The Application of Pharmacoat to Granulation in a Fluidizing Column

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Introduction

Pharmacoat (Hydroxypropyl methycellulose) is a material commonly used for tablet coating. In the present study, we investigated how to use this material as a binder of granulation in a fluidizing column.

Materials and Method

Three viscosity types of Pharmacoat(603, 606 and 615) were used in the study. The powder mixture for granulation was composed of lactose and corn starch used with or without drugs Paracetamol and Ascorbic acid. The drug content in the mixture was 30% and the ratio of lactose and corn starch was 7:3. The mixture was granulated using a FLOWCOATER FLO-5 (Freund Ind.)

Two systems for applying the binder were tested; one was to spray the binder solution onto the powder mixture (Solution Spray System) and the other was done by blending the binder with the mixture first and then water spraying it (Powder Blend System).

The granule products were evaluated by measuring the particle size distribution, the mean particle size(D50), the yield and others.

Results and Discussion

In the "Solution Spray System", the particle size distribution was more narrow, the bulk density was lower and the yield was higher than in the "Powder Blend System". In the "Solution Spray System", D50 was increased as the viscosity type of Pharmacoat increased. The higher contentof the binder also caused the increase of D50 in this system. In the "Powder Blend System", only the type 603 gave the same pattern as the "Solution Spray System". In the other two types, the D50 was not increased as the binder content increased. This may be due to the different hydration velocity of the binder; with high viscosity type, the hydration velocity is slow and the binding strength is not higher than the low viscosity type. Therefore, in the "Powder Blend System", the mean particle size can be controlled only by the content of Pharmacoat-603.

In the granulation of drug-containing mixture, similar results were observed. But it was necessary to change the operating condition according to the solubility of the drug.

In conclusion, Pharmacoat can be used as a binder of granulation in a fluidizing column

as well as a coating material of tablets. The properties of a granular product are different with each of the methods of applying thebinder.

Contents of the presentation

(Fig. 1)
The chemical structure of Pharmacoat (Hydroxypropy methylcellulose) is shown.

(Table 1)
The viscosity types of Pharmacoat used in the study are shown. The viscosityof an aqueous solution (2%) was measured by an Ubbellohde Viscomerer at 20℃.

(Fig. 2)
The granulation machine employed in the study is shown. The machine was a FLOWCOATER FLO-5 (Fruend Ind.).

(Table 2)
The test items and the test methods for a granular product are shown. The particle size distribution was measured by sieving the granules using a Ro-Tap shaker (Shaking for 5 minutes). The mean particle size (D50) was calculated according to the particle size of 75 – 500 μ m. The granule strength represented as an increase of less than 75 μ m in the shaking time of 5 minutes to 20 minutes. The moisture content was calculated from the loss on drying at 105 ℃ for 2 hours.

(Fig. 3)
The scheme of two systems having different ways of adding of the binder is shown. The "Solution Spray System" is to spray the binder solution on the fluidizing powder mixture. The "Powder Blend System" is to spray water on the powder mixture containing the binder.

(Table 3)
The formulation of a "non-drug containing mixture" in the solution spray system is shown. The mixture consisted of lactose and corn starch (7:3).

(Table 4)
The operating condition of the granulation of the non-drug containing mixture by the "Solution Spray System" is shown.

(Fig. 4)
The particle size distribution of the non-drug containing granules using the"Solution Spray

System" with various viscosity types of pharmacoat is shown. The slope represents the range of the distribution. There was not much difference in the three viscosity types of Pharmacoat. The yield was more than 90%.

(Table 5)

The D50 of the products are shown. As the viscosity value of Pharmacoat was higher, D50 was increased.

(Fig. 5)

The effect of the binder content on D50 is shown. As the content of Pharmacoat was increased, a higher D50 was observed.

(Fig. 6)

A brief procedure of the two systems having different ways of adding the binder is shown. The following results are of the "Powder Blend System" (right side).

(Table 6)

The formulation of a non-drug containing mixtue using the "Powder Blend System" is shown. 4 - 6% of Pharmacoat was blended with a lactose corn starch mixture.

(Table 7)

The operating condition of the granulation of the non-drug containing mixture by the "Powder Blend System" is shown. The air flow velocity, gun height and spray velocity were controlled at lower levels than in the "Solution Spray System" to obtain a better product.

(Fig. 7)

The particle size distribution of the non-drug containing granules using the "Powder Blend System" with various viscosity types of Pharmacoat is shown. Not so much difference was observed among the three types. The yield was more than 80%.

(Fig. 8)

The difference in the particle size distribution of the product between the "Solution Spray System" and the "Powder Blend System" is shown. The angle of the "Solution Spray System" was higher than that of the "Powder Blend System", which means that the distribution is more narrow with the "Solution Spray System".

(Table 8)

The D50 of the non-drug containing granules using the "Powder Blend System" is shown. The relationships between the viscosity types and D50 were different from that of the "Solution

Spray System"

(Fig. 9)

The effect of the binder content on D50 using the "Powder Blend System" is shown. With Pharmacoat-603, the relationship was the same with the "Solution Sparay System". With Pharmacoat-606 and -615, D50 did not increase as the content of the Pharmacoat was increased.

(Table 9)

A comparison of the granule strength and bulk density between the two systems is shown. There was no difference in the granule strength of the two systems. The bulk density of the granules by the "Powder Blend System" was higher than that of the "Solution Spray System".

(Fig. 10)

The scheme on the mechanism of the granulation by the two systems is shown. In the "Solution Sparay System", the nuclei are formed by the binder, then another particles of the binder make coalescence of nuclei. In the "Powder Blend System", water agglomerates the particles of the binder and other ingredients, then the binder dissolves in the water, causing the particles to adhere to each other.

(Fig. 11)

The microscopic views of the granules (100～140 mesh) as a result of the "Solution Spray System" and the "Powder Blend System" are shown. The particles by the "Powder Blend System" were more compact than those by the "Solution Spray System".

