Improving Powder Flow Properties of a Direct Compression Formulation Using a Two-Step Glidant Mixing Process

Hidaka Abe,*[,a] Shinichiro Yasui,[a] Aya Kuwata,[b] and Hirofumi Takeuchi[b]

[a] *Pharmaceutical Research Department, Mitsubishi Tanabe Pharma Corporation; 14 Sunayama, Kamisu, Ibaraki 314–0255, Japan: and* [b] *Laboratory of Pharmaceutical Engineering, Gifu Pharmaceutical University; 5–6–1 Mitahora-higashi, Gifu 502–8585, Japan.* Received October 6, 2008; accepted April 3, 2009; published online April 21, 2009

To improve powder flow of a high-dose direct compression formulation (drug content 30%), we compared a two-step operation for mixing glidants with a conventional one-step glidant mixing process. This two-step mixing operation was studied with two kinds of mixtures; an active pharmaceutical ingredient (API)-glidant combination and a direct compression excipient-glidant combination. The two-step operation permitted the selection of the optimum glidant type and concentration in each glidant-mixing procedure even though the formulation had different powder properties such as micronized API and enlarged direct compression vehicles, whereas the conventional approaches forced the selection of a certain glidant type and concentration at one-step mixing. The addition of 0.5% nonporous silica markedly improved API flow. In contrast, 1.0% porous silica was the appropriate glidant to enhance excipient flow at direct compression excipient-glidant mixing. The two-step operation dominantly enhanced powder flow when the appropriate API-glidant mixture and the suitable direct compression excipients-glidant mixture were blended compared to the one-step operation with its optimum glidant concentration. The results showed that the angle of repose was 43° and the critical orifice diameter was 10 mm in the two-step operation, whereas it was 47° and 16 mm in the one-step operation. The two-step operation of glidant mixing enhanced powder flow of the high-dose direct compression formulation compared with the one-step operation. The two-step operation eliminates the bottleneck of powder flow and allows direct compression to be more worth applying for formulation and process development trials.

Key words glidant; colloidal silicon dioxide; powder flow; direct compression; flowability; silica

Direct compression is a faster, simpler, and easier technique for tablet manufacturing compared to other processes such as wet and dry granulation techniques because it only requires mixing and compression. In addition to mixing and compression, wet granulation requires granulation, drying, and milling. Each additional step generates variability in the process and increases the risk of out-of-specification products. Fewer steps in the manufacturing process are advantageous for pharmaceutical industries; however, the application of direct compression has been limited due to issues of powder flowability, content uniformity and tabletability. A failure of powder flow often leads to abandon direct compression and adopt granulation process during formulation and process development trials. Flow has a direct impact on decision of whether to start out developing direct compression. Additionally, flowability and tabletability often develop into critical quality factors of high-dose tablets, while content uniformity causes the major concern in low-dose tablets.[1)] Therefore, unfavorable powder flow is the fundamental and serious bottleneck to be first eliminated in the direct compression processing.

Glidants are usually incorporated in direct compression formulations to improve powder flow and control tablet weight. Specifically, silica has been reported to be the most efficient glidant because of its small particle size and extremely low-density.[2)] Moreover, direct compression vehicles, such as spray-dried lactose and agglomerated lactose instead of fine-powder lactose, are commonly used to remedy flow properties. Several studies have reported that powder flowability can be significantly enhanced with the optimum concentration of porous or nonporous silica,[3)] appropriate mixing time,[4)] correct mixer type[5,6)] and hydrophilic or hydrophobic silica properties.[7)] However, most of the studies have focused only on the relationships between the glidant and the direct compression vehicles and have excluded an active pharmaceutical ingredient (API), even though API powder properties are quite different from these excipients for direct compression. Generally, APIs are micronized to improve solubility and bioavailability, and consequently tend to be cohesive. In contrast, the direct compression vehicles are usually agglomerated and enlarged to become free flowing. Therefore, micronized API and enlarged direct compression vehicles are the most interesting and noteworthy factors to comprehensively improve the flow properties of a direct compression formulation.

