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# Influence of Granulating Fluids in Hydroxypropylcellulose Binder Solution on Physical Properties of Lactose Granules

Kazumi Danjo,*,[a] Akira Kamiya,[b] Eiji Ikeda,[b] Sakiko Torii,[a] Hisakazu Sunada[a] and Akinobu Otsuka[a]

*Faculty of Pharmacy, Meijo University,[a] 150 Yagotoyama, Tempaku-ku, Nagoya 468, Japan and Pfizer Pharmaceuticals Inc., Nagoya Plant,[b] Taketoyo-cho, Chita-gun, Aichi 470–23, Japan.* *Received February 14, 1992*

**In the present study, a water/isopropyl alcohol system was selected as the solvent in a hydroxypropylcellulose (HPC) binder solution for the preparation of lactose granules.**

**With a fluidized bed granulation method, the mean granule diameter increased as the adhesion tension ($\gamma\cos\theta$) and lactose solubility increased. With an agitating granulation method, the mean granule diameter was independent of the adhesion tension and lactose solubility, but it increased as the viscosity of the binder solution increased.**

**With both granulating methods, granule hardness increased as the adhesion tension and lactose solubility increased, while the pore volume of the granules decreased as the adhesion tension and lactose solubility increased.**

**The quantitative relationship between the physical properties of the granules and several properties of the solvent solution was investigated by the application of multiple regression analysis.**

**Keywords** agitating granulation; fluidized bed granulation; mean granule diameter; adhesion tension; granule hardness; granule pore volume

Binding solutions are used in granule formation to improve the adhesiveness and cohesiveness of particles. In agitating and fluidized bed granulation processes, binder solutions play an important role in influencing the mechanical properties of the granules.

The distribution of binders within granules prepared by agitating and fluidized bed granulation has been investigated by Kristensen,[1)] Ormos[2)] and Nouh[3)] and the effects of concentration,[4)] types and viscosity[5)] of binders have been investigated by many workers. However, these experiments did not address the effects of the properties of water/organic solvent mixed solutions on the physical properties of granules. Wells and Walker,[6)] however, reported the influence of the properties of water/ethanol mixed binder solutions on granule size.

We reported[7)] that the physical properties of granules were affected by adhesion tension in the absence of a binder. In this study, we examined the effects of the properties of water/isopropyl alcohol mixed binder solutions on the physical properties of granules.

## Experimental

**Materials** The materials used to prepare the granules were lactose (JP XII, DMV 200 mesh), hydroxypropylcellulose (HPC) (JP XII Type L Nippon Soda Co., Ltd. HPC-L, $Mw=6.4\times10^4$), and isopropyl alcohol (IPA). Table I shows the composition of the granulating fluids in which the HPC-L was dissolved, as well as their physical properties.

**Granulation Method** Agitating Granulation Method: Granulation experiments were conducted using a Shinagawa Kogyo 5-DMV-r mixer. One hundred grams of a 5% w/w binder solution was added to 495 g of lactose and this was agitated for 5 min. The granules were dried overnight at 50 °C.

Fluidized Bed Granulation Method: Five hundred grams of a 5% w/w binder was sprayed onto 475 g of lactose. The following granulating conditions were kept constant for all batches: inlet air temperature, 30 °C; outlet air temperature, 35 °C; fluid flow-rate, 12 cm$^3$/min; shaking interval, 10 s/3 min.

**Measurement of Granule Diameter Distribution** Granule diameter distribution was determined using JIS standard sieves vibrated on a Ro-Tap sieve shaking machine. The mean granule diameter ($D_{50}$) is represented by median diameter.

**Granule Hardness Measurement** Granule hardness was measured with a hardness tester, described in our previous paper.[7)] The measurement values indicate the average of 20 granules.

**Friability Index** A Rocke-type friabilator (Kayagaki Rika Kogyo) was used for this test. Five grams of granules were placed in a vessel which rotated at 25 rpm for 30 min. The granules remaining after treatment were weighed. The friability index was calculated as the ratio of weight loss due to fracture *vs.* the initial weight of the granules.

**Pore Volume Measurement** Pore volume was carried out using a high pressure mercury porosimeter (Shimadzu-Micromeritics type 9305), with intrusion pressures ranging from 15 to 20000 psi, and with a low-pressure porosimeter, with pressure ranging from 0.6 to 14 psi. The pore diameter was calculated from the data of mercury porosimetry, with diameters ranging from 0.01 to 100 $\mu$m.