(Fig. 12)

The microscopic views of granules (200 mesh) as a result of the two system are shown. In the "Powder Blend System", many particles of ungranulated lactose and corn starch were observed.

(Table 10)

The two drugs used in the drug-containing granulation are shown. Paracetamol and ascorbic acid were used as a hydrophobic and a hydrophilic drug respectively.

(Table 11)

The formulation of the drug-containing mixture using the "Solution Spray System" is shown. The ratio of loctose and corn starch was 7 : 3 and the content of the drug in the mixture was 30 %.

(Table 12)

The operating condition of the drug-containing mixture by the "Solution Spray System" is shown. In the granulation of the paracetamol containing mixture, the air flow velocity and spray velocity were controlled at lower levels than in the non-drug containing granulation because the drug powder has static electricity. In the granulation of the mixture containing ascorbic acid, which has high solubility in water, the spray velocity was controlled at a lower level than in the non-drug containing granulation.

(Fig. 13)

The fluctuation of the moisture content in the granules during granulation under the condition of Table 12 is shown. The moisture content during spraying (until the peak) was controlled by the spray velocity.

(Fig. 14)

The particle size distribution of the drug-containing granules using the "Solution Spray System" is shown. The yield was more than 90%.

(Table 13)

The D50 of the drug-containing granules using the "Solution Spray System" is shown. Though the D50 was different among the three formulations, the relationship between D50 and the viscosity types of Pharmacoat was the same.

(Table 14)

The formulation of the drug-containing mixture by the "Powder Blend System" is shown. The amount of water spraying was different with the two drugs according to their difference in solubility in water.

(Table 15)

The operating condition of the drug-containing mixture using the "Powder Blend System" is shown. The gun height and spray velocity were changed in these formulations.

(Fig. 15)

The fluctuation of the moisture content during granulation using the "Powder Blend System" under the condition of Table 15 is shown. The same pattern was observed among the three formulations.

(Fig. 16)

The particle size distribution of the drug-containing granules using the "Powder Blend System" is shown. The yield was more than 80%.

(Fig. 17)

The effect of the binder content on the D50 of the drug–containing granules using Pharmacoat –603 as a binder is shown. The correlation was similar among the three formulations.

(Table 16)

A comparison of the granular strength and bulk density of the drug–containing granules in the two system is shown. In the paracetamol granules using the "Powder Blend System", the granule strength was lower than others.

(Fig. 18)

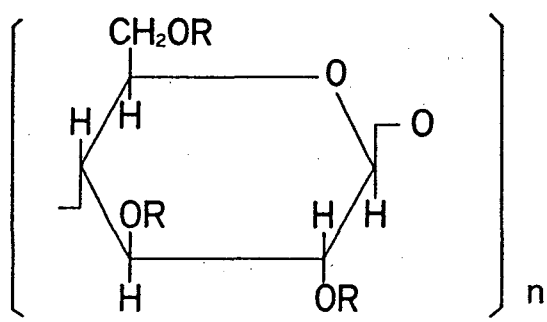
Microscopic views of granules of drug–containing formulation using the "Solution Spray System" and "Powder Blend System" are shown. With both drugs, the particles by the "Powder Blend System" were more compact than those by the "Solution Spray System".

(Table 17)

The conclusion of the study is summarized. In the "Solution Spray System", the particle size distribution was more narrow, the bulk density was lower and the yield was higher than in the "Powder Blend System". The mean particle size was altered by the viscosity type and the content of Pharmacoat. But the effect of the type and content was different in the two systems. In the drug–containing formulation, the operating condition should be changed according to the property of drug.

The Application of Pharmacoat to Granulation in a Fluidizing Column

Fig. 1 The Chemical Structure of Pharmacoat (Hydroxypropyl Methylcellulose)



R = -H, $-CH_3$, $-CH_2CH(OH)CH_3$

Table 1 The Viscosity Types of Pharmacoat

Type	Viscosity(cSt)*
Pharmacoat - 603	3.22
- 606	5.74
- 615	16.00

* 2 % aq., 20 °C

Fig. 2 The Granulation Machine

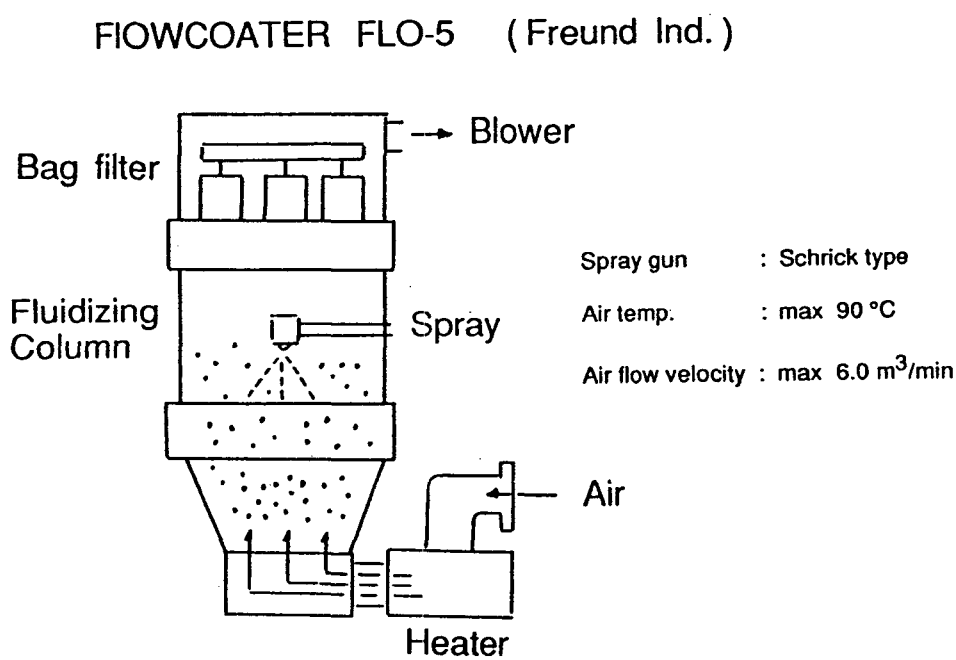


Table 2 Tests for Granular Products

Particle size distribution	Sieving by Ro-Tap shaker (5 min)
Mean particle size (D50)	Calculated from the particle size distribution
Yield	Fraction of 75 - 500 μm
Granule strength	An increase of less than 75 μm in the shaking of 5 to 20 min.
Bulk density	
Uniformity of drug content	
Microscopic view	S.E.M.
Moisture content during granulation	Loss on drying

