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Selection of Small Amounts of Glidant Capable of Improving the Tensile Strength of Ibuprofen Tablets

Tetsuo Ono,*,a,b Agata Ishikawa,a and Etsuo Yonemochi* ,a

a Department of Physical Chemistry, Hoshi University; 2–4–41 Ebara, Shinagawa-ku, Tokyo 142–8501, Japan; and b Research & Development Headquarters Self-Medication, Taisho Pharmaceutical Co., Ltd.; 1–403 Yoshinocho, Kita-ku, Saitama 331–9530, Japan.

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This study examined the selection of small amounts of excipients capable of improving the compactability of ibuprofen, thereby enabling the miniaturization of ibuprofen tablets. Various glidants in amounts of 1% of the total volume were added to dry surface-modified ibuprofen, and the tensile strengths of the resulting tablets were evaluated. The characteristics of the excipients that affected the tensile strengths of the tablets were then extracted using a tensile strength prediction model. We confirmed that the effective angle of the internal friction of the mixed powder, the coating form of the glidant, the packing fraction of the raw material, and the mixed powder affect the tensile strength of the tablet. A smooth particle layer was formed on the surface of the ibuprofen particles when a glidant with a packing fraction of <0.05 was used. In the sample with a smooth particle layer, the angle of the critical state line increased significantly and the tensile strength improved. We inferred that the smoothness of the particle layer allowed the ibuprofen particles to come into close contact with each other. Consequently, the number of junctions increased, and the frictional force between the particles improved, resulting in tablets with improved tensile strengths. In conclusion, the compactability of ibuprofen was improved by adding 1% glidant with a packing fraction of <0.05. The reduction in excipients will allow the creation of smaller tablets, making them easier to swallow. Therefore, the medication adherence of customers will be improved.

Key words tensile strength; packing fraction; internal friction angle; surface modification; dry powder coating; compactability

Introduction

OTC drugs are important solutions that allow consumers to deal with mild illnesses by themselves. 1 Since OTC drugs are selected and purchased by consumers themselves, not only the effectiveness and quality of these drugs but also added values, such as ease of swallowing and convenience, are important differentiating factors.

OTC drugs are generally a combination of drugs consisting of several active pharmaceutical ingredients (APIs). For example, analgesics include a combination of multiple analgesic ingredients, an antacid that protects the stomach, and caffeine to enhance the analgesic effect.2,3 Cold medicines are combinations of antipyretics, antitussives, expectorants, antihistamines, etc., added to combat various cold symptoms, and these medicines sometimes contain more than 10 different APIs mixed together.4,5

As the number of APIs increases, the total quantity of APIs also increases, which tends to lead to larger tablets. The larger the tablet, the more difficult it is to swallow, so avoiding increases in tablet size should be a consideration from the perspective of promoting medication adherence among customers.5 Consequently, the quantities of excipients should be reduced to avoid increases in tablet size if the quantity of APIs in each tablet increases.7,8

Tablets are a common dosage form favored by consumers because of their ability to mask the bitterness of medications and the ease with which tablets can be counted and handled. However, tablet formulation requires special consideration, such as the need for compactability and disintegration, uniformity, and the prevention of interactions caused by the adhesion of ingredients. Excipients play an important role in ensuring the compactability, disintegration properties, storage stability, content uniformity, and API elution of tablets. For this reason, simply reducing the quantities of excipients can cause quality defects and manufacturing difficulties; therefore, careful consideration is required.5,9–11

Ibuprofen is an API that is commonly used in OTC drugs. Ibuprofen is used not only as an analgesic, but also as a cold remedy and an anti-inflammatory analgesic ingredient with excellent effects.12 On the other hand, ibuprofen is relatively difficult to formulate because of its high dose, low melting point, cohesiveness, sublimation, and interactions with other APIs and excipients.13–15

Surface modification is a method for improving the cohesiveness and flowability of APIs using a small amount of additives.16 The surface modification method can alleviate problematic properties by coating the surface of API particles with fine-particle excipients or water-soluble polymers. In particular, the dry surface modification method is a simple coating method that involves simply mixing a drug and an excipient; several studies describing such methods have been reported.17,18 In recent years, several reports have described the development of dry powder inhalation (DPI) formulations in which, unlike the simple mixtures described above, each excipient particle is coated with fine API particles.19–21 In this type of dry surface modification, guest particles consisting of APIs or excipients are attached to the surfaces of core particles, so these guest particles should be sufficiently smaller...
Gildants are excipients that are mainly composed of inorganic components, and various types of gildants with different components and physical properties are available commercially. Silica-based gildants have features that are not found in other excipients, such as a nano-sized primary particle size, a high specific surface area, and a low bulk density. This type of gildant is an indispensable excipient in solid formulation design because of its ability to improve the flowability, cohesiveness and adhesion of powders through the addition of a few percent of gildant to the powder. However, no clear index exists for the selection of gildants, so in actual practice, the selection and amount of gildant to be added must be determined based on experience.

