator. However, the tumbling effect becomes insufficient when the core size decreases, and agglomeration of granules occurs, and products with consistent quality cannot be manufactured (Tanai and Inaba, 2002; Yamada et al., 2002). Moreover, it reports on manufacturing fine granules during the extrusion by the use of temperature senser (Misaki et al., 1995). Strengthening by laying a 5 mmØ × 1.0 mm t screen on a 0.4 mmØ × 0.4 mm t screen to enable extrusion has been investigated (Oosaka et al., 2002), but no effect can be expected in many cases because pressure on the screen increased due to a decrease in the ratio of holes. Moreover, a fine spherical granules with a high sphericity is not obtained. The most frequently used method is spray layering of a drug solution on the core of spherical carriers and subsequently coating them with film. However, when the drug content is high, use of fine granules is not prac-

* Corresponding author at: Central Research Laboratories, SSP Co., Ltd., Nanpeidai 1143, Narita-shi, Chiba 286-1511, Japan. Tel.: +81 476 27 1511; fax: +81 476 26 7948.
E-mail address: hideyoshi.kanbe@ssp.co.jp (H. Kanbe).

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tical because of limits in layering amounts due to particle size increase. In addition, it is a time consuming and costly process.

The present study intends to overcome those intrinsic disadvantages of the spray layering method by using more efficient extrusion/spheronization methods. For the manufacture of fine spherical granules of 500 μm or smaller in the spheronization process, a 0.4 mm or smaller pore size (Ø) screen has to be used in the extrusion process. However, the extrusion pressure must be increased when Ø is 0.4 mm or smaller due to increased resistance, and this increase deforms or breaks the screen. In order to reduce extrusion pressure, minimizing powder particle size and addition of lubricants such as macrogol, polyethylene glycol, poloxamer, and silicone oil were attempted (Misukami, 1993; Fukumori, 2002). However, this did little to help reduce the extrusion pressure and prevent mechanical break down of the screen.

In this study, we conducted formulation studies to determine optimal excipients that reduce extrusion pressure at the screen of pore size 0.4 mmØ (0.4 mm thickness, SUS316) in the extrusion process and that yield fine spherical granules in the spheronization process.

Addition of a large amount of L-HPC with swelling property decreased the extrusion pressure at the screen, and allowed extrusion through a 0.4 mmØ or smaller screen and easy production of fine spherical granules with high sphericity by the extrusion/spheronization methods.

2. Experimental

2.1. Materials

Diphenhydramine hydrochloride (milled product, Kongo Chemical Co., Ltd.) was of JP XIV grade. Low substituted hydroxypropylcellulose LH-31 (L-HPC, Sin-Etsu Chemical Co., Ltd.), lactose (200M, DMVCo., Ltd.), purified sucrose (powder sugar, Nissin Sugar Manufacturing Co., Ltd.), glucose monohydrate (#700, Nippon Shokuhin Kako Co., Ltd.), D-mannitol (D-Mannit P, Towakasei Co., Ltd.), carmellose calcium (ECG®-505, Gotoku Chemical Co., Ltd.), corn starch (corn starch, San-Ei Sucrocheimcal Co., Ltd.), and microcrystalline cellulose (Avicel®PH101, Asahi Kasei Co., Ltd.), were all of JP XIV grade. Croscarmellose sodium (Ac-Di-Sol, Asahi Kasei Co., Ltd.) was of USP grade.

2.2. Detection of extrusion pressure at the screen

As shown in Fig. 1 (Fuji Paudal, 2001), a pressure sensor was attached to the extruder screen, and extrusion was performed. The output of the pressure and electric current value during extrusion was A/D-translated and recorded (20 Hz).

Measurement instruments

Pressure sensor: VPRF-50K ⟨VALCOM⟩ 0–5 MPa.
A/D translator: NR-100 ⟨KEYENC⟩.
Monitor software: WAVE SHOT ⟨KEYENC⟩.
Extruder: Twin Dome Gran TDG-80type ⟨Fuji Paudal⟩.
0.4 mmØ × 0.4 mm thickness (t) screen (SUS 316).