**Measurement of Solubility** A saturated solution of lactose in the solvent was prepared by dissolving lactose crystals at 30 °C. The saturated solution was then filtered and the supernatant was evaporated to dryness at 60 °C, after which the residue was weighed.

**Measurement of Viscosity** The viscosity of a 5% w/w binder solution was measured at 20 °C with a B-type viscometer (Tokyo Keiki).

**Surface Tension Measurement** The surface tension of the granulating fluids was measured at 20 °C using a capillary rise method.

**Measurement of Contact Angle** Compacted powder was prepared in a highly polished steel punch and die assembly, 2.0 cm in diameter and 0.2 cm thick. The compacted powder was cut off at a length of 1.5 cm, width of 1.0 cm, and thickness of 0.2 cm. The formed plates were suspended from a strain gauge (Type UT200GR Minebea Co., Ltd.) and used in a modified Wilhelmy gravitational measurement method.[8)] The compacted powder plate is allowed to make contact with a liquid of known surface energy by raising the liquid on a platform. As soon as contact is made, a force $f$ is observed. The force $f$ is related to the contact angle by the following equation:

$$\cos\theta=(f\boldsymbol{g})/(P\gamma_1) \qquad (1)$$

where $P$ is the perimeter of the plate, $\gamma_1$ is the interfacial free energy between the liquid and vapor, and $\boldsymbol{g}$ is the acceleration due to gravity.

## Results and Discussion

**Physicochemical Properties of Solvent Solutions** Table I shows the physicochemical properties of the granulating fluids. The specific gravity of the solvent solutions had a minimum value when pure IPA was used. The viscosity was obtained with a 5% w/w HPC-L solution. The maximum value for the viscosity of the binder solution was expressed at a concentration of 50% w/w water/IPA and the lactose solubility decreased as the concentration of IPA was increased.

**Effects of Adhesion Tension on Physical Properties of Granules** Figure 1 shows the relationship between the mean granule diameter ($D_{50}$) and the adhesion tension

Table I. Composition of Granulating Fluids (5% HPC-L Included) and Their Physicochemical Properties at 20 °C

| Ratio of water/IPA (% w/w) | Surface tension[a] $\gamma$ (mN/m) | Viscosity[a] $\eta$ (mPa·s) | Contact angle[b] $\theta$ (°) | Solubility[b] $Sb$ (g/m$^3$) | Specific gravity[b] ($\times 10^3$ kg/m$^3$) |
|---|---|---|---|---|---|
| 100/0 | 44.1±0.3 | 54.0±1.0 | 33.9±0.4 | 151.0±3.0 | 1.11 ±0.003 |
| 75/25 | 28.2±0.2 | 147.0±3.0 | 31.3±0.2 | 44.0±2.0 | 0.973±0.002 |
| 50/50 | 24.3±0.2 | 163.0±3.0 | 22.5±0.2 | 11.0±1.0 | 0.915±0.002 |
| 25/75 | 23.0±0.3 | 126.0±3.0 | 18.7±0.2 | 1.0±0.2 | 0.862±0.002 |
| 0/100 | 20.1±0.2 | 95.0±2.0 | 27.4±0.1 | 0.1±0.4 | 0.795±0.002 |

*a*) Mean±standard deviation ($n=5$). *b*) Mean±standard deviation ($n=3$).

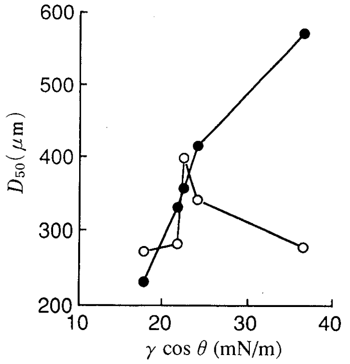

Fig. 1. Relationship between Adhesion Tension ($\gamma\cos\theta$) and Mean Granule Diameter ($D_{50}$)

○, agitating granulation method; ●, fluidized bed granulation method.

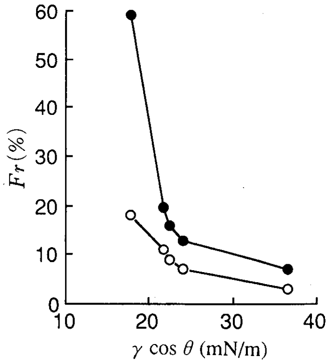

Fig. 3. Relationship between Adhesion Tension ($\gamma\cos\theta$) and Friability Index ($Fr$)

○, agitating granulation method; ●, fluidized bed granulation method.