Fig. 3 Two Systems of Addition of Binder

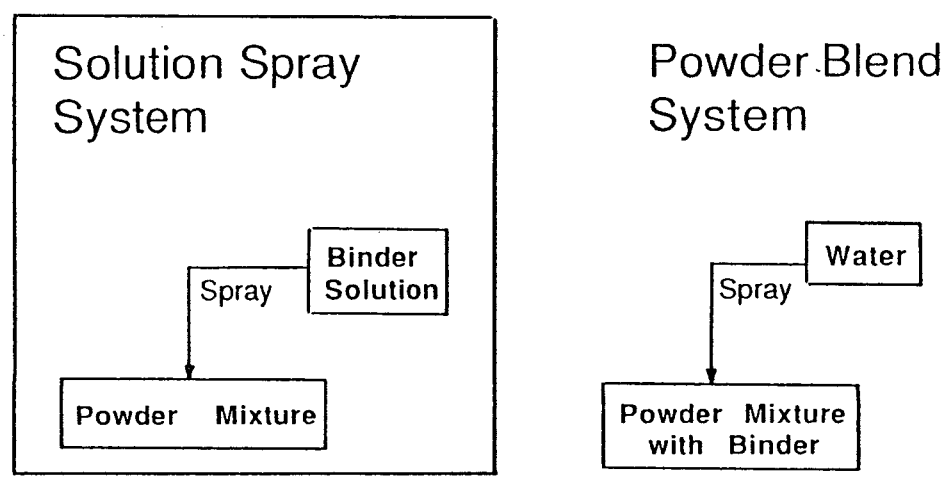


Table 3 **The Formulation of the Non-Drug Containing Mixture (The Solution Spray System)**

Lactose	2800 (g)
Cornstarch	1200
Binder *	80~200

* As a 4~10 % aqueous solution

Table 4 **The Operating Condition (The Solution Spray System)**

Inlet air temp.	80 °C
Air flow velocity	4.0 m^3/min
Gun height	40 cm
Spray velocity	100 g/min
Spray air pressure	3.0 kg/cm^2
Shaking	For 6 sec. at 30-sec. intervals
Post drying	Until outlet temp. reaches 35 °C

Fig. 4 The Particle Size Distribution (The Solution Spray System)

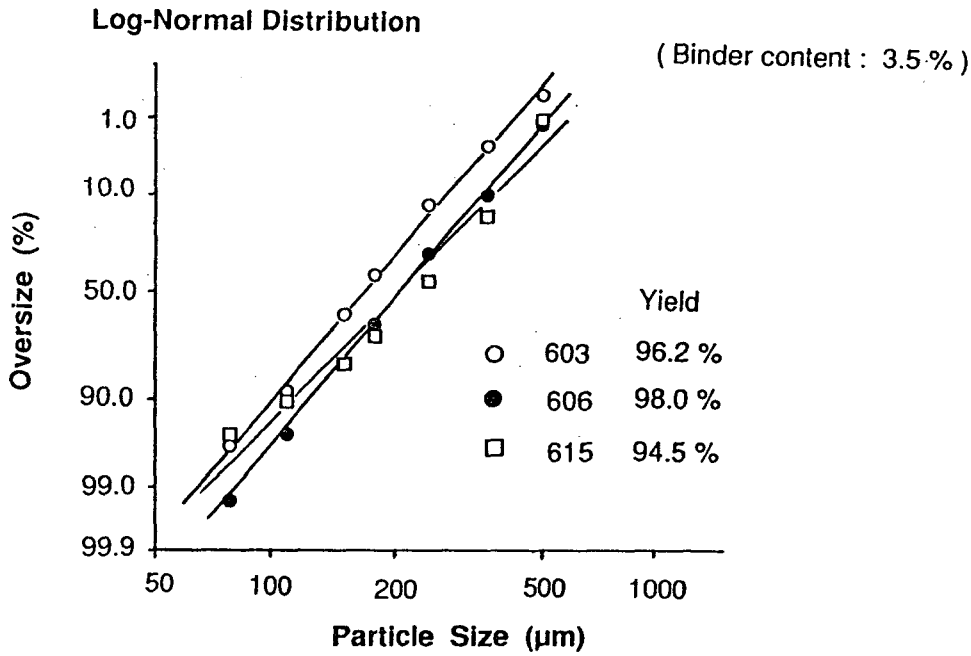


Table 5 A Comparison of D50 (The Solution Spray System)

Binder	D50(μm)
Pharmacoat - 603	162
- 606	206
- 615	225

(Binder content : 3.5 %)

Fig. 5 The Effect of the Binder Content on D50
(The Solution Spray System)