Shear mixing plays a critical role in blending for direct compression, particularly for low-dose drug products containing lubricants (*e.g.*, magnesium stearate and calcium stearate). The homogeneity of the low-dose API requires sufficient mixing and results in excessive shear on magnesium stearate. The excessive shear mixing of the lubricant reduces the mechanical strength of the direct compression tablets by producing a surplus coating of the finely divided magnesium stearate particles.[8)] In this particular case, the mixing of the API and the lubricant is separated to meet the quality specifications of homogeneity and tablet hardness; API and the other excipients, except for the lubricant, are mixed to achieve homogeneity, and then the mixed powder is blended with the lubricant. Shear mixing of the glidant is also considered to be as important as the lubricant because the glidants are required to coat the entire surface of all host particles; however, the glidant has always been mixed with micronized API and enlarged direct compression vehicles in one operation. Additionally, several types of colloidal silicon dioxide are currently available so that formulators have a wide range of options for improving powder flow.

* To whom correspondence should be addressed. e-mail: Abe.Hidaka@mg.mt-pharma.co.jp

To improve powder flow of high-dose tablet including all the micronized and enlarged particles, we split glidant mixing into two independent steps; API-glidant mixing and pharmaceutical excipient-glidant mixing. In this proposed two-step operation, the glidant is mixed with API, another glidant is mixed with the direct compression vehicles, and the two mixed powders are blended for tabletting. This method allows the different glidant types of their proper concentrations to be optimized for each particle characteristic at each glidant mixing step. In this paper, we identify the (I) characteristics of silica (II) optimum silica for API, and (III) appropriate silica for direct compression vehicles. This study demonstrates a two-step operation to blend an API-glidant mixing powder and a direct compression excipient-glidant mixing powder improve flowability when compared with the one-step operation in (IV) comparison of flowability between two-step and one-step operations. In this study, the high-dose direct compression formulation contained 30% API because the drug content of direct compression is generally limited to approximately 30% or approximately 50 mg.[9)]

Experimental

Powder Sample The following ingredients were used: API (Mitsubishi Tanabe Pharmaceutical Corporation, Japan), lactose (Pharmatose® DCL-11 (SuperTab® 11SD), DMV-Fonterra Excipients Gmbh & Co. KG, Netherlands), microcrystalline cellulose (Ceolus® PH-302, Asahi Kasei Corporation. Japan), sodium starch glycolate (Primojel®, DMV-Fonterra Excipients Gmbh & Co. KG, Netherlands), and magnesium stearate (Vegetable grade, Merck Ltd., Germany). Two types of silicon dioxide were tested as glidants; nonporous silica (silicon dioxide, highly dispersed, extra pure; Merck Ltd., Germany) and porous silica (Sylysia® 320, Fuji Silysia Chemical Ltd., Japan).

Manufacturing Process Flow diagrams of the two-step manufacturing operation and the one-step glidant mixing process are shown in Figs. 1 and 2, respectively. All mixing processes were performed in a 1-l high-shear mixer (Mechanomill MM-20N, Okada Seiko Co., Ltd., Japan) at an agitator rotational speed of 900 rpm for 5 min.

The API was combined with different concentrations of porous and nonporous silica (Table 1), and the direct compression excipients were mixed with different concentrations of porous and nonporous silica (Table 2). After identifying the optimum glidant and concentration, the two-step mixing process was carried out to produce the proper formulation (Table 3). For the one-step method, the glidant proportions were optimized and mixed in three batches with different concentrations of porous and nonporous silica (Table 3).

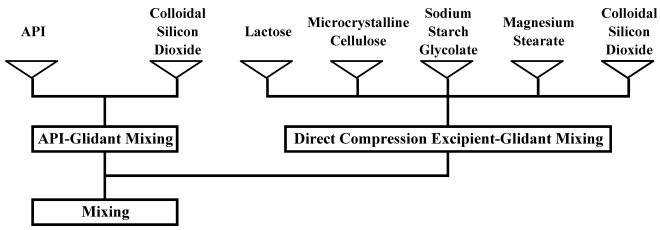

Fig. 1. Schematic Diagram of the Two-Step Operation of the Glidant Mixing Process

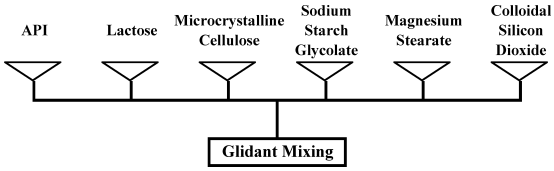

Fig. 2. Schematic Diagram of the One-Step Operation of the Glidant Mixing Process