To improve the flowability of ibuprofen through dry surface modification, the authors investigated the effect of mixing various inorganic excipients as gildants in various amounts on flowability. As a result, the largest improvement in flowability was obtained by the addition of about 1% of a gildant with a packing fraction $\phi < 0.1$. Furthermore, use of the packing fraction, which is a simple index calculated from the bulk density of the inorganic excipient, allowed the improvement in flowability to be estimated regardless of the composition and physical properties of the formulation.

To develop ibuprofen-containing tablets with an API concentration of 90% or more, this paper focused on improving the compactability of ibuprofen through the use of a gildant. Therefore, we compared the tensile strength of tablets prepared by adding various inorganic excipients at an API ratio of 1% and investigated the effects of these gildants. We analyzed the mechanism of the effect of the gildant in improving compactability by comprehensively analyzing the tensile strength of tablets, the physical properties of the mixed powder containing the gildant, and the physical properties of the gildant itself. We also extracted characteristics common to gildants that are effective for improving the compactability of ibuprofen and attempted to establish an index for gildants that are effective in improving the tensile strength of ibuprofen.

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This study is expected to help problematic physical properties encountered during the development of formulations containing ibuprofen to be overcome by minimizing the addition of excipients. Therefore, the results are expected to contribute to both the compounding of APIs, including ibuprofen, and the miniaturization of tablets, thereby improving the medication adherence of consumers.

### Experimental

#### Materials

**Ibuprofen**

Ibuprofen (S250 grade, Strides Shasun, India) was selected as the model API, since difficulties in tableting particles of this drug have been described, due to their low flowability, cohesiveness and low melting point.

A laser diffraction particle size analyzer (MT-3000; Microtrac, U.S.A.) was used to measure the particle size of ibuprofen. It was measured 3 times using the dry method at a dispersion pressure of 0.2 MPa and a measurement time of 10 s, and the average of MV was used as the mean particle size.

A surface area analyzers (Gemini VII 2390; Micromeritics, U.S.A.) was used to measure the specific surface area of ibuprofen. It was measured 10 points method with N$_2$ gas as an adsorption gas. Before the measurement, the sample was depressurized overnight and replaced with N$_2$ gas.

**Gildants**

As the gildant, 13 types of inorganic excipients with different compositions and particle properties were used. Three types of silica as Aerosil (Nippon Aerosil, Japan) and 2 types as Adsolider (Freund Industry, Japan), 3 types of magnesium metasilicate aluminate as Neusilin (Fuji Chemical Industry, Japan), 2 types of titanium oxide (Evonik, Ishihara Sangyo Kaisha, Japan), Florite RE (Tomita Pharmaceutical Co., Ltd., Japan), Alcamac, and anhydrous calcium hydrogen phosphate (both Kyowa Chemical Industry, Japan) were used.

Most of the gildants that were used were agglomerates composed of nano-sized primary particles, and it was difficult to measure some of the properties with good reproducibility. Therefore, the nominal values provided by the manufacturers were used as the values for the true density $\rho$ and the specific surface area $S$.

The primary particle diameter $D_{pp}$ was calculated from the values for $\rho$ and $S$ of each guest particle (Supplementary Table 2) using a modification of the equation reported by Hayashi et al.:

$$D_{pp} = 6/(\rho \cdot S)$$ (1)

### Methods

#### Preparation of Mixed Powders

A high shear granulator (VG-5L; Powrex, Japan) was used to prepare the mixed powders using the dry mixing method. The amount of gildant to be added was fixed at 1% of the total amount that was obtained the largest improvement in flowability in previous study. To prepare the mixed powders, 495 g of ibuprofen and 5 g of the gildant were weighed into a polyethylene bag and mixed by hand. The mixtures were then poured into a granulator and dry-mixed for 15 min under the following conditions: main blade rotation at 500 rpm and chopper blade rotation at 1500 rpm.

A decrease in the melting point is known to occur with the addition of lubricants, such as magnesium stearate, to ibuprofen. In addition, since ibuprofen tablets can be made without the addition of a lubricant, only mixed powders consisting of ibuprofen and a gildant were used for tableting in this study.

#### Preparation of the Tablets

Tabflex (Okada Seiko, Japan) was used for the tableting. A weighed total of 200 mg of the mixed ibuprofen powder was compacted with an 8-mm flat die. Tableting was performed 5 times for each sample. All tableting were performed under the following conditions: compaction pressure, 10 kN; compaction speed, 10 mm/s; and no holding time. The die and punch were made of SKD steel without any coating.

#### Characterization of the Powder Properties

**Water Content of the Gildant**

Equilibrium relative humidity (ERH) was measured using a water activity measuring instrument (LabMaster-aw; Novasina, Switzerland) at 25°C and an equilibration time of 5 min. In this measurement, the sample mass was set at approximately 1 g. For samples that were bulky and could not be filled to the specified weight, the sample cup was filled to approximately 80% of its total volume.