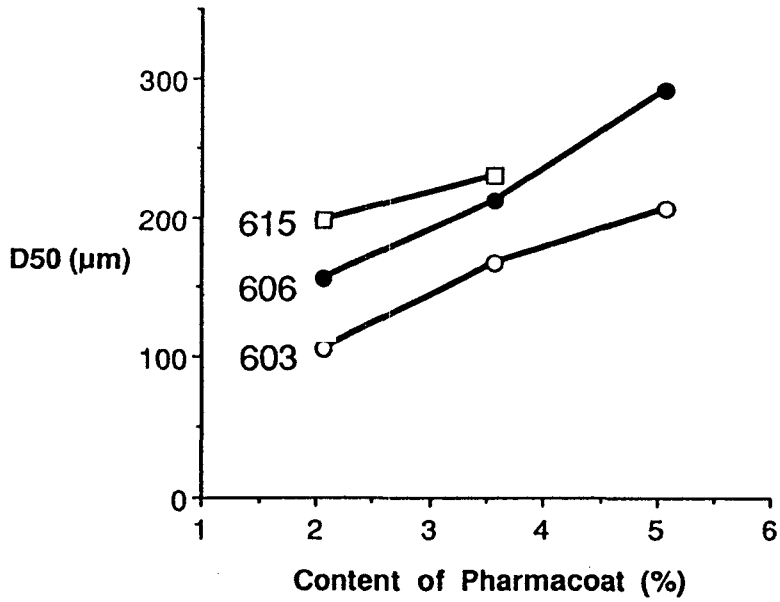


Fig. 6

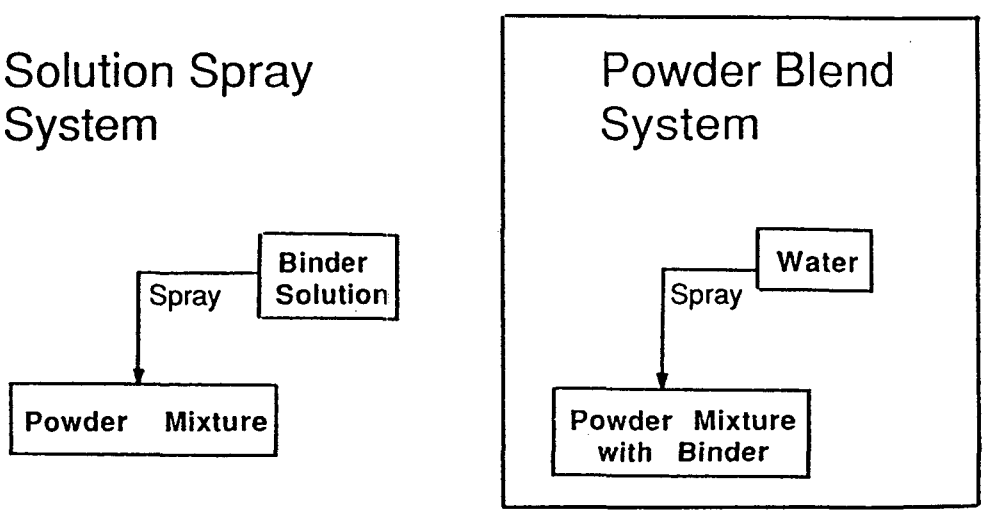


Table 6 The Formulation of Non-Drug Containing Mixture (The Powder Blend System)

Lactose	2800 (g)
Cornstarch	1200
Binder	80~320
Water	1600

Table 7 The Operating Condition (The Powder Blend System)

Inlet air temp.	80 °C
Air flow velocity	2.2 m^3/min
Gun height	25 cm
Spray velocity	80 g/min
Spray air pressure	3.0 kg/cm^2
Shaking	For 6 sec. at 30-sec. intervals
Post drying	Until outlet temp. reacnes 35 °C

Fig. 7 The Particle Size Distribution
(The Powder Blend System)

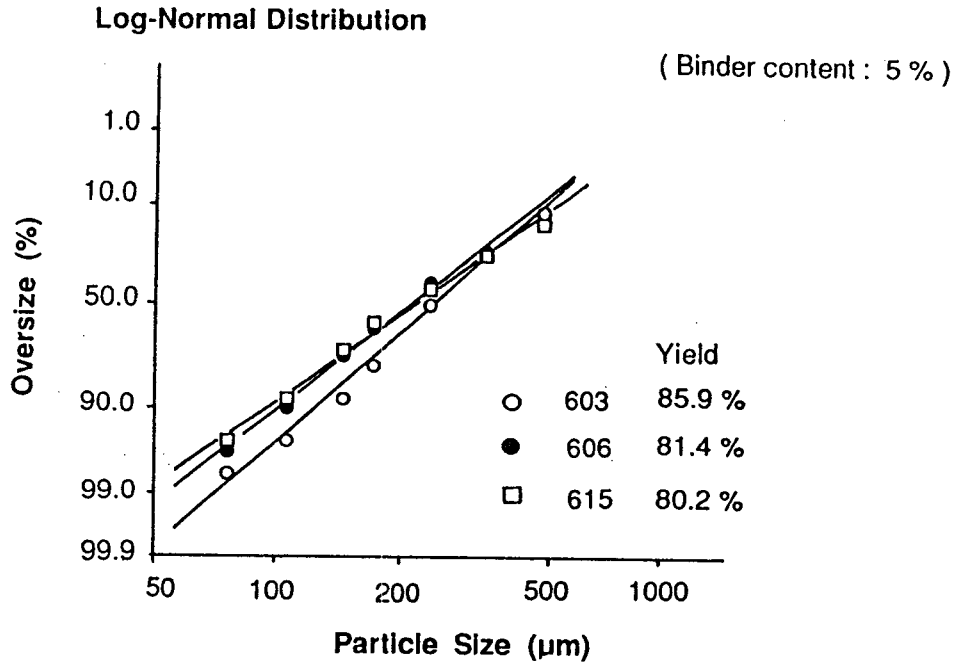


Fig. 8 A Comparison of the Particle Size Distribution between the Solution Spray System and the Powder Blend System