Table 1. Components and Compositions for API-Glidant Mixing

	A	B	C	D	E	F	G	H	I
API	100.0	99.5	98.0	95.0	92.0	99.5	99.0	98.0	95.0
Silicon dioxide, nonporous silica (Merck)	0	0.5	2.0	5.0	8.0	0	0	0	0
Silicon dioxide, porous silica (Sylysia® 320)	0	0	0	0	0	0.5	1.0	2.0	5.0

Table 2. Components and Composition for Direct Compression Excipient-Glidant Mixing

	J	K	L	M	N	O	P	Q	R
Lactose (Pharmatose® DCL-11)	74.0	73.9	73.5	72.0	69.0	73.9	73.5	73.0	72.0
Microcrystalline cellulose (Ceolus® PH-302)	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0
Sodium starch glycolate (Primojel®)	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Magnesium stearate (Merck)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Silicon dioxide, nonporous silica (Merck)	0	0.1	0.5	2.0	5.0	0	0	0	0
Silicon dioxide, porous silica (Sylysia® 320)	0	0	0	0	0	0.1	0.5	1.0	2.0

Table 3. Components and Composition for the Two-Step and One-Step Operations

	1	2	3	4
	Two-step operation	One-step operation		
API	30.00	30.00	30.00	30.00
Lactose (Pharmatose® DCL-11)	43.15	43.50	43.00	43.15
Microcrystalline cellulose (Ceolus® PH-302)	20.00	20.00	20.00	20.00
Sodium starch glycolate (Primojel®)	5.00	5.00	5.00	5.00
Magnesium stearate (Merck)	1.00	1.00	1.00	1.00
Silicon dioxide, nonporous silica (Merck)	0.15[a)]	0.50	0	0.15
Silicon dioxide, porous silica (Sylysia® 320)	0.70[b)]	0	1.00	0.70

a) Equivalent to 0.5% glidant concentration in API-glidant mixing. *b*) Equivalent to 1% glidant concentration in direct compresion excipient-glidant mixing.

Characterization Methods The shape and surface morphology of the ingredients was examined with a scanning electron microscope (SEM) (VE-9800, Keyence Corporation, Japan). The dry particles were mounted on a plate and coated with gold palladium under vacuum using an ion coater. The coated specimen was photographed under the microscope.

The particle-size distribution was analyzed using laser diffraction (Master Sizer, Malvern Instruments Ltd., U.K.). The sample was introduced into the sample cell *via* a dry-powder feeder (Malvern Instruments Ltd., U.K.). An external vacuum was connected to the other side of the sampling cell to simultaneously disperse and remove the particles from the system, and the median volume diameters (d_{50}) were recorded.

Flow properties of the mixed powder were characterized by critical orifice diameter, angle of repose, and compressibility index. The critical orifice diameter was obtained using a critical orifice diameter tester (Konishi Seisakusho, Co., Ltd., Japan) and defined as the minimum-diameter orifice through which 10-g powder flows could be identified. The angle of repose was determined in triplicates using a powder tester (PT-R, Hosokawa Micron Corporation, Japan) by vibrating an 850 μm sieve and mounting the sample powder on an 8-cm diameter plate. The midpoint of the corned powder was measured with a protractor. The bulk and tapped densities were measured using a powder tester to determine the compressibility index. The compressibility index[10,11] was calculated by the following equation:

$$CI=(1-\rho_{bulk}/\rho_{tap})\times 100 \quad (1)$$

where, CI is the compressibility index, ρ_{bulk} is the bulk density, and ρ_{tap} is the tapped density. The bulk density (mass/volume) was determined by adding powder into a 250-ml graduated cylinder. The tapped density was determined by attaching an accessory to the cylinder for additional volume, filling it with powder, and tapping it 300 times. After the accessory and excess powder were removed, the remaining tapped powder in the cylinder was weighed and the tapped density was determined by mass/volume.

Results and Discussion

(I) Physicochemical Properties of the API, Direct Compression Excipients, and Colloidal Silicon Dioxide Figure 3 shows the SEM micrographs of the API, the direct compression vehicles and the colloidal silicon dioxide. Table 4 summarizes the physicochemical properties of the raw materials. The SEM micrographs revealed the micronized API featured a smooth and flat surface, whereas the spray-dried lactose, the microcrystalline cellulose and the porous silica had a rough surface and grainy structure. The observed particle size of porous silica was smaller than that of nonporous silica. However, the primary particle diameter of the porous silica (3 μm) was almost two orders of magnitude larger than that of the nonporous silica (1×10^{-2} μm).