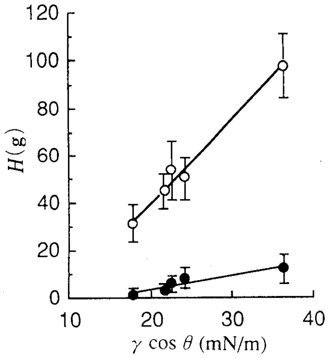

Fig. 2. Relationship between Adhesion Tension ($\gamma\cos\theta$) and Granule Hardness ($H$)

○, agitating granulation method; ●, fluidized bed granulation method.

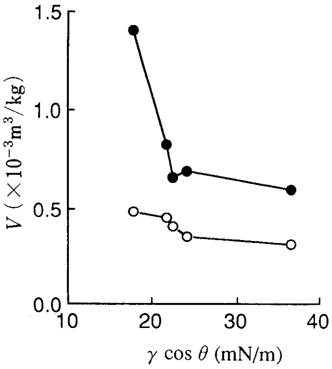

Fig. 4. Relationship between Adhesion Tension ($\gamma\cos\theta$) and Total Pore Volume of Granule ($V$)

○, agitating granulation method; ●, fluidized bed granulation method.

($\gamma\cos\theta$), determined by measuring the surface free energy. With the agitating granule method, the mean granule diameter had a maximum value at 21.8 (mN/m) adhesion tension (50/50% w/w water/IPA), while the mean granule diameter when granules were prepared by the fluidized bed granulation method increased proportionately as the adhesion tension increased. Wells and Walker[6] obtained maximum granule diameter with a 25/75% w/w water/ethanol system.

The relationship between the hardness ($H$) of granules prepared by the agitating and fluidized bed granulation methods and adhesion tension is shown in Fig. 2. Granule hardness increased with increasing adhesion tension in both methods, but the degree of increase was more rapid with agitation than with the fluidized bed granulation method. On the other hand, the friability index ($Fr$) of granules prepared by both methods decreased proportionately as the adhesion tension increased, as shown in Fig. 3.

It is speculated that surface free energy influences the internal structure of granules. We therefore measured the total pore volume of the granules; this was done by mercury porosimetry. Figure 4 shows the relationship between the adhesion tension and the total pore volume of granules prepared by the agitating and fluidized bed granulation methods. It was found that the value of the total pore volume decreased with increasing adhesion tension.

**Effects of Lactose Solubility on the Physical Properties of Granules** The effects of the granulating fluids as binder solutions governing the physical properties of granules were investigated. The relationship between mean granule diameter and lactose solubility is shown in Fig. 5. For the agitating granule method, the mean granule diameter was maximum at 11 kg/m$^3$ (50/50% w/w water/IPA), while for

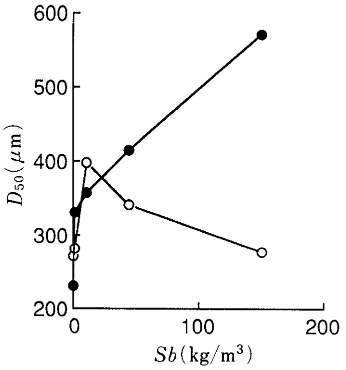

Fig. 5. Relationship between Lactose Solubility (*Sb*) and Mean Granule Diameter ($D_{50}$)

○, agitating granulation method; ●, fluidized bed granulation method.

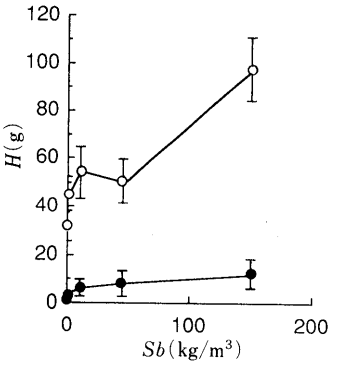

Fig. 6. Relationship between Lactose Solubility (*Sb*) and Granule Hardness (*H*)

○, agitating granulation method; ●, fluidized bed granulation method.