2.3. Influence of the amount of kneading liquid on the extrusion pressure

Six hundred grams of the excipients (L-HPC, Ac-Di-Sol, or ECG-505) were mixed with 600–2160 g of the kneading liquid, and kneaded for 1 min by a vertical granulator VG-25. This kneaded mass was subjected to extrusion using a 0.4 mmØ screen-attached extruder [80 rpm].

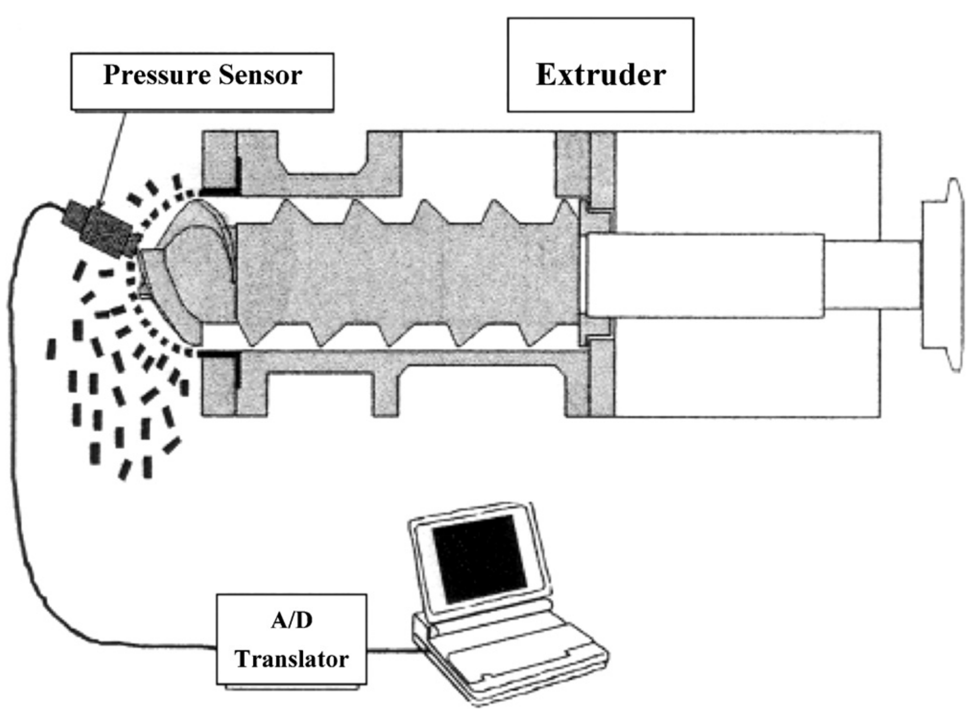

Fig. 1. Detection system of the extrusion pressure.

Table 1
Required kneading liquid volume in the extrusion/spheronization method for excipients

	Excipients								
	Lactose 1000 g	Purified sucrose 1000 g	Glucose mono hydrate 1000 g	D-mannitol 1000 g	ECG-505 1000 g	Ac-Di-Sol 1000 g	L-HPC 1000 g	corn starch 1000 g	Avicel PH101 1000 g
Required kneading liquid 15% ethanol/water (g)	75	50	150	50	3000	3000	3000	300	600

After extruding variety of excipients, it was found that the swelling property of excipients was one of the key factors to reduce the resistance at the screen outlet.

2.4. Preparation of fine spherical granules

The ingredients shown in Tables 1 and 5 were mixed using a vertical granulator VG-25, respectively, as shown in Fig. 2. Kneading liquid (15% ethanol/water) was added, and the mixture was kneaded for 1 min. This kneaded mass was subjected to extrusion by an extruder with a screen pore size of 0.4 mmØ [80 rpm], and spheronized by a marumerizer [500 rpm, 10 min]. The granules were then dried in a fluidized bed granulator (inlet temperature: 80 °C), and sieved using a JIS 16 Mesh sieve (1000 μm).

2.5. Rate of extrusion

The rate of extrusion (ability of extrusion) was calculated by the equation:

$$R_E = \frac{W_E}{T}$$

where R_E is the rate of extrusion, W_E represents the amount of extrudate and T is the time of extrusion.