The SEM micrographs and the physicochemical properties suggest that the porous silica has a rough surface; by contrast, the nonporous silica has a tendency to form soft agglomerates. The nonporous silica generally appears to be a more spherical particle than that of porous silica from the report.[12] The primary particle of porous silica is composed of a large number of sub-particles, whereby leads to make the porous structure and the rough surface.[13] These studies and findings of colloidal silicon dioxide suggest that other than the fundamental difference in the existence of porosity, primary particle size and shape are also different between the porous and nonporous silica. These different geometric structures of silica, *i.e.*, primary particle size and shape, were used to improve the flow properties of the API and the direct compression vehicles (spray dried lactose, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate) at glidant mixing processes of the one-step and two-step operations (Fig. 1).

(II) Optimum Glidant at API-Glidant Mixing Each

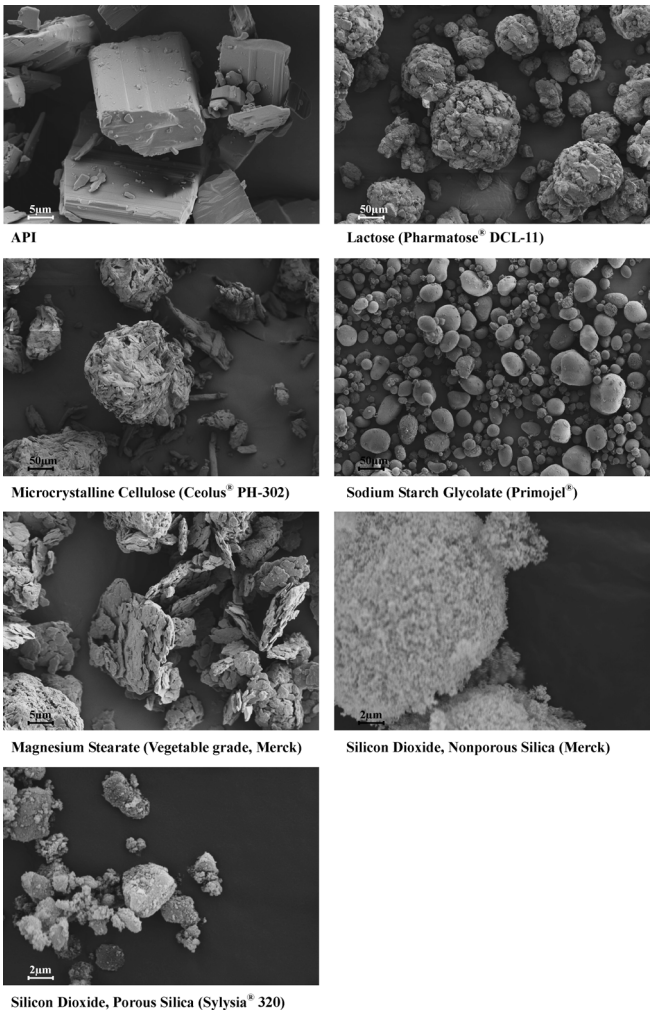

Fig. 3. SEM Micrographs of the API and Direct Compression Excipients

Table 4. Physicochemical Properties of the Raw Materials

	D_{50} (μm)	Volume test[a] (ml/5 g)	Specific surface (m^2/g)	Pore size (nm)	Pore volume (ml/g)
API	10	—	—	—	—
Lactose (Pharmatose® DCL-11)	123	—	—	—	—
Microcrystalline cellulose (Ceolus® PH-302)	125	—	—	—	—
Sodium starch glycolate (Primojel®)	40	—	—	—	—
Magnesium stearate (Merck)	19	—	—	—	—
Silicon dioxide, nonporous silica (Merck)	1×10^{-2} [b]	120[c]	205[c]	—	—
Silicon dioxide, porous silica (Sylysia® 320)	3[b]	100[c]	300[b]	21[b]	1.60[b]

a) Complied with Japanese Pharmacopoeia. *b*) Manufacturer technical information. *c*) Manufacturer lot certificate of analysis.

colloidal silicon dioxide, nonporous silica and porous silica, was mixed with micronized API to select the optimum glidant for improving the flow properties of the API. Figures 4 and 5 show the influences of the geometric structure (primary particle size and shape) and the concentration of colloidal silicon dioxide on the angle of repose and compressibility index of the API mixture. Adding colloidal silicon dioxide drastically improved the powder flow of the API. Nonporous silica enhanced powder flow more than porous silica. Adding 0.5% nonporous silica to the API mixture resulted in a minimum angle of repose of 47.5° and a compressibility index of 37.6%, indicating that addition of 0.5% nonporous silica appropriately improved API flow.