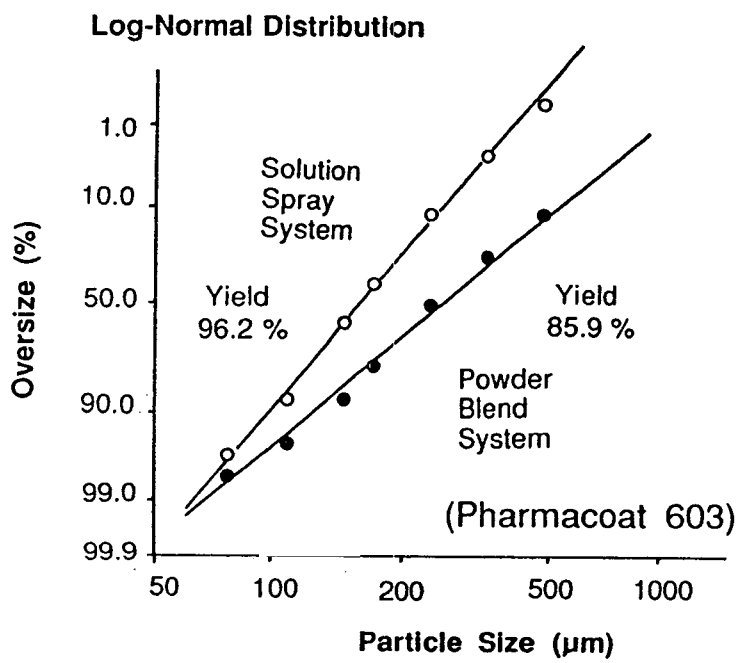


Table 8 A Comparison of D50
(The Powder Blend System)

Binder	D50(μm)
Pharmacoat - 603	247
- 606	211
- 615	210

(Binder content : 5 %

Fig. 9 The Effect of the Binder Content on D50
(The Powder Blend System)

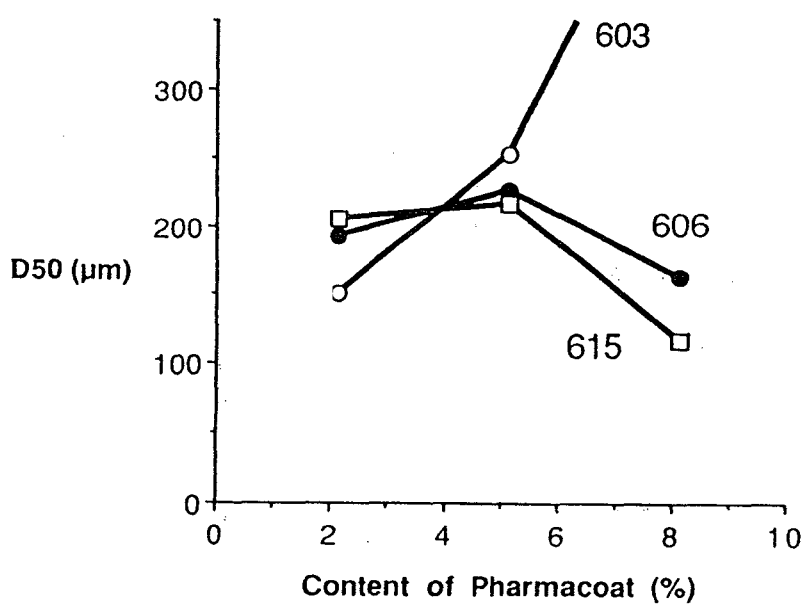
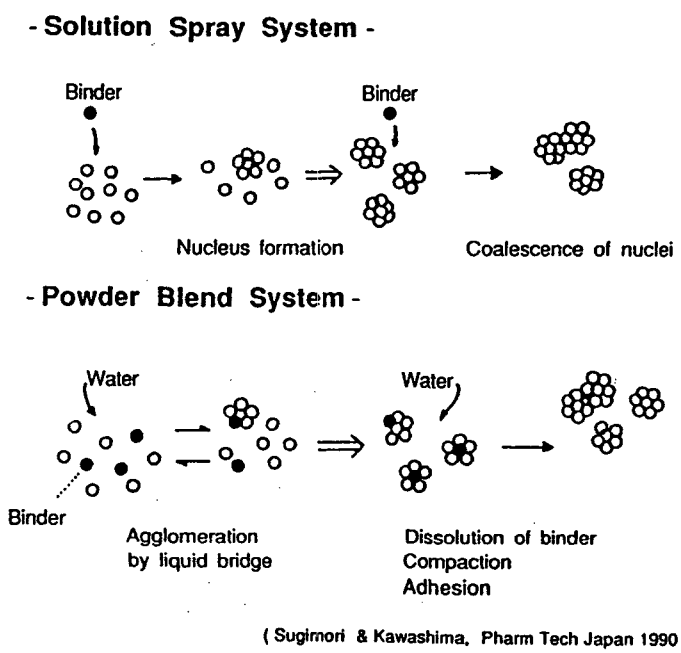


Table 9 The Granule Strength and Bulk Density of the Non Drug Containing Mixture

	The Solution Spray System	The Powder Blend System
Granule Strength (% less than 75 μm)	0.2	0
Bulk Density (g/ cm^3)	0.42	0.55

(Binder : Pharmacoat 603)