2.6. Physical properties of granules

(1) Particle size distribution: The sample (10 g) was weighed and vibrated for 3 min and subjected to particle size determination with a micro electromagnetic vibrating siever M-2 (Tsutsui Rikagaku Kikai Co., Ltd.). JIS 20 Mesh (840 μm), 30 Mesh (500 μm), 42 Mesh (355 μm), 60 Mesh (250 μm) and 200 Mesh (74 μm) sieves were used for the determination.

(2) Yield of fine granules (500–74 μm): The sample (30 g) was weighed and vibrated for 3 min and subjected to yield determination of fine granules by a micro electromagnetic vibrating siever M-2 (Tsutsui Rikagaku Kikai Co., Ltd.). JIS 30 Mesh (500 μm), 200 Mesh (74 μm) sieves were used for the determination. The yield of fine granules (500–74 μm) was defined as follows:

$$Y = \left(\frac{Y_{500\text{–}74\,\mu\text{m}}}{Y_{\text{Total}}}\right) \times 100$$

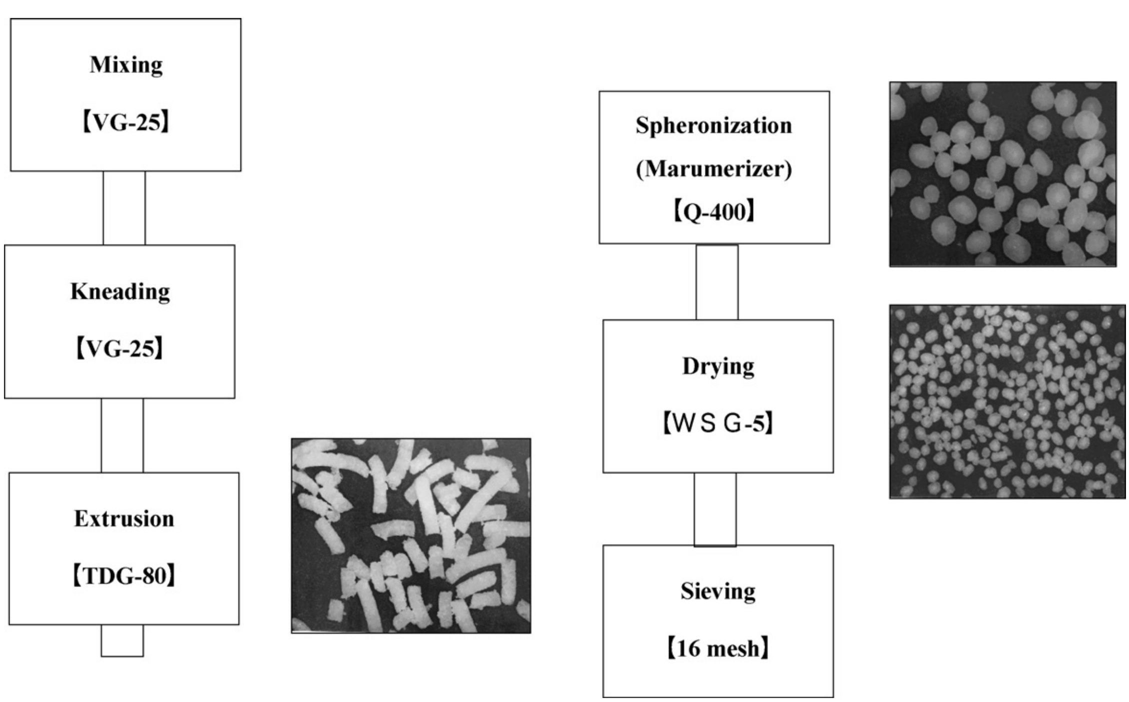

Fig. 2. Production process flow chart.

