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Pharmaceutical Preparations of Crude Drug Powder. III.[1-3) The Effects of the Physical Properties of the Binder Solution on the Characteristics of the Granule from the Mixed Powders

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The granulation from mixed crude drug powders was carried out by fluidized bed and agitation methods. The effects of the physical properties of the binder solution, such as the contact angle on the powder compact, the viscosity, on the granule characteristics, the average granule size, angle of repose, bulk density, granule strength, compressibility, and strength of compact, were examined.

Correlation between the physical properties of the products obtained by fluidized bed granulation and agitation granulation, and those of the binder solution were analyzed by using the correlation formula derived from multiple regression analysis. A highly confident multiple correlation was found and the relationship between physical properties of the binder solution and those of the granules can be expressed quantitatively.

It suggests the possibility that formulation of powder materials for production of granules having desirable physical properties can be easily determined and, also, the granulating manipulation which has been performed experimentally or qualitatively, can be done quantitatively and rationally, by using the results.

Keywords Senna powder; crude drug powder; fluidized bed granulation; agitation granulation; regression analysis; granule characteristic

Introduction

The value of crude drugs has recently been attracting public attention. However, crude drug powders are inconvenient to handle because they consist of fibrous materials. For this reason, they are generally used in the form of granules or tablets prepared from extract.[4] Although it appears very useful to produce granules and tablets out of a crude drug powder,[5] particles come in a variety of forms, and the fluidity of particles is poor due to the high fibrous and strong adhesiveness. The effects of the physical properties of the binder solution, such as the contact angle on the powder compact, viscosity, *etc.*, on the granule characteristics, the mean granule size, angle of repose, bulk density, granule strength and compressibility, were examined.[3]

This paper deals with the granulation of the mixture of six types of crude drug powders by fluidized bed and agitation methods.

Experimental

Materials Hydroxypropylcellulose (HPC EF-P) was obtained from Shin-Etsu Chemical Co., Ltd., sodium carboxymethylcellulose (CMC–Na F01MC) was obtained from Gotoku Chemical Co., Ltd., and polyvinyl pyrorridone (PVP K30, K90) was obtained from BASF Japan Co., Ltd. Six types of crude drug powder were supplied by Honso Pharmaceutical Co., Ltd., the mixing ratio of these powders and their physical properties are shown in Table I.

Determination of the Physical Properties of the Binder Solution The viscosity of the binder solution was determined use of a rotational Visconic E_{ED} viscometer (Tokyo Keiki Co., Ltd.) at 20 °C. The contact angle was determined by photographs of droplets on the tablet provided using a Universal compressing machine autograph AG-5000D (Shimadzu Co., Ltd.) at a pressure of 0.95 t/cm^2. A Glatt Process Technology CPCG-1 type fluidized granulator was used for fluidized bed granulation, and agitation granulation was carried out using Multiplex granulator FM-MP-10 (Powrex Co., Ltd.). Granulation conditions are listed in Table II.

Determination of the Physical Properties of the Granules Particle size distribution, mean particle diameter, angle of repose and the apparent density of the granules was determined in the same way as used in a previous paper.[3] Twenty particles of each granulated product passing through a 35# sieve and left on a 42# sieve were subjected to a strength test using granule strength tester which we developed.[2,3,6] Strength of granules $St(G)$ was calculated by Eq. 1.[7,8]