The loss on drying (LOD) of the gildant was measured following exposure to 105°C for 30 min using a heat-drying moisture meter (MX-50; A&D, Japan). The mass of the
sample used was about 5 g, and bulky samples that could not be filled to the specified mass were filled to the upper limit of the sample dish.

In addition, the amount of adsorbed water per specific surface area (LOD/S) was calculated by dividing LOD by S.

Flow Property Measurement by Powder Rheometer Powder rheometry (FT-4; Freeman Technology, U.K.) was used to evaluate the flow characteristics of the powder. For the measurement, a 50 × 160 mL cell was used, and the stability and variable flow rate method were used to obtain the conditioned bulk density (CBD), basic flow energy (BFE), and specific energy (SE) after the conditioning cycle.  

The packing fraction of each powder was calculated from the CBD value using the following formula (n denotes the amount of glidant added [%]).  

$$\phi_n = \frac{\text{CBD}_{100}}{\rho}$$  

$$\phi_n = \frac{\text{CBD}_{100}}{\left( \rho_0 \cdot \frac{100-n}{100} + \rho \cdot \frac{n}{100} \right)}$$  

Furthermore, the coordination number $Z_g$, which indicates the number of surrounding particles in contact with the primary particles of the raw materials, was calculated from the packing fraction using the Ridgway–Tarbuck Eq.  

$$Z_g = 13.8 - \sqrt{175 - 232 \cdot \phi_n}$$  

The flow energy per contact point $FEC_{cp}$ in the mixed powder was calculated by the following equation.  

$$FEC_{cp} = SE_{in} \cdot (\phi_n \cdot Z_m)$$  

Shear Force Test for the Mixed Powder A shear force test of the mixed powder was performed, and the compressibility index $C_i$, the angle of the critical state line $\theta_{cc}$, and the flow factor $ff$ at each preconsolidation stress were measured. A constant-volume shear tester (NS-S; Nanoseeds, Japan) was used to measure the mixed powders once for each sample.  

For the measurement, upper and lower split-type cylindrical cells were filled with the mixed powder in a manner such that the powder layer after consolidation was higher than the shear surface (lower cell powder filling depth: 5 mm). Then, the upper lid was lowered with a servomotor to apply a predetermined preconsolidation stress to the powder layer. The measurement conditions were as follows: cylindrical cell diameter, 30 mm; preconsolidation stress, 50, 100, and 150 N (only Aerosil P25 was measured at 10, 20, and 30 N because of stick-slip); lower cell horizontal movement speed, 10 μm/s; indentation gap, 0.2 mm; and indentation speed, 0.2 mm/s.

The change ratio in the flow factor resulting from the preconsolidation stress was calculated using the following equation (Subscripts: preconsolidation stress [N]):  

$$ff\text{ ratio} = \frac{ff_{50}}{ff_{150}}$$  

Evaluation of the Compaction Characteristics and Tablet Physical Properties The pressure transmission behavior during tabletting and tablet properties of each mixed powder were evaluated. All values represent averages of 5 measurements.

The pressure transmission behavior was measured for each tablet using the Tabletting Pressure Data Acquisition System (DAATSU III, Okada Seiko, Japan). The peak values of the upper punch load $Lu$, the lower punch load $Ll$, the die wall force $Lw$, and the ejection force $Le$ were measured from compression to discharge.  

Regarding the measurement of the physical properties of the tablets, the diameter d and thickness h were measured using a micrometer (MDQ-30M; Mitutoyo, Japan), and the hardness of the tablets H was measured using a tablet hardness meter (MultiTest50; Dr. Schleuniger, Switzerland).

The pressure transmission ratio $Pr$ was calculated from the measured pressures using the following equation:  

$$Pr = \frac{Lu}{Ll}$$  

The tensile strength $T$ of the tablets was calculated from Eq. 8 as follows.  

$$T = 2H/\pi \cdot d \cdot h$$  

$$T \text{ ratio} = T/T_0$$  

Evaluation of the Particle Morphology A scanning electron microscope (SEM) (S-4300; Hitachi High-Technologies, Japan) was used to confirm the particle shape and the status of the coating of the mixed powder surface. To impart conductivity, the measurement sample was coated with 15 nm of platinum prior to the measurement.

Glidant Cluster Size Measurement The size $Dc$ of the glidant cluster attached to the surface of the ibuprofen particles was determined by image analysis using ImageJ (Ver.1.52a, NIH, U.S.A.) as the image analysis software. An SEM image (magnification, 15000 times) of each mixed powder was used for the image analysis. The Feret diameter of 20 glidant clusters attached to the ibuprofen particles was measured, and the average was calculated. When the glidant adhered in a planar shape, the measurement of 20 pieces was difficult. Therefore, measurements were obtained at 20 locations located at intervals of 0.5 μm or more.