Table 2
Extrusion pressure, rate of extrusion, and electric current value in the extrusion process of excipients ($n = 4$)

	Excipients								
	Lactose	Purified sucrose	Glucose monohydrate	D-mannitol	ECG-505	Ac-Di-Sol	L-HPC	corn starch	Avicel PH101
Extrusion pressure (MPa)	1.09 ± 0.23	0.80 ± 0.16	1.02 ± 0.18	0.80 ± 0.12	0.42 ± 0.08	0.23 ± 0.06	0.34 ± 0.06	0.51 ± 0.18	3.00 ± 0.52
Rate of extrusion (R_E) (g/s)	30.6 ± 2.2	4.7 ± 1.0	2.3 ± 0.8	3.4 ± 1.2	11.2 ± 1.8	12.0 ± 1.2	38.9 ± 1.3	5.0 ± 0.8	[a]
Electric current value (A)	5.5 ± 0.6	5.5 ± 0.5	4.8 ± 0.4	4.8 ± 0.6	5.4 ± 0.4	5.5 ± 0.2	4.8 ± 0.2	4.8 ± 0.4	9.0 ± 1.00

Values are average ± S.D.
[a] The extrusion pressure was markedly high and extrusion was practically difficult.

where Y is the yield of fine granules (500–74 μm), $Y_{500\text{–}74\mu m}$ the amount of granule fraction 500–74 μm (30–200 Mesh), Y_{Total} is the total amount of sample (30 g).

(3) Sphericity: The length and breadth of spherical granules were measured using an imaging processing system (LA-555, PI-AS Inc.), and the sphericity of the particles was obtained from the breadth/length ratio.

(4) Apparent specific gravity: Apparent specific gravity of granules was measured using a Kawakita bulk density measurement instrument IH-2000 (Seisin Enterprise Co., Ltd.).

(5) Degree of swelling: Granules (10 cm^3, initial volume: V_0) were put into a measuring cylinder (100 cm^3), suspended with 15% ethanol/water and adjusted to 100 cm^3. The solution was kept standing for 60 min, and the volume of the granule layer (V_{60}) was measured. The degree of swelling (S) of the granules was calculated by the equation:

$$S = \left[\frac{V_{60} - V_0}{V_0}\right] \times 100$$

3. Results and discussion

3.1. Extrusion pressure and spheronization characteristics of excipients

In Tables 2 and 3, operational parameters and physical characteristics of fine granules made of excipients alone by the extrusion/spheronization method are shown, respectively. In the extrusion process, the extrusion pressure of Ac-Di-Sol, ECG-505 and L-HPC were below 0.50 and lower than other excipients, though the electric current values for all excipients were within small fluctuation range of 4.8–5.5 except Avicel PH101. As shown in Table 3, particle distribution of L-HPC was very sharp, i.e., 66.2% was within 355–500 μm. Yield was 97.3%.

In the spheronization process, it was found that L-HPC gave the highest sphericity of 0.868, while those of Ac-Di-Sol and ECG-505 were unsatisfactorily at 0.687 and 0.744, respectively. L-HPC contains a 3.5% water-soluble component (Shin-Etsu, 1991) and it apparently gives a sufficient plastic deforming property in the spheronization process by which the strength of the

Table 3
Physical characteristics of fine spherical granules of excipients prepared by the extrusion/spheronization method

	Excipients								
	Lactose	Purified sucrose	Glucose monohydrate	D-mannitol	ECG-505	Ac-Di-Sol	L-HPC	Com starch	Avicel PH101
Particle size distribution (%)									
<840 μm	17.9	3.8	45.3	15.4	11.3	2.4	0.8	NA	NA
840–500 μm	2.3	5.5	29.1	4.9	22.1	5.8	1.8	NA	NA
500–355 μm	11.8	46.4	20.2	31.6	38.5	7.8	66.2	NA	NA
355–250 μm	15.5	20.3	3.4	13.2	20.9	35.7	29.3	NA	NA
250–74 μm	28.0	9.0	0.9	21.4	6.3	25.5	1.8	NA	NA
>74 μm	24.5	15.0	1.1	13.5	0.9	22.8	0.1	NA	NA
Yield of fine granules (500–74 μm) (Y, %)	55.3	75.7	24.5	66.2	65.7	69.0	97.3	NA	NA
Degree of sphericity (breadth/length) (average ± S.D.)	0.823 ± 0.144	0.623 ± 0.175	0.766 ± 0.136	0.749 ± 0.197	0.744 ± 0.175	0.687 ± 0.184	0.868 ± 0.100	NA	NA

NA, not available.