$$St(G)=4P/\pi D^2 \quad (1)$$

TABLE I. Physical Properties of Powders and Formulation

	Glycyrrhiza	Senna leaf	Rhubarb	Magnolia bark	Peony root	Cenidium rhizome	Mixture
Density (g/cm^3)	1.44	1.38	1.42	1.43	1.46	1.44	—
Feret's diameter (μm)	8.50	10.1	9.30	5.00	9.90	9.10	—
Heywood's diameter (μm)	8.30	10.0	9.50	5.10	10.3	9.40	—
Shape factor	0.55	0.51	0.53	0.54	0.53	0.53	—
Water content (%)	4.59	8.50	7.29	9.78	6.09	4.61	—
Angle of repose (°)	53	51	53	56	54	55	55
Compressibility	53	51	47	52	53	51	55
Angle of spatula (°)	71	71	69	78	73	75	67
Cohesiveness	18.2	21.0	11.8	39.6	31.2	40.9	39.3
Fluidity index	36.0	36.0	36.0	23.5	33.5	27.0	29.0
Components (%)	10.0	25.0	30.0	10.0	15.0	10.0	

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Table IIa. Operating Conditions of Fluidized Bed Granulation

Equipment	GPCG-1 (Glatt)
Crude drug	0.5 kg
Inlet temperature	70 °C
Fluidizing air rate	0.7 m^3/min
Nozzle orifice	1.2 mm
Nozzle type	Pneumatic atomization
Concentration of binder	5, 7 w/v% HPC, PVP K30, PVP K90 1, 2 w/v% CMC–Na soln.
Amount of binder solution	150—400 ml
Spraying rate	25 ml/min
Single shaking interval	5 s/min
Twin shaking interval	5 s/5 min
Product temperature at drying	36 °C

Table IIb. Operating Conditions of Agitation Granulation

Equipment	FM-MP-10 (Powrex Co.)
Crude drug	0.5 kg
Concentration of binder	5 w/v% HPC, PVP K30, PVP K90 2 w/v% CMC–Na soln.
Amount of binder solution	100—200 ml
Impeller speed	300 rpm
Drying time	30 min
Drying temperature	70 °C
Air rate	120 m^3/h

where P is load (kg) at crushing and D is the mean diameter (cm) of granules. Using a Universal compressing machine autograph AG-5000D, 1.0 g of granules was compressed with a pressure of 2.0 t/cm^2 at the rate of 1 mm/min thickness. From the compression curve obtained in this procedure, the bulk decrease (C) was calculated, and an attempt was made to apply the formula of Kawakita (2), (3)[9] which is known as a compression formula for powder, to this calculation.

$$C=(V_0-V)/V_0 \tag{2}$$

$$P/C=1/ab+P/a \tag{3}$$

where V_0, V is the volume of initial and after a compression, P is compressing pressure (kg) a, b is Kawakita's constant.

The tablets were subjected to a radial compression test, and the radial compression strength (St) was calculated from Eq. 4.[3,6,10]

$$St=2P/\pi DL \tag{4}$$

where P is load (kg) at crushing and D, L is mean diameter (cm) and thickness (cm) of tablets.

Regression Analysis In this analysis these independent variables (factors) were normalized in such a way that the minimum value was zero and the maximum one was 100[3,12,13] as shown in Table III.

The equation of regression used in this analysis is[14]

$$\text{physical property}=v_1\cdot V+v_2\cdot V^2+w_1\cdot W+w_2\cdot W^2+n_1\cdot\eta+n_2\cdot\eta^2+a_1\cdot(°)+a_2\cdot(°)^2+C_0 \tag{5}$$

where V is the amount of binder solution (the amount of water in binder solution), W is the amount of binder in binder solution added, η is the viscosity of the binder solution added and (°) is the contact angle of the droplet on the tablet and v_1, v_2, w_1, w_2, n_1, n_2, a_1 and a_2 are the coefficients of each variable, and C_0 is a constant.