The finding that flow properties were improved by adding the glidant is consistent with the reports.[14,15] The effect of glidant on improved flow properties may be explained by the ratio of the van der Waals and the gravitational forces or a ball-bearing type of action.[5,16] When the fine glidant particles adhere to the surface of the granules they separate the two host granules and increase the distance between them. This action leads to a reduction in the van der Waals forces between the host granules and allows the gravitational force to prevail. During a ball-bearing type of action, the glidants form a monoparticle layer on the host particles causing them to roll over one another, which reduces the frictional and adhesive forces that operate between the surfaces. Assuming that the glidants act like the ball bearing, it is reasonable to suggest that the nonporous silica is preferable because its primary particle has a more spherical shape than that of porous silica as described in previous section (I).

The primary particles of nonporous silica are linked to relatively stable aggregates, which, in turn, form larger agglomerates.[5] By the shear forces of mixing, the glidant agglomerates are separated into smaller particles, and the glidant particles are distributed on the surface of the host particles. If only a small amount of the glidant is added to the powder, the glidant is not proportional to the large number of host particles, whereas addition of an excess amount of glidant keeps the glidant particles from spreading out. Therefore, powder flowability is sensitive to glidant concentration.

(III) Optimum Glidant at Direct Compression Excipient-Glidant Mixing Each colloidal silicon dioxide, nonporous silica and porous silica, was mixed with the direct compression excipients to identify the optimum glidant for improving the flow properties of the excipients. Figures 6 and 7 indicate the effects of the geometric structure (primary particle size and shape) and the concentration of colloidal silicon dioxide on the angle of repose and the compressibility index of the direct compression excipient mixture. The addition of either type of silica improved the powder flow of the direct compression excipient mixture and the API mixture. However, in contrast to the API mixing, porous silica improved the direct compression excipient flow more than the nonporous silica. The addition of 1.0% porous silica to the pharmaceutical excipients produced a favorable 37.3° angle of repose and an excellent 6.9% compressibility index.

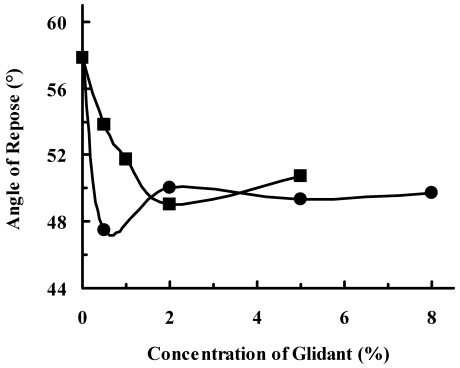

Fig. 4. Relationships between the Angle of Repose of the API and Various Concentrations of Glidants

●, nonporous silica; ■, porous silica.

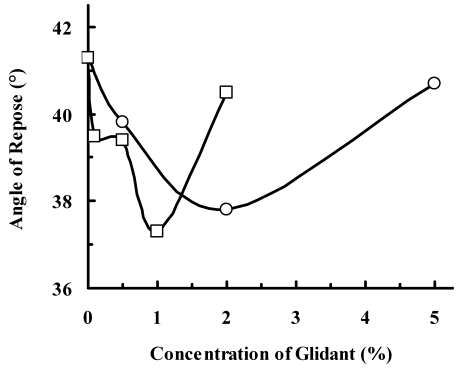

Fig. 6. Relationships between the Angle of Repose of the Direct Compression Excipients and Various Concentrations of Glidants

○, nonporous silica; □, porous silica.