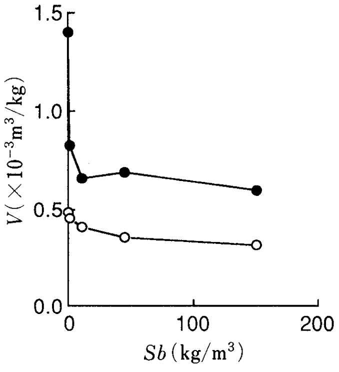

Fig. 7. Relationship between Lactose Solubility (*Sb*) and Total Pore Volume of Granule (*V*)

○, agitating granulation method; ●, fluidized bed granulation method.

the fluidized bed granulation method, the mean granule diameter increased proportionately as lactose solubility increased.

Figure 6 shows the relationship between granule hardness and lactose solubility. Granule hardness increased with increasing lactose solubility with both methods, but the degree of increase was slightly greater with the agitating granulation method. It is clear, therefore, that lactose solubility contributes significantly to granule hardness. This effect, presumably, is due to secondary binding which occurs as a result of the recrystallization of dissolved lactose.

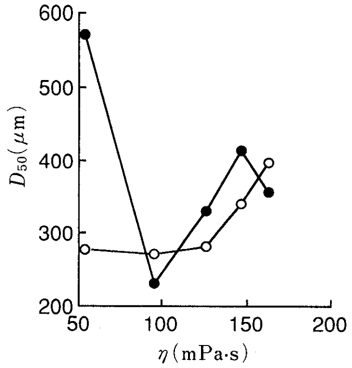

Fig. 8. Relationship between Viscosity of Binder Solution ($\eta$) and Mean Granule Diameter ($D_{50}$)

○, agitating granulation method; ●, fluidized bed granulation method.

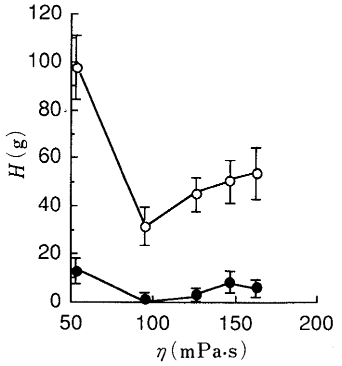

Fig. 9. Relationship between Viscosity of Binder Solution ($\eta$) and Granule Hardness (*H*)

○, agitating granulation method; ●, fluidized bed granulation method.

With both methods, the total pore volume of the granules decreased with increasing lactose solubility, as shown in Fig. 7; however, with the fluidized bed granulation method, the total pore volume of the granules decreased rapidly with slight increases in lactose solubility.

**Effects of Binder Solution Viscosity on the Physical Properties of Granules** The effects of binder solution viscosity on the physical properties of granules had been discussed by Ritala *et al.*[9] and Leuenberger.[10] If the binder solutions are highly viscous, the binder will not be homogenously distributed, and this might result in weaker granules due to insufficient bonding forces, since liquid bonding agents are freely mobile.

Figure 8 shows the relationship between the viscosity of binder solution ($\eta$) and mean granule diameter ($D_{50}$). For the agitating granulation method, the mean granule diameter increased as the viscosity increased, but for the fluidizing bed granulation method, the mean granule diameter fell rapidly and rose at a viscosity of 95 mPa·s.

These results showed a remarkably different mean granule diameter depending on the granulating method used. In general, then, effects of adhesion tension, solubility, and viscosity of the binder solution on granule size cannot be compared, since the granulating mechanism differs with different granulating methods.

Figure 9 shows the relationship between the viscosity of the binder solution ($\eta$) and granule hardness (*H*). As the viscosity increased, granule hardness decreased rapidly and then increased slightly (for the agitating granule

Table II. Responses and Factors

| Response | $b_0$ | $b_1$ | $b_2$ | $b_3$ | $b_4$ | $b_5$ | $b_6$ | $b_7$ | $b_8$ | $b_9$ | $R^2$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Agitating granulation method | | | | | | | | | | | |
| $D_{50}$ | 37.36 | −2.385 | −1.575 | −6.635 | −0.087 | 0.230 | — | −0.143 | 0.016 | — | 0.96116 |
| $H$ | 9.58 | −1.378 | — | 19.72 | 0.052 | 0.085 | −0.188 | −0.016 | −0.007 | −0.242 | 0.98974 |
| $Fr$ | −3.85 | −3.849 | −0.956 | 2.204 | — | −0.167 | — | 0.113 | 0.041 | 0.057 | 0.99800 |
| $V$ | −0.53 | −0.531 | −0.531 | −1.913 | 0.004 | 0.004 | — | 0.009 | — | −0.0004 | 0.99989 |
| Fluidized bed granulation method | | | | | | | | | | | |
| $D_{50}$ | −0.305 | −0.682 | — | 13.82 | −0.006 | −0.164 | −0.086 | 0.106 | — | −0.063 | 0.99740 |
| $H$ | 1.885 | 0.820 | −0.160 | 2.594 | −0.001 | — | −0.011 | −0.003 | 0.004 | −0.021 | 0.99989 |
| $Fr$ | 216.4 | −4.114 | −3.677 | −1.380 | 0.051 | — | — | — | 0.016 | 0.033 | 0.97691 |
| $V$ | 169.4 | −2.862 | −2.285 | −7.228 | — | −0.094 | 0.076 | 0.052 | 0.012 | 0.126 | 0.99473 |