Table III. Unnormalized and Normalized Factor Levels

Factor	Fluidized bed granulation		Agitation granulation	
	Unnormalized level	Normalized level	Unnormalized level	Normalized level
V	150.0	0.0	100.0	0.0
	200.0	20.0	120.0	20.0
	250.0	40.0	140.0	40.0
	300.0	60.0	160.0	60.0
	350.0	80.0	180.0	80.0
	400.0	100.0	200.0	100.0
W	2.0	0.0	2.0	0.0
	2.5	1.92	2.4	5.0
	3.0	3.85	2.8	10.0
	3.5	5.77	3.2	15.0
	4.0	7.69	3.6	20.0
	5.0	11.5	4.0	25.0
	6.0	15.4	5.0	37.5
	7.0	19.2	6.0	50.0
	10.0	30.8	7.0	62.5
	12.5	40.4	8.0	75.0
	14.0	46.2	9.0	87.5
	15.0	50.0	10.0	100.0
	17.5	59.6		
	20.0	69.2		
	21.0	73.1		
	24.5	86.5		
	28.0	100.0		
η	2.8	0.0	2.8	0.0
	3.8	1.68	25.6	58.8
	16.2	22.5	32.4	76.3
	25.6	38.3	41.6	100.0
	32.4	49.7		
	41.6	65.2		
	61.9	99.3		
	62.3	100.0		
(°)	50.1	0.0	50.1	0.0
	52.7	8.33	61.7	52.0
	54.7	14.7	62.3	54.7
	61.7	37.2	72.4	100.0
	62.3	39.1		
	66.4	52.2		
	72.4	71.5		
	81.3	100.0		

V, amount of binder solution (amount of water); W, amount of binder; η, viscosity of binder solution added; (°), contact angle.

Table IV. Contact Angle and Viscosity of Binder Solution

Binder	Concentration (w/v%)	Contact angle (°)	Viscosity (cP)
HPC EF-P	5	62.3	25.6
	7	66.4	62.3
PVP K30	5	50.1	2.8
	7	52.7	3.8
PVP K90	5	72.4	32.4
	7	81.3	61.9
CMC–Na	1	54.7	16.2
	2	61.7	41.6

Results and Discussion

Contact angle and viscosity of binder solution are shown in Table III.

Regression analysis was performed on all of the obtained data as shown in Eqs. 6—12 in which the coefficients of each variable are significant, but no significant interactions between each variable in the t-test at the 5% level.

Mean Particle Size The results of fluidized bed granulation, as shown in Fig. 1a, shows that the mean granule size tends to increase with increases in the concentration of the binder solution. The mean particle size was found to be closely related to the amount of binder, amount of the binder solution, viscosity of binder solution, and contact angle.

The equation of regression is:

$$D_{50}=2.57\cdot V-8.03\times10^{-2}\cdot V^2+6.07\times10^{-2}\cdot W^2+133 \tag{6a}$$

$$(n=35,\ SD=20.7,\ F(3,31)=102.3,\ R=0.953)$$

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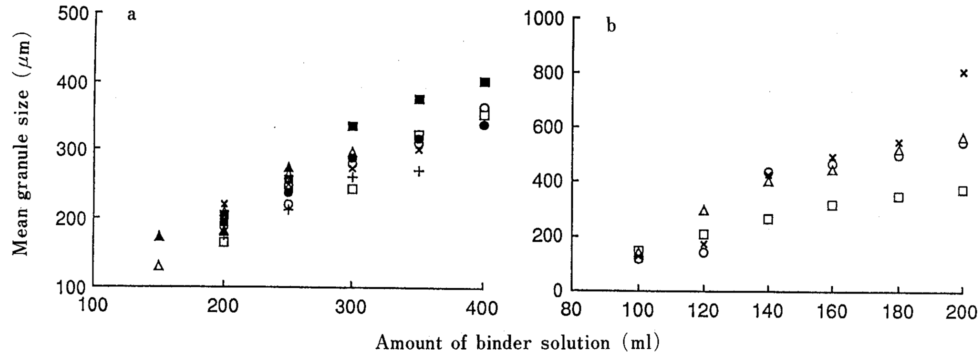

Fig. 1. Relation between Amount of Binder Solution (Amount of Water) and Mean Granule Size

a, fluidized granulation; b, agitation granulation. ○, HPC 5%; □, PVP K30 5%; △, PVP K90 5%; ×, CMC–Na 2%; ●, HPC 7%; ■, PVP K30 7%; ▲, PVP K90 7%; +, CMC–Na 1%.