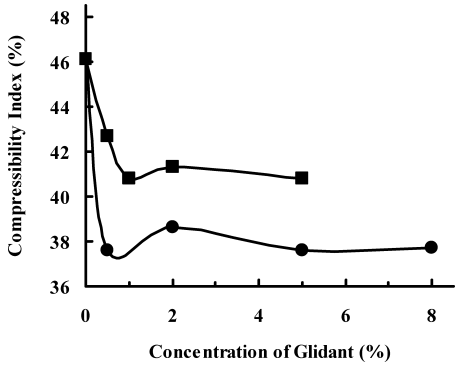

Fig. 5. Relationships between the Compressibility Indices of the API and Various Concentrations of Glidants

●, nonporous silica; ■, porous silica.

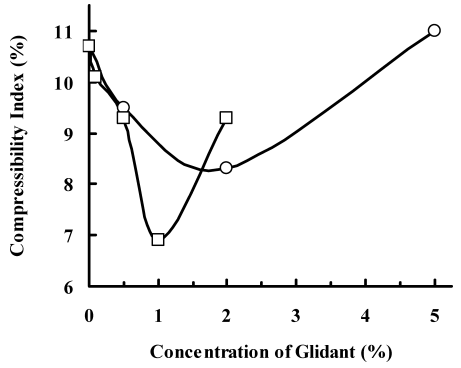

Fig. 7. Relationships between the Compressibility Indices of the Direct Compression Excipients and Various Concentrations of Glidants

○, nonporous silica; □, porous silica.

Table 5. Comparative Powder-Flow Properties from the Two-Step and One-Step Operations

	1	2	3	4
	Two-step operation	One-step operation		
Composition of mixture				
Silicon dioxide, nonporous silica (Merck)	0.15[a)]	0.50	0	0.15
Silicon dioxide, porous silica (Sylysia® 320)	0.70[b)]	0	1.00	0.70
Flow properties				
Angle of repose (°)	43.3	47.5	47.2	44.8
Compressibility index (%)	22.7	29.9	27.7	28.6
Critical orifice diameter (mm)	10.0	16.0	16.0	12.5

a) Equivalent to 0.5% glidant concentration in API-glidant mixing. *b*) Equivalent to 1% glidant concentration in direct compresion excipient-glidant mixing.

The appropriate proportion and type of glidant for the direct compression excipients is different than for the API. This discrepancy can be attributed to the different particle surfaces between the API and the direct compression excipients as well as the difference in the particle size between porous and nonporous silica. Spray-dried lactose, which is the primary component in the group of direct compression excipients, features a rough surface for good tabletability compared with the properties of API (Fig. 3). The small particles of the glidant, which are localized and hidden into gaps on the irregular surface of lactose, would neither act like ball bearings nor increase the distance between the excipients. Nonporous silica is much smaller than porous silica. In general, if mixed sufficiently, the agglomerates of nonporous silica are broken down to smaller nanoparticles that can coat the surface of the large particles.[7,17)] The agglomerates of nonporous silica seem to be separated into the smaller nanoparticles of aggregates in this experimental condition of shear mixing, and then their particles become reduced in almost the same size as the primary particles. In contrast, primary particles of porous silica are almost two orders of magnitude of larger than those of nonporous silica and are more suited to avoid the negative mixing properties resulting from the distinguished irregular surface of lactose. Thus, porous silica appears to be the optimum glidant for improving the powder flow of the direct compression excipients.

(IV) Comparison of Flowability between the Two-Step and One-Step Operations The optimized API-0.5% nonporous-silica mixture and the appropriate pharmaceutical excipient-1.0% porous silica mixture were blended, and its flowability was evaluated and compared to that of the one-step operation. Table 5 shows the comparison of the powder-flow properties between the two-step and the one-step operations. The results of batches 1, 2, and 3 show that the suitable glidant combinations with their optimum concentrations increased flowability of the two-step operation compared with the one-step operation. The angle of repose was 43° and the critical orifice diameter was 10 mm in the two-step operation, whereas it was 47° and 16 mm in the one-step operation. In the one-step operation, the powder flow of the direct compression formulation was almost the same regardless of the type of silica that was added with its appropriate concentration. The results of batches 1 and 4 indicate that the two-step operation improved the flow over the one-step operation in the same powder formulation, showing compressibility index of 22.7% and 28.6% and critical orifice diameter of 10.0 mm and 12.5 mm, respectively.