At $p<0.05$. —, not found.

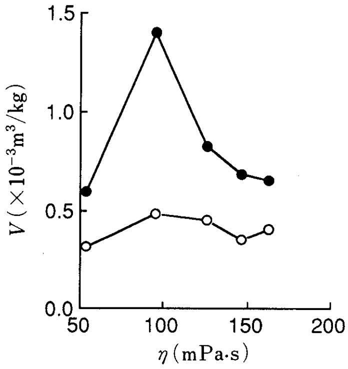

Fig. 10. Relationship between Viscosity of Binder Solution ($\eta$) and Total Pore Volume of Granule ($V$)

○, agitating granulation method; ●, fluidized bed granulation method.

method), or decreased slightly (for the fluidized bed granulation method). The weaker granules were produced as a result of insufficient bonding forces due to the viscosity of the binder solution being 95 mPa·s.

The total volume of granules had a maximum value at a viscosity of 94 mPa·s, as shown in Fig. 10. At this viscosity (94 mPa·s), the granules had a high pore volume, resulting in weaker granules, as shown in Fig. 9.

The physical properties of the granules were influenced by many factors such as surface tension, solubility and the viscosity of the binder solution. In the present study, we used five binders of different components to assess the importance of binder film-substrate adhesion on the hardness of granules prepared by both the fluidized bed and agitating methods.

Granule hardness depends on lactose solubility since lactose provides secondary binding due to its recrystallization from solution.

Based on these results, we carried out statistical analysis of the data by applying multiple regression analysis. We calculated the coefficient of the polynomial for each examined physical property of the granules. A response "$Y$" (which may be: mean granule diameter, hardness, *etc.*) can be represented by a regression equation of the following form:

$$Y=b_0+b_1X_1+b_2X_2+b_3X_3+b_4X_1X_2+b_5X_1X_3 +b_6X_2X_3+b_7X_1^2+b_8X_2^2+b_9X_3^2 \qquad (2)$$

where $b_0, b_1, b_2, \cdots, b_9$ are different coefficients, $X_1$ is the adhesion tension, $X_2$ is the viscosity of binder solution, $X_3$ is the lactose solubility.

The effects of three physicochemical factors and the second-order interaction of these physical properties were determined by multiple regression analysis. The significances are shown in Table II, when the significance, $p$, is less than 0.05.

The following equation was used to normalize the different levels:

$$N=[(X-L)/(H-L)]\times 100 \qquad (3)$$

where $N$ is the normalized factor level, $X$ is the non-normalized factor level, and $L$ and $H$ are the lowest and highest levels, respectively, for a specific factor.

A summary of the significant coefficients of the factors and factorial interactions of the four responses studied is shown in Table II. Mean granule diameter indicated the significance of the adhesion tension and solubility for the agitating granulating method, whereas in the fluidized bed granulation method, solubility was most significant. With both methods, the hardness and friability of granules were affected by adhesion tension and solubility.

The physical properties of granules such as mean granule diameter, granule hardness, friability and pore volume of granules are affected by the following fractors in the following order except the friability index ($Fr$) prepared by fluidized bed granulation:

$$Sb>\gamma\cos\theta>\eta$$

## Conclusions

Mechanical properties of granules such as hardness and friability were influenced by the granulating fluid used in the granulation process.

The total pore volume of the granules varied in proportion to increase of certain components of the granulating fluids, and this effect resulted in a decrease in granule hardness. Granule hardness, friability, and pore volume correlated well with lactose solubility, since solid deposits of lactose make a secondary binder.

The results of the multiple regression analysis carried out here can be applied to quantitative relationships between the physical properties of granules and such properties of the solvent solution as surface tension, contact angle, viscosity, and solubility.

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