Fig. 10 The Mechanism of the Granulation



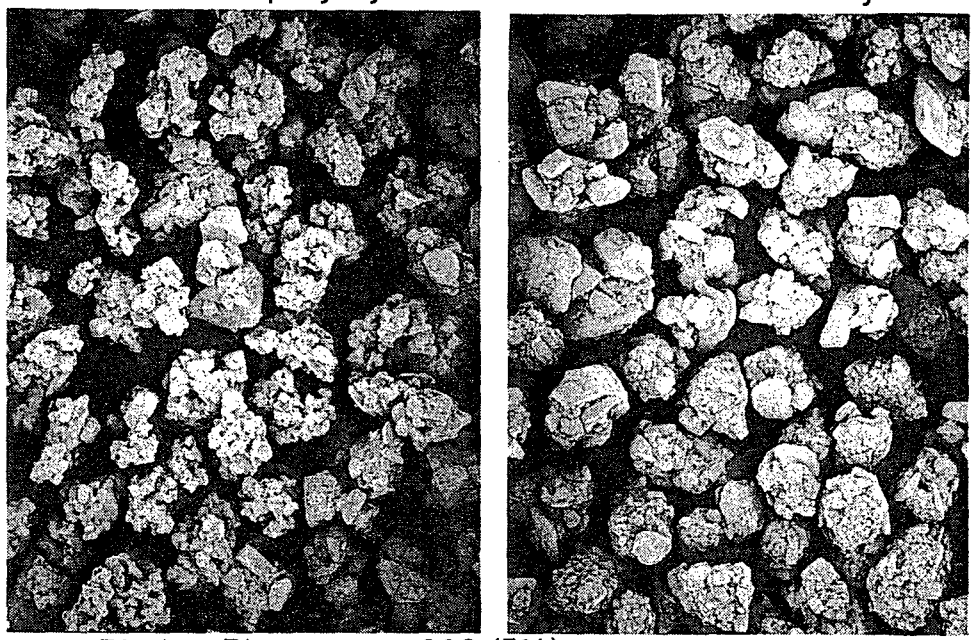
(Sugimori & Kawashima, Pharm Tech Japan 1990)

Fig. 11 The Microscopic Views of the Granules

(106 - 150 μm)

The Solution Spray System

The Powder Blend System



Binder: Pharmacoat 603 (5%)

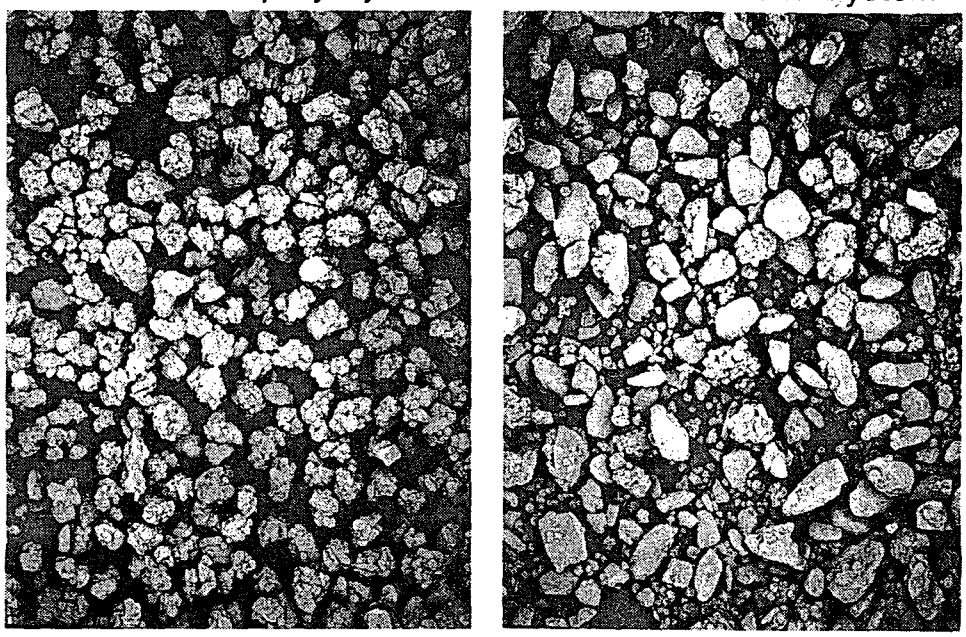
x 70

Fig. 12 The Microscopic Views of the Granules

(< 75 μm)

The Solution Spray System

The Powder Blend System



x 70

Table 10 The Granulation of Drug Containing Formulation

Hydrophobic drug	:	Paracetamol
Hydrophilic drug	:	Ascorbic acid

Table 11 The Formulation of the Drug Containing Mixture (The Solution Spray System)

Lactose	1960 (g)
Cornstarch	840
Drug	1200
Binder*	140

* As a 7 % aqueous solution

Table 12 The Operating Condition
(The Solution Spray System)

	Non-drug	Paracetamol	Ascorbic acid
Air flow velocity (m^3/min)	4.0	3.2	4.0
Spray velocity (g/min)	100	80	90

Other items were the same as the non-drug granulation.

Fig. 13 The Fluctuation o. ... in the Granules during Granulation
(The Solution Spray System)

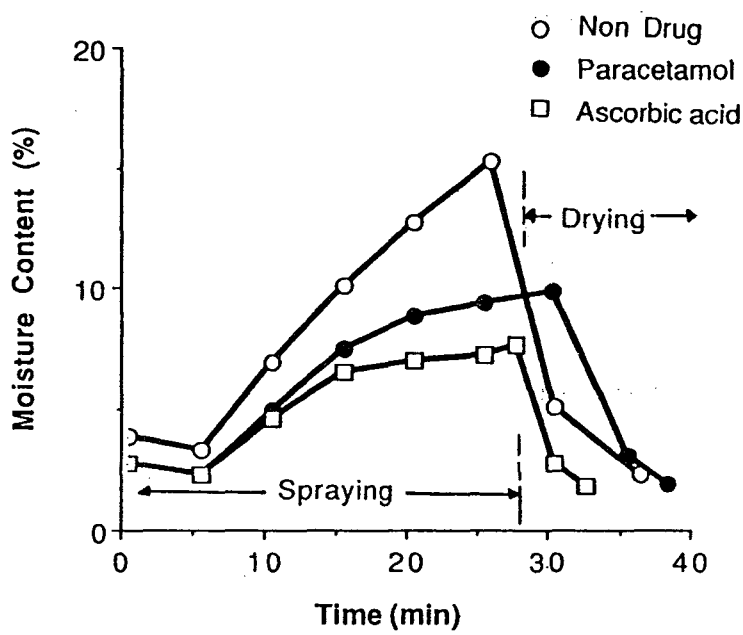


Fig. 14 The Particle Size Distribution of the Drug Containing Granules (The Solution Spray System)