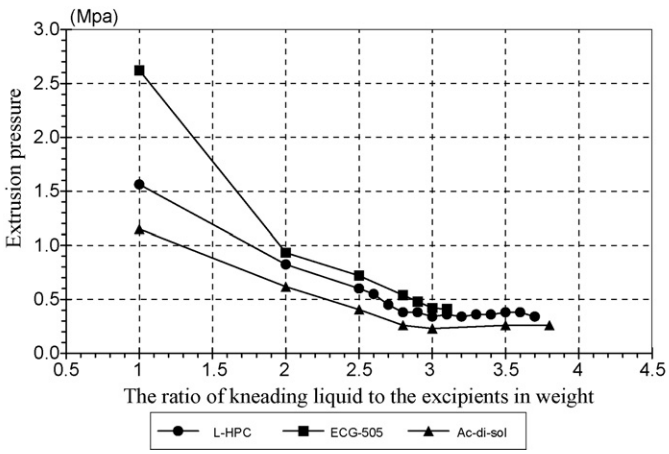

Fig. 3. Extrusion pressure as a function of the ratio of the kneading liquid to excipients in weight.

granules and yield of fine granules (500–74 μm) increase. It is important that, in the spheronization process, the plastic deforming property of an excipient is the major factor to acquire a high degree of sphericity.

Fig. 3 shows the extrusion pressure as a function of the ratio of kneading liquid to excipients in weight. The extrusion pressure significantly decreased by kneading liquid addition, and leveled off for the ratio 2.5 or higher. These results strongly suggest that the decrease in the extrusion pressure due to addition of excipients is related to their swelling property and that excipients with a high swelling property are the key factors for the screen pressure reduction in the extrusion process. The extrusion pressure of the excipients alone was low because of their high swelling property. Particularly, as shown in Table 2, the rate of extrusion of L-HPC was also about 3 times higher than those of ECG-505 and Ac-Di-Sol.

Table 4
Swelling of the disintegrators ($n = 3$)

	Degree of swelling (retention water, %)[a]
L-HPC	635.1 ± 5.6
ECG-505	369.2 ± 4.2
Ac-Di-Sol	487.3 ± 3.1
Avicel PH101	140.5 ± 6.8

Each value presents the mean ± S.D. ($n = 3$).
[a] The measured value that used keading liquid (15% ethanol/water).

As shown in Table 4, L-HPC swells 635% of its volume in the kneading liquid, and, therefore, retains much larger volume of the liquid than ECG-505, Ac-Di-Sol and Avicel PH101. At the extrusion process, the extrusion pressure will squeeze the liquid out of the particles that results in reduction of resistance and the particle size at the extrusion screen outlet.

When Avicel PH101 alone was extruded, the extrusion pressure was markedly high, and extrusion was practically difficult. For corn starch, it was neither sufficiently swellable nor bindable.

3.2. Manufacture of diphenhydramine hydrochloride fine spherical granules

3.2.1. Effect of L-HPC on extrusion pressure

To manufacture fine spherical granules with a particle size below 500 μm containing 10% diphenhydramine hydrochloride, the amount of L-HPC incorporated was changed, and the extrusion pressure at the screen was measured. The screened formulations are listed in Table 5.

As shown in Fig. 4, the pressure decreased with the increase in the amount of L-HPC, and the value was kept constant when the L-HPC content was about 30% or higher. As shown in Table 6,

Table 5
Formulations of diphenhydramine hydrochloride fine spherical granules and the required amount of kneading liquid in the extrusion/spheronization methods

	Amount of L-HPC LH31 (%)								
	10	20	30	40	50	60	70	80	90
Diphenhydramine hydrochloride (g)	100	100	100	100	100	100	100	100	100
L-HPC (LH31) (g)	100	200	300	400	500	600	700	800	900
Lactose 200 M (g)	800	700	600	500	400	300	200	100	–
Total (g)	1000	1000	1000	1000	1000	1000	1000	1000	1000
Required kneading liquid content (%)	28.6	41.7	50.0	56.5	61.5	65.5	68.8	69.4	74.4

Table 6
Effect of L-HPC on extrusion pressure, rate of extrusion and electric current value in the extrusion process of diphenhydramine hydrochloride fine spherical granules ($n = 4$)