Evaluation of the Charge Amount of the Powders A suction-type Faraday cage meter (EA-02; U-TEC Corporation, Japan) was used to measure the charge amount induced by triboelectrification.

A weighed amount of 1 g of the measurement sample was placed in a glass bottle and mixed with a vortex mixer for 90 s. The mixed sample was placed in a sample dish and suctioned for about 10 s to measure the charge amount of the sample. The measurement was performed 3 times for each sample.

The difference in the charge amount $C_m$ of the mixed powder and the charge amount $C_m0$ of ibuprofen was calculated as $\Delta C_m$.

Creation of a Prediction Model and Estimation of the Effect of Each Feature In order to identify the characteristics of the glidant and mixed powder that have a high influence on the tensile strength of tablets, we first created a prediction model with the tensile strength as the objective variable. Then, the physical properties of the powder, which has a high influence on the prediction, were extracted from the created model.

DataRobot (Ver.cfc767e, DataRobot, U.S.A.) was used to create the prediction model. Property of glidant, mixed powder, and tabletting parameters were used as training data (Fig. 1, Tables 1–2, Supplementary Tables 1–2).

In this study, the accuracy of the model was verified ac-
Table 1. Properties of Mixed Powder

| Mixed powder | Glidant | Results of flow property measurement | Results of shear force test | Dc (μm) | Ccp (μc/g) |
|--------------|---------|--------------------------------------|----------------------------|---------|------------|
| ID           |         | CBDn (g/mL) | BFE (mL/g) | SEp (mL/g) | φn (%) | Zn (m/g) | FEcp (deg) | θc (°) | Ci (%) | f∥fo (---) | f∥fo (---) | f∥fo (---) | f∥fo (---) | |
| Mib          | None    | 0.365      | 812       | 9.16       | 0.332  | 3.90     | 7.07       | 25.79   | 26.81  | 3.7       | 8.5       | 12.8      | 3.5       | 0.22  |
| MS-1         | Aerosil 380 | 0.479     | 1422      | 8.73       | 0.431  | 5.14     | 3.94       | 40.87   | 12.45  | 2.0       | 2.2       | 3.6       | 1.8       | 7.17  |
| MS-2         | Aerosil 200 | 0.491     | 1491      | 8.70       | 0.442  | 5.29     | 3.72       | 41.64   | 10.79  | 2.6       | 4.5       | 6.3       | 2.4       | 4.83  |
| MS-3         | Aerosil 50 | 0.493     | 1321      | 8.37       | 0.444  | 5.31     | 3.55       | 32.13   | 9.97   | 3.2       | 6.6       | 7.0       | 2.2       | 0.78  |
| MS-4         | Adsolider 101 | 0.515     | 1313      | 8.06       | 0.464  | 5.59     | 3.11       | 37.64   | 8.98   | 3.3       | 4.2       | 6.3       | 1.9       | 1.49  |
| MS-5         | Adsolider 102 | 0.445     | 776       | 9.78       | 0.401  | 4.74     | 5.15       | 28.27   | 21.00  | 3.7       | 4.6       | 5.1       | 1.4       | 0.00  |
| MN-1         | Neusilin UFL2 | 0.513     | 1677      | 8.72       | 0.462  | 5.56     | 3.39       | 29.32   | 11.82  | 6.8       | 8.4       | 7.8       | 1.1       | 0.65  |
| MN-2         | Neusilin FL1 | 0.487     | 867       | 7.26       | 0.439  | 5.25     | 3.15       | 26.10   | 13.02  | 5.7       | 6.0       | 6.0       | 1.1       | 0.64  |
| MN-3         | Neusilin FH1 | 0.465     | 794       | 9.73       | 0.419  | 4.98     | 3.80       | 25.25   | 20.11  | 4.9       | 5.9       | 6.9       | 1.4       | 0.35  |
| MT-1         | Aerosil TiO2 | 0.531     | 2236      | 9.56       | 0.470  | 5.68     | 3.58       | 47.09   | 9.24   | 4.6       | 2.4       | 2.3       | 0.5       | 4.31  |
| MT-2         | Titanium dioxide A100 | 0.513     | 996       | 7.26       | 0.455  | 5.46     | 2.92       | 32.98   | 9.96   | 5.9       | 6.6       | 4.2       | 0.7       | 0.48  |
| MF-1         | Florite-RE | 0.377     | 844       | 10.70      | 0.338  | 3.98     | 7.95       | 25.57   | 22.37  | 2.0       | 1.6       | 1.3       | 0.1       | 0.61  |
| MH-1         | Alcamac VF | 0.490     | 1054      | 8.65       | 0.441  | 5.28     | 3.71       | 25.74   | 15.89  | 2.9       | 6.4       | 6.4       | 3.5       | 3.75  |
| MP-1         | Anhydrous dibasic calcium phosphate light type | 0.377     | 793       | 8.81       | 0.338  | 3.97     | 6.57       | 26.22   | 25.26  | 9.9       | 8.1       | 8.7       | 0.9       | 0.00  |