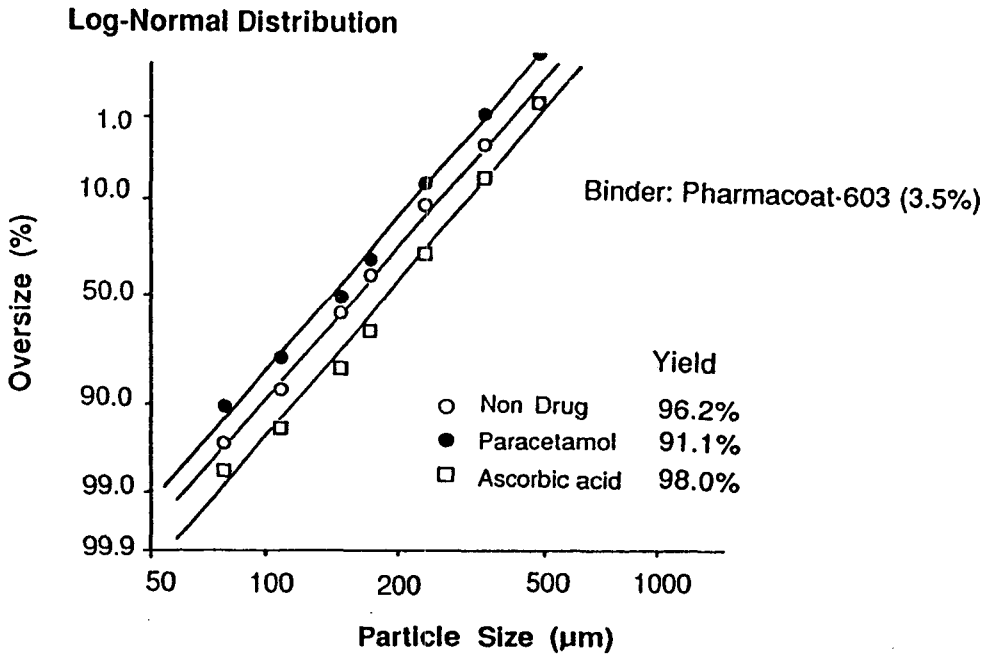


Table 13 A Comparison of D50 (The Solution Spray System)

Binder	D50 (μm)		
	Non drug	Paracetamol	Ascorbic acid
Pharmacoat - 603	162	153	207
- 606	206	213	290

Table 14 The Formulation of the Drug Containing Mixture (The Powder Blend System)

Lactose	1960	(g)
Cornstarch	840	
Drug	1200	
Binder	200	
Water	2000	for Paracetamol
	1600	for Ascorbic acid

Table 15 The Operating Condition (The Powder Blend System)

	Non-drug	Paracetamol	Ascorbic acid
Gun height (cm)	25	40	25
Spray velocity (g/min)	80	80	70

Other items were the same as the non-drug granulation.

Fig. 15 The Fluctuation of the Moisture Content of Granules during Granulation (The Powder Blend System)

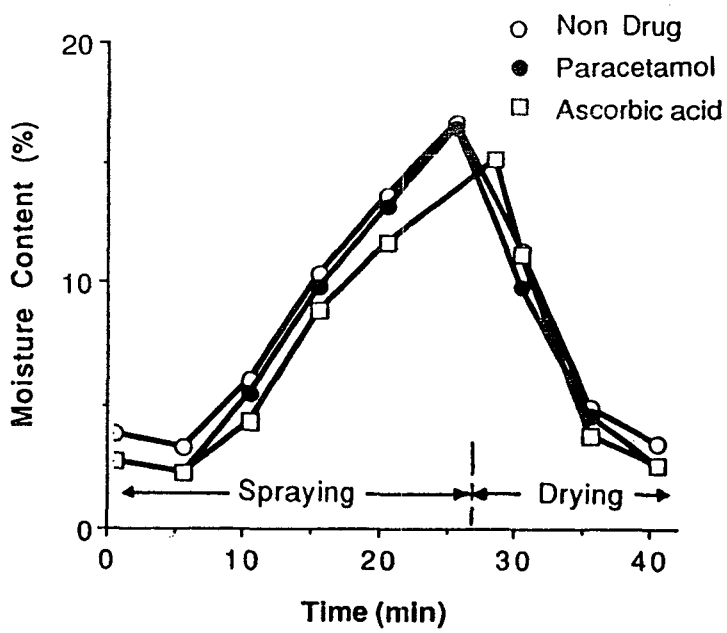


Fig. 16 The Particle Size Distribution of the Drug Containing Granules (The Powder Blend System)