	Amount of L-HPC (%)								
	10	20	30	40	50	60	70	80	90
Extrusion pressure (MPa)	1.51 ± 0.27	0.81 ± 0.18	0.61 ± 0.10	0.61 ± 0.04	0.49 ± 0.04	0.41 ± 0.03	0.32 ± 0.04	0.35 ± 0.05	0.40 ± 0.05
Rate of extrusion (R_E) (g/s)	16.7 ± 2.1	25.6 ± 1.4	40.0 ± 1.2	55.0 ± 1.1	53.3 ± 0.9	44.4 ± 1.0	45.9 ± 0.7	43.5 ± 0.6	46.7 ± 0.6
Electric current value (A)	6.3 ± 0.8	5.4 ± 0.5	5.5 ± 0.1	5.1 ± 0.1	5.5 ± 0.1	5.1 ± 0.1	5.4 ± 0.1	5.4 ± 0.1	5.6 ± 0.1

Values are in average ± S.D.

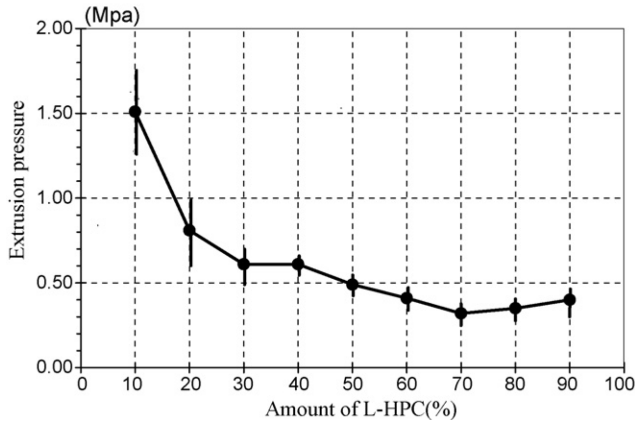

Fig. 4. Extrusion pressure as a function of incorporated L-HPC in diphenylhydramine hydrochloride fine spherical granules.

the rate of extrusion significantly increased when the amount of L-HPC increased to 30% or larger. And the electric current of the extruder (A: amperes) showed a similar tendency to the extrusion pressure, but the differences were smaller than those in the extrusion pressure (MPa), suggesting that the extrusion pressure is more useful as a scale of extrusion state for evaluation of small differences.

It is assumed that the decrease in the extrusion pressure due to addition of L-HPC is closely related to the swelling property of L-HPC. As shown in Table 5, the required kneading liquid content in the kneaded mass was 28.6% at 10% L-PHC; and increased to 41.7% at 20% L-HPC and 50% at 30% L-HPC, respectively, which clearly indicates that swelling has decreased the extrusion pressure.

3.2.2. *Effect of L-HPC on sphericity*

Table 7 shows the equivalent diameter, length, breadth, and breadth/length obtained by image processing of diphenhydramine hydrochloride fine spherical granules of 10–90% L-HPC. Compared to addition of 10–40% L-HPC, when 50% or more L-HPC was added in extrusion/spheronization, the breadth/length more than 0.8 and close to 1, showing that spherical granules meeting the fine granule specifications with ideal sphericity for coating were prepared (Tanai and Inaba, 2002).

3.2.3. *Physical properties of diphenhydramine hydrochloride fine granules*

Table 8 shows the physical characteristics of the fine granules. In the particle size distribution, addition of 20% or more L-HPC provided fine spherical granules with sharp particle size distribution, meeting the fine granule specification. When 20–50% and 80–90% L-HPC were added, 30–42 Mesh (500–355 μm) and 42–60 Mesh (350–250 μm) fine spherical granules were mainly produced, respectively.