Table 2. Tabletting Behavior and Tablet Properties

| ID           | Lu (kN) | Li (kN) | Le (kN) | Lw (kN) | Pr (---) | w (mg) | d (mm) | h (mm) | H (kP) | T (MPa) |
|--------------|---------|---------|---------|---------|----------|--------|--------|--------|--------|---------|
| Mib          | 11.42   | 12.60   | 0.31    | 0.31    | 0.06     | 200.2  | 8.66   | 0.08   | 0.79   |
| MS-1         | 11.32   | 12.45   | 0.37    | 0.36    | 0.10     | 200.2  | 8.25   | 0.08   | 0.79   |
| MS-2         | 11.25   | 12.35   | 0.37    | 0.34    | 0.91     | 200.0  | 8.41   | 1.10   | 0.23   |
| MS-3         | 11.46   | 12.55   | 0.33    | 0.32    | 0.93     | 199.6  | 8.66   | 0.72   | 0.59   |
| MS-4         | 11.27   | 12.33   | 0.35    | 0.34    | 0.94     | 199.2  | 8.06   | 0.84   | 0.17   |
| MS-5         | 11.42   | 12.61   | 0.33    | 0.32    | 0.96     | 199.8  | 8.04   | 1.08   | 0.20   |
| MN-1         | 11.38   | 12.64   | 0.31    | 0.31    | 0.90     | 200.0  | 8.57   | 0.90   | 0.26   |
| MN-2         | 11.43   | 12.58   | 0.32    | 0.32    | 0.98     | 201.6  | 8.48   | 1.05   | 0.42   |
| MN-3         | 11.35   | 12.51   | 0.31    | 0.29    | 0.97     | 200.8  | 8.58   | 0.86   | 0.32   |
| MT-1         | 11.54   | 12.60   | 0.32    | 0.32    | 0.91     | 200.2  | 8.57   | 0.72   | 0.57   |
| MT-2         | 11.45   | 12.60   | 0.33    | 0.33    | 0.90     | 200.8  | 1.85   | 0.65   | 0.42   |
| MF-1         | 11.29   | 12.52   | 0.30    | 0.29    | 0.96     | 200.8  | 8.06   | 1.12   | 0.15   |
| MH-1         | 11.57   | 12.71   | 0.32    | 0.31    | 0.91     | 199.6  | 8.04   | 1.20   | 0.42   |
| MP-1         | 11.54   | 12.70   | 0.30    | 0.32    | 0.90     | 198.6  | 0.80   | 0.86   | 0.14   |

Fig. 1. Fishbone Diagram for Tensile Strength of Tablet
according to the DataRobot default method for validation and testing. First, the data are divided into 5 parts, one fraction (20%) is used as holdout data, and the model is created with the remaining 4 fractions (80%). In model creation, 80% of the data excluding the holdout data was further divided into 5 parts, 64% as training data, and 16% as validation data, and a 5-fold cross-validation test was performed to verify the accuracy. The accuracy of the created model was further verified using holdout data.

Using Root Mean Squared Error (RMSE) as an index, we selected the top 3 models with high accuracy from the generated prediction models. The blender model was excluded. The impact If of the features was calculated for these models. For the calculated features, the parameter with the largest impact in each model was set to 100%, and the other variables were shown as relative proportions according to their impacts. Therefore, the degree of influence Ip of each feature on the total impact of all the features was calculated using the following equation:

\[
Ip = \frac{If}{\sum If} \times 100
\]  

Results and Discussions

Extraction of Factors That Highly Affects on the Tensile Strength of Tablets

The tensile strength T was compared for tablets prepared from a mixed powder containing various glidants at a proportion of 1% (Table 2). As a result, in most mixed powders, the tensile strength of tablets decreased due to the addition of the glidant as compared with ibuprofen alone. However, the mixed powder to which the four glidants were added showed a slight but 1–7% higher tensile strength than ibuprofen alone. The four types of glidant with improved tensile strength did not have common physical properties such as components and specific surface area. Based on this result, we realized that the tensile strength of ibuprofen tablets was unexpectedly reduced when the wrong glidant was selected. Therefore, the importance of selecting a glidant with properties that contribute to the tensile strength of ibuprofen was clarified.

A prediction model was created using the tensile strength of ibuprofen tablets as the objective variable, with various raw material and mixed powder parameters used as explanatory variables. From there, the physical properties of the powder that strongly influence tensile strength were extracted (Fig. 1). The impacts of the features of the three predictive models with the highest accuracies were averaged, and the parameters with a high influence on the tensile strength were identified (Table 3).