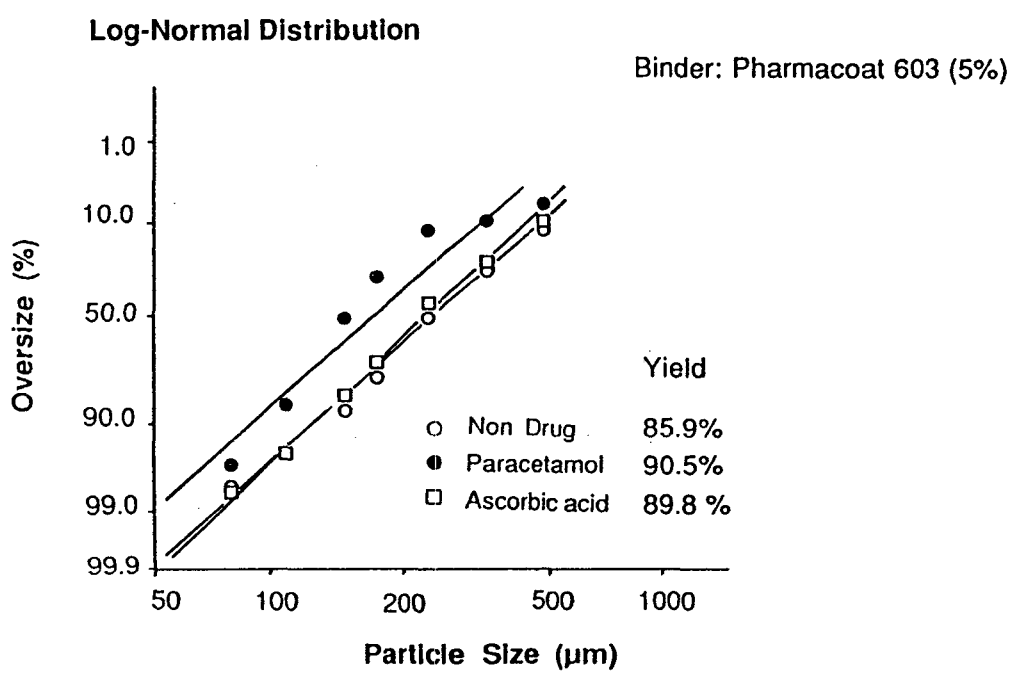


Fig. 17 The Effect of the Binder Content on D50 (The Powder Blend System)

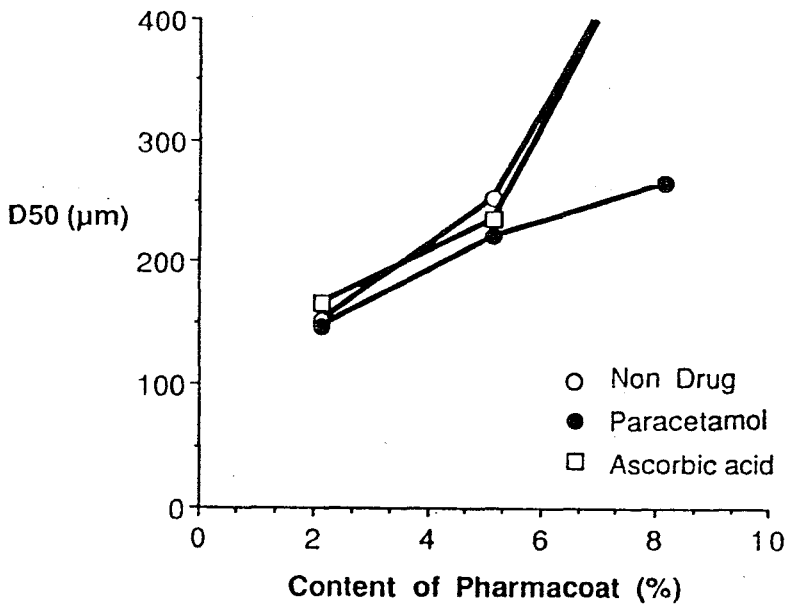


Table 16 The Granule Strength and Bulk Density of the Drug Containing Granules

	The Solution Spray System		The Powder Blend System	
	Paracetamol	Ascorbic acid	Paracetamol	Ascorbic acid
Granule Strength (% less than 75 μm)	0	0.2	4.1	0.2
Bulk Density (g/cm^3)	0.32	0.46	0.43	0.51

(Binder : Pharmacoat 603)

Fig 18 Microscopic Views of the Drug Containing Granules.

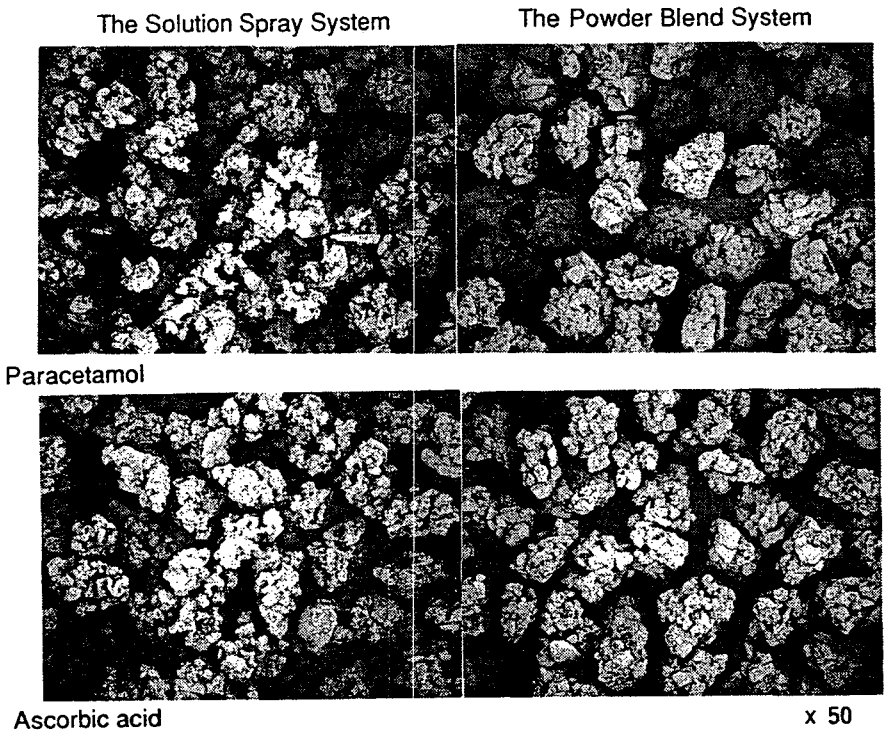


Table 17

Conclusion

Particle Size Distribution :

Solution Spray System < Powder Blend System

Bulk Density

Solution Spray System < Powder Blend System

Yield

Solution Spray System > Powder Blend System

Mean Particle Size

It changes with the content and viscosity grade of Pharmacoat in the Solution Spray System.

In the Powder Blend System, the effect of the content and viscosity grade is different from that of the Solution Spray System.