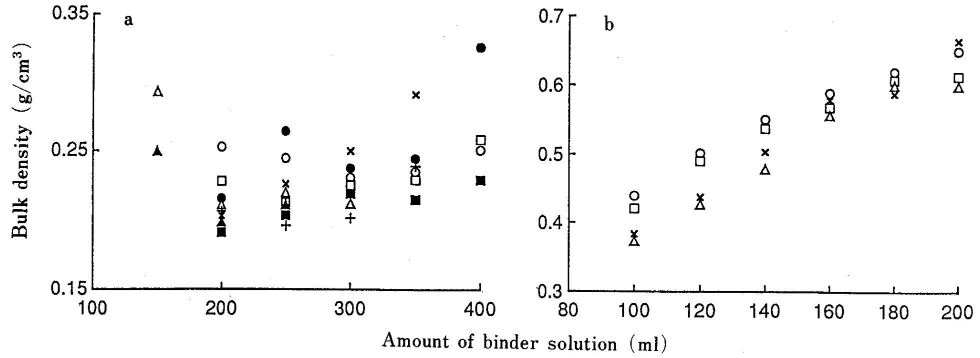

Fig. 2. Relation between Amount of Binder Solution (Amount of Water) and Bulk Density

a, fluidized granulation; b, agitation granulation. ○, HPC 5%; □, PVP K30 5%; △, PVP K90 5%; ×, CMC–Na 2%; ●, HPC 7%; ■, PVP K30 7%; ▲, PVP K90 7%; +, CMC–Na 1%.

where n is sample number, SD is the standard deviation, $F(3,31)$ is the F-value in the F-test, and R is the multiple correlation coefficient. The correlation coefficient was 0.953, which is significant in the F-test at the 5% level.

In such case, the amount of binder added may be the major factor affecting the mean particle size.

Figure 1b showed that the mean granule size of agitation granulation tends to increase with the increases in concentration of the binder solution, as shown in the case of fluidized bed granulation. The fraction of the coarse and fine grains tended to increase in this process because of the strong impellar's shearing and impact force to the particles. The following equation was obtained by regression analysis:

$$D_{50}=5.13\cdot V+7.71\cdot W-7.40\times10^{-2}\cdot W^2+2.11\times10^{-2}\cdot\eta^2-120 \quad (6b)$$

$$(n=24,\ SD=55.9,\ F(4,19)=53.2,\ R=0.958)$$

In this case, the major factors affecting the average particle size may be not only the amount of the binder but also the binder solution added.

Angle of Repose and Apparent Density As shown in Figs. 2a, b increases in the amount of binder solution led to increases in the bulk density of the granulated products but the bulk density of granules by fluidized bed granulation had a minimum value, which was smaller than that of agitation granulation. The reason is considered to be that, to a certain amount, increasing the amount of binder solution increased interaparticle and intraparticle space, after which further addition of binder solution led to decreases in space.

By regression analysis, the following equation was obtained for granules of fluidized bed granulation:

$$\text{angle of repose}=-5.63\times10^{-2}\cdot V+2.93\times10^{-2}\cdot(°)-0.28\times10^{-3}\cdot\eta^2+48.8 \quad (7a)$$

$$(n=35,\ SD=1.39,\ F(3,31)=21.8,\ R=0.824)$$

For granules of agitation granulation:

$$\text{angle of repose}=-4.93\times10^{-2}\cdot V-8.01\times10^{-2}\cdot W-1.29\times10^{-1}\cdot(°)+1.43\times10^{-3}\cdot(°)^2+55.1 \quad (7b)$$

$$(n=24,\ SD=1.55,\ F(4,19)=32.8,\ R=0.935)$$

For the granules of fluidized bed granulation:

$$\text{bulk density}=-1.28\times10^{-3}\cdot V+0.02\times10^{-3}\cdot V^2+0.28\times10^{-3}\cdot\eta+0.231 \quad (8a)$$

$$(n=35,\ SD=0.024,\ F(3,31)=7.16,\ R=0.640)$$

For the granules of agitation granulation:

$$\text{bulk density}=1.66\times10^{-3}\cdot V+5.55\times10^{-3}\cdot W+0.02\times10^{-3}\cdot\eta^2-0.01\times10^{-3}\cdot(°)^2+0.257 \quad (8b)$$

$$(n=24,\ SD=0.014,\ F(5,18)=162,\ R=0.989)$$

From these equations, it is shown that the factors of increasing particle size are closely related to the factors of decreasing angle of repose and the factors of increasing bulk density.

Strength Test of Granulated Products Each granulated product with a particle diameter within a certain range were subjected to the strength test, and the results are

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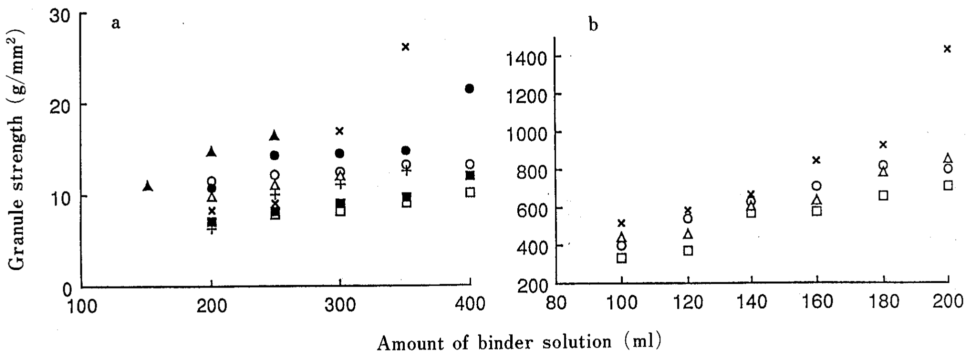

Fig. 3. Relation between Amount of Binder Solution (Amount of Water) and Granule Strength

a, fluidized granulation; b, agitation granulation. ○, HPC 5%; □, PVP K30 5%; △, PVP K90 5%; ×, CMC–Na 2%; ●, HPC 7%; ■, PVP K30 7%; ▲, PVP K90 7%; +, CMC–Na 1%.

shown in Figs. 3a, b. It was found that the granules made by agitation granulation had considerable hardness, since they had been subjected to great shearing force, while the granules made by fluidized bed granulation were soft and flexible.

For granules of fluidized bed granulation:

$$GS=8.25\times10^{-2}\cdot V+7.68\times10^{-2}\cdot\eta+4.11 \quad (9a)$$

$$(n=33,\ SD=2.58,\ F(2,30)=25.1,\ R=0.791)$$

For granules of agitation granulation:

$$GS=3.61\cdot V+4.13\times10^{-2}\cdot V^2+5.77\cdot W-8.51\times10^{-2}\cdot W^2+1.78\times10^{-2}\cdot\eta^2+263 \quad (9b)$$

$$(n=24,\ SD=70.0,\ F(5,18)=45.9,\ R=0.963)$$

It is observed from these equations that the factors of increasing particle size are closely related to the factors increasing the strength of granules, particularly in agitation granulation.