Among the parameters related to tablet properties in the tableting process, only the ejection load was extracted. On the other hand, the parameters related to mixed powders accounted for the majority of extracted factors, with 6 different extracted parameters. In particular, the top two factors were the shear test results: the flow factor \(ff_{100}\) and the angle of the critical state line \(\sin \theta_{cd}\). Note that \(\sin \theta_{cd}\) corresponds to the effective angle of internal friction.

This suggests that the physical properties of the mixed powder, especially the flow characteristics under pressure, strongly affect the tensile strength.

The mixed powder consisted of ibuprofen and a glidant added at a ratio of 1% relative to the amount of API. Therefore, the difference in physical properties of the mixed powder is due to the characteristics of the added glidant.

The characteristics of the extracted glidant were not the flow energy, but rather the packing fraction \(\phi_g\), the charge amount \(C_g\), and the adsorbed water LOD/S.

Therefore, the glidant characteristics that were thought to be effective for improving T were clarified by analyzing the mechanism by which the characteristics of these glidants acted on the flowing characteristics of the mixed powder under pressure.

Effect of Various Powder Parameters on Tensile Strength

Relationship between Tensile Strength of Tablet and Flowability of Mixed Powder under Stress

First, we verified the relationship between the tensile strength and the results of the powder shear test of the mixed powder, which had a large effect on the tensile strength (Fig. 2). We found that the smaller the flow factor \(ff_{100}\) which had the greatest influence, the higher the T value (Fig. 2a). In other words, the poorer the flowability under pressure, the higher the tensile strength.

Next, a strong correlation was observed between the angle of the critical state line \(\sin \theta_{cd}\) and T, with larger \(\sin \theta_{cd}\) values associated with higher T values (Fig. 2b). The angle of the critical state line was increased by the addition of a glidant to the formulation, compared with ibuprofen alone without a glidant. However, when the increase in \(\sin \theta_{cd}\) was 1.2 times or less, the tensile strength of the tablet was lower than that of ibuprofen alone. On the other hand, when the value increased to 1.4 times or more, the tensile strength exceeded the value of ibuprofen alone.

Considering the above-described results for \(ff_{100}\) and \(\sin \theta_{cd}\), the friction between particles (\(\sin \theta_{cd}\) ) increased as a result of the addition of the glidant, while \(ff\) deteriorated under pressure. On the other hand, the tensile strength decreased in most cases, and the T value clearly improved when a frictional force above a certain level was generated.

| No. | Category  | Parameter  | Impact of parameters |
|-----|-----------|------------|----------------------|
| 1   | e         | \(ff_{100}\) | 24.86                |
| 2   | e         | \(\sin \theta_{cd}\) | 15.16                |
| 3   | c         | \(Dc\) | 11.89                |
| 4   | a         | LOD/S | 5.95                 |
| 5   | c         | \(\Delta c_m\) | 4.80                 |
| 6   | b         | \(\phi_g\) | 4.57                 |
| 7   | f         | \(Lc\) | 3.78                 |
| 8   | e         | \(Ci\) | 3.42                 |
| 9   | d         | \(\phi_m\) | 3.38                 |
| 10  | a         | \(C_g\) | 3.36                 |

Table 3. Extraction of Factors That Have a High Influence on Tensile Strength
The above results clarified that the angle of the critical state line of the mixed powder strongly influences the tensile strength. Therefore, the flow characteristics of the mixed powder that affect the angle of the critical state line were evaluated.

As a result, we found that a smaller compressibility index $C_i$ of the mixed powder was associated with a larger $\sin \theta_{csl}$ value (Supplementary Fig. 3). The compressibility index was obtained from the volume change before and after the preliminary compression in the shear test. A low compressibility index means that the mixed powder particles were packed more densely when the powder was filled in the die at the time of tableting.

We also found that the compressibility index was correlated with the flow energy $FE_{cp}$ at the time of particle contact in the mixed powder, and that the compressibility index also decreased as the cohesive force was suppressed and the $FE_{cp}$ decreased (Fig. 3).

From these results, the relationship between the angle of the critical state line and the flowability of the powder was considered as follows. First, the cohesive force between the particles of the mixed powder was reduced by mixing with a glidant ($FE_{cp}$ reduction), allowing the mixed powder to fill the cell more densely (compressibility index $C_i$ reduction). This dense filling of the cell increases the contact points between the particles and increases the total amount of frictional force. The internal frictional force was thought to increase as the total amount of this frictional force increased.

Relationship between Shear Properties and Flowability of Mixed Powder The above results clarified that the angle of the critical state line of the mixed powder strongly influences the tensile strength. Therefore, the flow characteristics of the mixed powder that affect the angle of the critical state line were evaluated.