For extrusion/spheronization, addition of Avicel PH101 is a practical method to manufacture spherical granules with high sphericity (Alvarez et al., 2004; Heng, 2001; Nighttime et al., 2005; Zgarcia and Ghaly, 2001), but Avicel PH101 generated higher resistance at the screen of pore size 0.4 mmØ during extrusion. Thus, production of 500 μm or smaller fine spheri-

Table 7
Effect of L-HPC on sphericity of diphenhydramine hydrochloride fine spherical granules

	Amout of L-HPC (%)								
	10	20	30	40	50	60	70	80	90
Equivalent diameter (μm)	587.1 ± 67.8	531.9 ± 84.5	525.6 ± 49.5	480.2 ± 39.5	433.1 ± 33.9	442 ± 31.1	441.6 ± 29.8	435.1 ± 28.7	431.5 ± 34.4
Length (μm)	708.5 ± 119.2	613.8 ± 138.2	525.6 ± 89.5	561.7 ± 81.1	483.7 ± 53.4	480.4 ± 49.2	471.1 ± 39.9	473 ± .940.4	460.5 ± 37.7
Breadth (μm)	476.5 ± 45.1	463.4 ± 63.4	427.4 ± 89.9	409 ± 30.1	391.1 ± 33.7	406.7 ± 30.1	413.3 ± 30.5	400.2 ± 36.4	406.5 ± 43.3
Breadth/length	0.687 ± 0.103	0.778 ± 0.137	0.684 ± 0.116	0.742 ± 0.110	0.817 ± 0.099	0.854 ± 0.095	0.881 ± 0.070	0.849 ± 0.008	0.885 ± 0.088

Values are in average ± S.D.

Table 8
Physical characteristics of diphenhydramine hydrochloride fine spherical granules

	Amount of L-HPC LH-31 (%)								
	10	20	30	40	50	60	70	80	90
Apparent density (g/ml)	0.65	0.63	0.63	0.65	0.68	0.69	0.70	0.72	0.75
Angle of repose (°)	32	32	32	32	32	32	32	32	32
Particle size distribution (%)		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
<840 μm	0.0	3.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
840–500 μm	16.9	77.9	86.8	73.2	70.0	52.0	42.5	18.2	25.8
500–355 μm	68.2	16.8	8.5	22.1	27.5	43.1	53.9	76.0	70.4
355–250 μm	12.8	1.9	4.5	4.6	2.5	4.9	3.6	5.8	3.8
250–74 μm	1.3	0.4	0.2	0.1	0.0	0.0	0.0	0.0	0.0
Swelling (average ± S.D., %)	88 ± 2.9	98 ± 2.9	108 ± 2.9	122 ± 2.9	180 ± 5.0	233 ± 5.8	243 ± 5.8	312 ± 7.6	382 ± 7.6

cal granules with high sphericity using Avicel PH101 was not practically feasible.

For extrusion/spheronization, addition of Avicel PH101 gives granules with high sphericity that increases with an increase in the amount of Avicel PH101, but at the same time the extrusion pressure also increases due to increase of resistance at the extrusion screen outlet. To manufacture fine spherical granules by the extrusion/spheronization method, a 0.4 mmØ or smaller screen has to be used. Thus, production of 500 μm or smaller fine spherical granules with high sphericity using Avicel PH101 is practically difficult.

Addition of L-HPC with high swelling property instead of Avicel PH101 decreased the resistance loaded at the screen during extrusion and enabled extrusion using a 0.4 mmØ or smaller screen. It allowed simple production of fine spherical granules with high sphericity that meets specifications in the spheronization process. In addition, the 3–4 times larger volume of kneading liquid added to L-HPC was removed in the drying process, which reduced the volume of the extruded granules and provided smaller spherical granules. When a large amount of L-HPC was added (generally 80% or more), utilization of the drying-induced shrinking phenomenon enabled simple production of fine spherical granules meeting the fine granule specifications by extrusion using a 0.5 or 0.6 mmØ screen.

Table 8 shows, the dried spherical granules retain the swelling property of L-HPC, allowing easy production of fine spherical granules that has swelling properties, increase the volume about 1.8–4.8 times.

4. Conclusions

To produce spherical granules with high sphericity by extrusion/spheronization method, addition of very extrusive Avicel PH101 is the usual method. However, due to increased resistance load at the screen, extrusion through a 0.4 mmØ or smaller screen was difficult and production of fine spherical granules with high sphericity meeting the fine granule specifications failed.

As described above, addition of a large amount of L-HPC decreased the resistance loaded at the screen during extrusion, and allowed production of fine granules with particle size below 500 μm and high sphericity in the spheronization process using a marumerizer.

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