Compression Test (Compressibility) When the results from this compression test were plotted on a graph conforming to the formula of Kawakita, (2) there appeared a close linear relationship. In the formula, (3) a refers to the bulk decrease, and the larger the value of a, the greater the volume change during the compression. Furthermore, $1/b$ relates to the yield stress, and the larger the value of $1/b$, the greater the yield stress of the particle, indicated that particles have poor compressible plasticity. Figures 6a, b, Figs. 7a, b indicate the relationship between the amount of binder solution and constant a and $1/b$, respectively. The results show that the a values of the products of fluidized bed granulation are greater than with agitation granulation, and tend to decrease with increases in the amount of binder solution, particularly in the case of agitation granulation:

$$a=1.94\times10^{-3}\cdot V-0.02\times10^{-3}\cdot V^2+0.01\times10^{-3}\cdot W^2+0.01\times10^{-3}\cdot(°)-0.66\times10^{-3}\cdot(°)^2+0.810 \quad (10a)$$

$$(n=35,\ SD=0.0142,\ F(4,19)=9.57,\ R=0.789)$$

For granules of agitation granulation:

$$a=-2.27\times10^{-3}\cdot W+0.02\times10^{-3}\cdot W^2+0.50\times10^{-3}\cdot(°)-0.01\times10^{-3}\cdot V^2+0.01\times10^{-3}\cdot\eta^2+55.1 \quad (10b)$$

$$(n=24,\ SD=0.0086,\ F(4,19)=40.5,\ R=0.958)$$

It is observed from these equations that the factors of increase in the particle size are closely related to the factors decreasing the a value in agitation granulation, whereas it is not very significant in fluidized bed granulation. It is considered that the amount of binder solution added to a certain limit caused increases in interparticle space. On the other hand, $1/b$ increases with increases in the amount of binder solution in agitation granulation. This means that granules become harder to compress with increases in binder solution. It is observed from this equation that the factors of increasing the particle size are closely related to the factors increasing the $1/b$ value in agitation granulation.

There is no significant regression equation for granules of fluidized bed granulation.

Regression analysis for agitation granulation is:

$$1/b=1.35\times10^{-1}\cdot V+0.95\times10^{-3}\cdot V^2-3.68\times10^{-2}\cdot\eta+12.5 \quad (11)$$

$$(n=24,\ SD=1.60,\ F(3,20)=14.5,\ R=0.842)$$

Radial Compression Test The strength in fluidized bed granulation is independent of the amount of binder solution, while in agitation granulation the strength tends to decrease with increases in the amount of binder solution.

This may be due to close binding among the granules by the addition of binder resulting in hard granules, since the volume of the micropores decreases when the amount of binder increases, and the bulk density increases. Thus, properties of granules can be changed by varying the binder solution.

For granules of fluidized bed granulation:

$$St=-5.71\times10^{-2}\cdot W+0.47\times10^{-3}\cdot W^2+6.27\times10^{-1}\cdot(°)+0.83\times10^{-2}(a)^2-1.21\times10^{-3}\cdot\eta+7.77 \quad (12a)$$

$$(n=35,\ SD=0.680,\ F(3,20)=14.2,\ R=0.843)$$

For granules of agitation granulation:

$$St=-1.94\times10^{-1}\cdot W+0.95\times10^{-3}\cdot W^2+6.83\times10^{-2}\cdot(°)-1.33\times10^{-1}\cdot\eta+15.2 \quad (12b)$$

$$(n=24,\ SD=0.621,\ F(3,20)=66.7,\ R=0.968)$$

It is clear from these equations that the factors of increasing the particle radial strength are closely related to the factors increasing the particle size and $1/b$ value, and decreasing the strength of granulated products.

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Conclusion

It was found that the physical properties of the products of both agitation granulation and fluidized bed granulation are closely related to the amount of binder, the amount of binder solution, the viscosity of the binder solution, the angle of repose. Correlation between physical properties of the products obtained by fluidized bed granulation and agitation granulation, and those of the binder solution was analyzed by using the correlation formula derived from multiple regression analysis. A highly confident multiple correlation was found and the relationship between physical properties of the binder solution and those of the granules can be quantitatively expressed.

It suggests a possibility that formulation of powder materials for production of granules having desirable physical properties can be easily determined and also, the granulating manipulation which has been performed experimentally or qualitatively, can be done quantitatively and rationally, by using the results.

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