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**Relationship between Flowability of the Mixed Powder and Physical Properties of the Glidant**

The properties of the glidant, which affects the compactability of the mixed powder, were verified. Except for MF-1 (Florite), both the compressibility index $C_i$ and $FE_{cp}$ tended to decrease as the packing fraction $\phi_g$ of the glidant decreased (Fig. 4).

$FE_{cp}$ converged to a constant value when $\phi_g \leq 0.1$. This change was thought to represent the frequency of the interposition of glidant particles at the points of contact with the ibuprofen particles. The $FE_{cp}$ gradually decreased because of the presence of the glidant particles at the ibuprofen particle contacts. When the contact points above a certain level were covered with the glidant particles, the characteristics of the glidant appeared strongly and showed a constant value.

Florite behaved differently from the other glidants because of its plate-like structure and larger particle size. These differences were thought to arise from the crushing of the plate-like structure during the mixing operation.41

Based on the above results, we concluded that the packing fraction $\phi_g$ of the glidant acts on the compressibility index and the $FE_{cp}$ of the mixed powder, with lighter glidants (smaller $\phi_g$) resulting in a lower compressibility index and $FE_{cp}$. Therefore, glidants with a low packing fraction can be advantageous for improving the angle of the critical state line of the mixed powder.

In addition to $\phi_g$, the charge amount $C_g$ and the adsorbed moisture LOD/$S$ were also identified as influential factors. These parameters were strongly correlated with $\phi_g$ (Supplementary Fig. 6), while their relationships with other parameters of the mixed powder were not as clear. Therefore, $\phi_g$ was regarded as being a reasonable parameter for evaluating the characteristics of glidants.

**Properties of Glidant Required to Improve the Tensile Strength of Ibuprofen**

In this study, the angle of the critical state line of the mixed powder was found to affect the tensile strength of the tablet greatly, and the smaller the packing fraction $\phi_g$, the higher the angle of the critical state line. However, only four types of glidants conferred an improved tensile strength, compared with the absence of additives. Therefore, we extracted the characteristics common to these four types of glidants and clarified the physical properties that are required to improve tensile strength.

A comparison of SEM images of the mixed powder to which each glidant had been added (Fig. 5) showed that a wide and smooth glidant particle layer ($D_e \geq 1 \mu m$) was observed for the glidants that conferred an improved tensile
strength. On the other hand, in the glidants that resulted in a reduced tensile strength, a rough surface with scattered point-like adhesions \((Dc < 1 \mu m)\) was observed.

In general, the tensile strength of a tablet represents the total of the intermolecular forces at the particle contacts inside the tablet, with a larger number of contact points resulting in a higher tensile strength.\(^{42,43}\) In other words, when the glidant forms a smooth particle layer, the particles are less likely to get caught on each other under low load conditions, and agglomeration is less likely to occur (small \(FE_{cp}\)). Therefore, the particles can be densely packed in the die (small compressibility index), and the number of contact points increases. This situation is thought to increase the friction among particles (large \(\sin \theta_{cs}\)), thereby improving tensile strength.

As shown in Fig. 2b, the addition of the glidant caused the tensile strength \(T\) to decrease even though the angle of the critical state line \(\sin \theta_{cs}\) increased. This result is because the \(FE_{cp}\) decreased because of the formation of the glidant particle layer, and the mixed powder particles were densely packed, thereby increasing the angle of the critical state line \(\sin \theta_{cs}\). However, the presence of relatively large glidant particles between the ibuprofen particles hindered the close contact between the ibuprofen particles. Therefore, the tensile strength \(T\) decreased.

As shown in the model diagram (Fig. 6), these results suggest that glidants capable of coating the API particle surface thinly and smoothly are effective for improving the tensile strength.

The amount of glidant required to coat the API particles depends on the thickness of the particle layer.\(^{44}\) Since this layer thickness depends on the size of the glidant particle clusters, the smaller the particle cluster size, the wider the area that can be covered even with the same amount of glidant. The particle cluster size depends on the ease with which the inorganic particle agglomerates, dispersing the glidant. The coordination number \(Z_g\) is an index of the ease of dispersion. When the number of particles around the primary glidant particles is small, the cohesive force (intermolecular force, electrostatic force, etc.) acting on each particle is also small, making dispersal through mixing easier. This coordination number \(Z_g\) depends on the packing condition of the particles, \(i.e.,\) the packing fraction \(\phi_g\) of the glidant. Therefore, a light glidant with a low packing fraction \(\phi_g\) is thought to have a low coordination number \(Z_g\) and to be easily dispersed, enabling...
the API particle surface to be widely coated even with the addition of a small amount of glidant.\(^\text{22}\)

Since Aerosil 50 is about four times larger in primary particle size than other light glidants, such as Aerosil 200, the thickness of the particle layer is increased. Similarly, in a previous report, the addition of a larger quantity of Aerosil 50, compared with the quantity of Aerosil 200, was required to cover the particle surface.\(^\text{20}\) In the present study, the amount of added glidant was fixed at 1%; consequently, the added amount was insufficient. Even though the packing fraction \(\phi_g\) of Aerosil 50 was relatively low, the particle layer was considered to be sparse, as shown in Fig. 5.