Two factors likely contributed to the improved powder flow that resulted from using the two-step operation. First, the proposed two-step operation permits the selection of the optimum silica type with its suitable concentration for the API and the direct compression vehicles at each glidant mixing step, whereas a particular silica type and its optimum concentration must be chosen at the one-step process. Secondly, the two-step operation allows the glidants to form the appropriate layer on the surface of API and on the direct compression vehicles because of the independent glidant mixing process. In this regard, the one-step process makes it difficult to form the appropriate layer on the surface of a mixed powder with different particle sizes and densities properties. This idea is supported by the resultant flow properties of the same powder formulation using the two glidant mixing operations in batches 1 and 4 of Table 5. In addition, the particle state of silica reportedly has considerable influence on the flow characteristics of a powder during the mixing process; in the mixing process the agglomerates of nonporous silica are sufficiently broken down to smaller nanoparticles that can provide the uniformity of coverage on the surface of host particles, and then the homogeneous distribution of silica particles qualitatively correlated to the flow-enhancement.[7)] Therefore, the superior flow-improvement of two-step operation can be related to the two factors: (a) the selection of optimum silica at a suitable concentration in each the API mixing and the direct compression excipient mixing and (b) the formation of a proper silica-particle layer on each of the API and pharmaceutical-excipient host particles.

Conclusion

The proposed two-step operation of glidant mixing improved the powder-flow properties of the high-dose direct compression formulation compared with the conventional one-step operation. This favorable comprehensive improvement stems from the following features: (a) the selection of optimum silica at a suitable concentration in each the API mixing and the direct compression excipient mixing and (b) the formation of a proper silica-particle layer on each of the API and pharmaceutical-excipient host particles.

The two-step operation eliminates the principal bottleneck of powder flow and allows direct compression to be more worth applying for the formulation and process development trials.

References

1) Shiromani P. K., *Pharma & Bio Ingredients*, **January**/**February**, 30—34 (2006).
2) Sheth B. B., Bandelin F. J., Shangraw R. F., "Pharmaceutical Dosage Forms: Tablets," Vol. 1, Marcel Dekker, New York, 1980, pp. 141—143.
3) Ohta K. M., Fuji M., Chikazawa M., *Pharm. Res.*, **20**, 804—809 (2003).
4) Sindel U., Schweiger A., Zimmermann I., *J. Pharm. Sci.*, **87**, 524—526 (1998).
5) Jonat S., Hasenzahl S., Drechsler M., Albers P., Wagner K. W., Schmidt P. C., *Powder Technol.*, **141**, 31—43 (2004).
6) Jonat S., Albers P., Gray A., Schmidt P. C., *Eur. J. Pharm. Biopharm.*, **63**, 356—359 (2006).
7) Jonat S., Hasenzahl S., Gray A., Schmidt P. C., *J. Pharm. Sci.*, **93**, 2635—2644 (2004).
8) Mehrotra A., Llusa M., Faqih A., Levin M., Muzzio F. J., *Int. J. Pharm.*, **336**, 284—291 (2007).
9) Jivraj M., Martini L. G., Thomson C. M., *Pharm. Sci. Technol.*, **3**, 58—63 (2000).
10) "United States Pharmacopeia, USP XXX," NF 25, United States Pharmacopeial Convention, Rockville, MD, 2006, pp. 643—646.
11) Carr R. L., *Chem. Eng.*, **18**, 163—168 (1965).
12) Ohta K. M., Toyoshima K., Fuji M., Takei T., Chikazawa M., *J. Soc. Powder Technol.*, **41**, 169—176 (2004).
13) Okuyama K., Masuda H., Higashitani K., Chikazawa M., *J. Soc. Powder Technol.*, **22**, 451—475 (1985).
14) Cabot Corporation, "Technical Data Sheet, Properties of CAB-O-SIL® M-5P Fumed Silica," ⟨http://www.cabot-corp.com/⟩ 1995.
15) Cabot Corporation, "Technical Data Sheet, Influence of CAB-O-SIL® M-5P on the Angle of Repose and Flow Rates of Pharmaceutical Powders," ⟨http//:www.cabot-corp.com/⟩ 2005.
16) Jonat S., "The Mechanism of Hydrophilic and Hydrophobic Colloidal Silicon Dioxide Types as Glidants," ⟨http://w210.ub.uni-tuebingen.de/dbt/volltexte/2005/1712/⟩ 2005.
17) Evonik Industries AG (Degussa), Technical Information, AEROSIL® Colloidal Silicon Dioxide for Pharmaceuticals, TI 1281-1/Apr06.