The present results showed that glidants capable of conferring an improved tensile strength were concentrated at a packing fraction \(\phi_g < 0.05\). Therefore, a packing fraction of \(\phi_g < 0.05\) and a coordination number of \(Z_g < 1.0\) were considered to be two criteria for the selection of a glidant capable of conferring an improvement in compaction properties (Fig. 7). Since the bulk volume of the glidant contained some voids, the coordination number \(Z_g\) was 1 or less. The packing fraction \(\phi_g\) did not show the highest impact among the parameters extracted from the prediction model. However, a good correlation was found between the tensile strength and the packing fraction \(\phi_g\). From this result, if the packing fraction of the glidant is evaluated, it is possible to estimate the effect of improving the compactability of the API without mixing or tableting process. Therefore, it is expected that the efficiency of prescription design work will be improved.

**Conclusion**

Compactability is an important issue in designing high-dose tablets containing ibuprofen. In the present report, we selected a glidant capable of improving compactability when added in a small amount (1%) during dry surface modification.

The addition of 13 different glidants and a comparison of the resulting tensile strengths of the tablets showed that the tensile strength increased with the addition of only 4 of the tested glidants, compared with the tensile strength of tablets without the addition of a glidant. An analysis of the features that contributed to the tensile strength prediction model showed that the flowability of the mixed powder under the compaction process was extracted as a characteristic of the mixed powder that affected the tensile strength of the tablets.

The angle of the critical state line of the mixed powder increased with the addition of the glidant. An improvement in the tensile strength was observed when the angle of the critical state line was increased by up to 1.4 times, compared with tablets without the addition of a glidant. Mixed powders with a high angle of the critical state line had a low compressibility index, and this compressibility index was found to be positively correlated with the packing fraction of the glidant.

Among the mixed powders resulting in tablets with higher tensile strengths, compared with tablets that did not contain a glidant, a feature that all the mixed powders had in common was the formation of smooth particle layer of glidant on the particle surface. The addition of a glidant with a low packing fraction reduces agglomeration among particles and reduces the compressibility index. In particular, when a smooth particle layer was formed, the ibuprofen particles were in close contact with each other via the glidant particle, and the frictional force among the particles increased, suggesting that the tensile strength also increased. We clarified that a low packing fraction, which affects the dispersibility of the glidant, is important for the formation of a smooth particle layer and that a value of 0.05 or less is desirable as a guideline for the packing fraction of glidant.

From the above results, we clarified that the compactability of ibuprofen can be improved even with the addition of a small amount of glidant at an API ratio of 1% if the glidant has a packing fraction of \(\phi_g < 0.05\). This makes it possible to prepare ibuprofen-containing tablets with the addition of only a small amount of excipients, and medication adherence is expected to be improved by decreasing the size of tablets.

**Nomenclature**

- \(\rho\): true density of the materials (g/mL)
- \(S\): specific surface area of the materials (m\(^2\)/g)
- \(D_{pp}\): diameter of the primary particles (calculated) (nm)
- \(L\text{OD}\): loss on drying of the materials (%)
- \(ERH\): equilibrium relative humidity of the materials (%)
- \(LOD/S\): Adsorbed water amount per relative surface area (mg/m\(^2\))
- \(CBD\): conditioned bulk density (g/mL)
- \(BFE\): basic flow energy (mJ)
- \(SE\): specific energy (mJ/g)
- \(\phi\): packing fraction
- \(Z\): coordination number
- \(FECp\): flow energy per contact point (mJ/g)
- \(C\): charge amount (µC/g)
- \(Dc\): diameter of glidant cluster on API particle (µm)
- \(Lu\): maximum load of upper punch (kN)
- \(Ll\): maximum load of lower punch (kN)
- \(Lw\): maximum load of die wall force (kN)
- \(Le\): maximum load of ejection force (kN)
- \(w\): weight of tablet (mg)
- \(d\): diameter of tablet (mm)
- \(h\): thickness of tablet (mm)
- \(H\): hardness of tablet (kP)
- \(Pr\): pressure transmission ratio
- \(T\): tensile strength of tablet (MPa)
- \(\theta_{csl}\): angle of critical state line (deg)
- \(f_f\): flow factor
- \(Ci\): compressibility index of mixed powder (%)
- \(If\): feature impact (%)
- \(Ip\): impact of parameter (%)
Subscripts
\( g \) : glidant
\( m \) : mixed powder
\( 0 \) : ibuprofen only

Conflict of Interest  Tetsuo Ono is currently employee of Taisho Pharmaceutical Co., Ltd.

Supplementary Materials  The online version of this article contains supplementary materials.

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