

eye on excipients

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This edition of the column assesses the attributes and applications of a coprocessed excipient for the direct compression of orally disintegrating tablets

Developing orally disintegrating tablets (ODTs) is a worldwide trend, but it's particularly popular in Japan, where formulators at innovator companies, generic drug companies, and contract manufacturers compete to develop new ODTs. In fact, Japan accounts for the largest share of ODTs in the world [1].

Traditionally, manufacturing ODTs was a wet process that required special manufacturing equipment. Lyophilization is one example. In recent years, however, new excipients and excipient blends have enabled manufacturers to produce ODTs using conventional equipment, i.e., blenders and tablet presses.

When compressing ODTs, the main concern is ensuring the formation of water absorption routes, which typically means tableting at a low compression force to create highly porous tablets that retain sufficient hardness to withstand handling. Meeting these seemingly contradictory product attributes—high porosity and high tablet hardness—requires using excipients that can achieve high tablet hardness even when compressed with low compression force.

One such product is Granfiller-D, a coprocessed excipient that comprises a specific ratio of compendial excipients that have undergone a proprietary granulation method [2, 3]. Because Granfiller-D's particles themselves provide the water-intake route, the excipient can be tableted at compression

forces that would—if applied to conventional ODT excipients—reduce porosity and thus diminish tablet performance. In addition, Granfiller-D (grade GNF-D211) has a US drug master file (DMF) and is used in marketed drug products in Japan.

Powder properties and basic characteristics

Granfiller-D includes four excipients listed in the USP, EP, and JP: mannitol, crospovidone, carmellose, and microcrystalline cellulose. These are coprocessed using a water-based granulation method, resulting in two grades of the excipient that differ only in particle size: GNF-D211 has particles of 100 microns, and GNF-D215 has particles of 160 microns (Table 1).

To make ODTs using this coprocessed excipient, you add one or more active pharmaceutical ingredients (APIs), a flavoring agent, a sweetener, and a lubricant; blend them; and then compress the mixture on a standard tablet press. Tablet formation and disintegration are typically satisfactory without the addition of binders or disintegrants, which simplifies ODT formulation and manufacture (Figure 1).

Differences from conventional concept

The coprocessed excipient also accepts large doses of API while maintaining high hardness and rapid disintegration. Due to this high dose capacity, the excipient also gives you the flexibility to formulate controlled-release tablets, mask bitter tastes, and stabilize APIs.

Of course, the excipient also disintegrates rapidly. That's because the particles themselves act as the water-intake route—a new concept for ODT excipients—as does tablet porosity, which is the conventional approach and which requires tableting at low compression force. No other direct-compression ODT excipient provides faster disintegration. In one case, the disintegration time of small ODTs made with Granfiller-D was equivalent to that of lyophilized ODTs that disintegrated in 5 seconds.

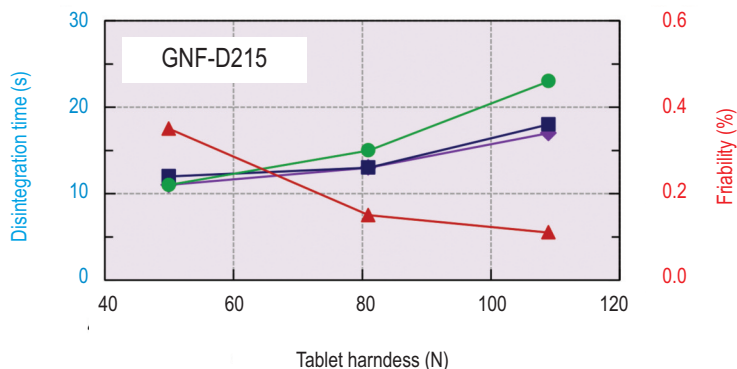
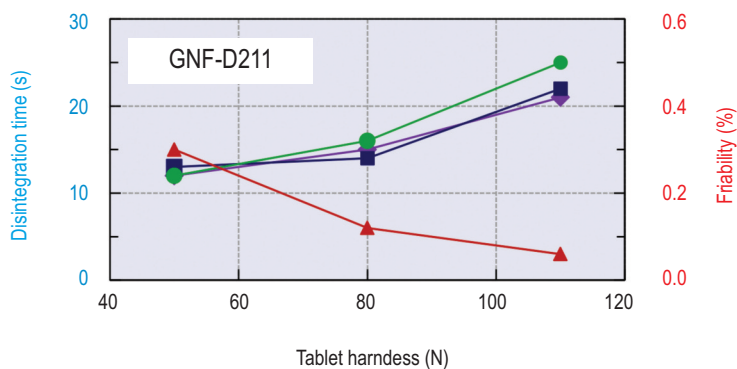
The excipient also allows the application of high compression force, although high force is not required to form a proper tablet. An assessment of placebo tablets made using conventional ODT excipients and compressed at 40 to 50 newtons showed

TABLE 1

Properties		
Median particle size (microns)	100	160
Density (g/cm ³)	0.30 (bulk), 0.44 (tapped)	0.30 (bulk), 0.44 (tapped)
Angle of repose (degrees)	41	41
Orifice diameter (mm)	6.3	4.0

FIGURE 1

Hardness, disintegration time, and friability of placebo ODTs



- ◆ Disintegration time (pharmacopoeia)
- Oral disintegration time (in vivo)
- Oral disintegration time (in vitro)
- ▲ Friability

Note: Flat, 8-millimeter-diameter tablets of 250 milligrams made on a rotary tablet press from blend of Granfiller-D (99.5 percent) and magnesium stearate (0.5 percent).

that they disintegrated in 20 to 30 seconds, about the same time required for ODTs made using Granfiller-D. However, when compressed to a higher hardness range, only tablets made using Granfiller-D retained their short disintegration times. This superior hardness-disintegration property enables formulators to incorporate a wider variety of APIs into ODTs (Figure 2).

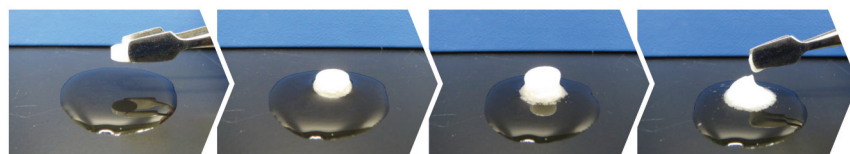
The way that our company's excipient disintegrates also differs from that of many ODT excipients. As ODTs that use conventional excipients disintegrate, they divide into block-like pieces. But when ODTs made using Granfiller-D disintegrate, they exhibit a cream-like consistency, which

improves mouth-feel (photos).

The following sections illustrate some of the excipient's important attributes.

Examples of attributes

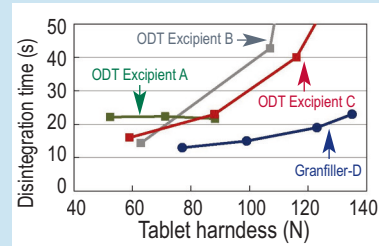
High dose capacity. Even if an API accounts for 30 to 70 percent of a tablet's weight, trial ODTs made with Granfiller-D exhibited satisfactory hardness (greater than 40 to 50 newtons) and rapid disintegration (less than 20 to 30 seconds). This result



As the ODT disintegrates, it exhibits a cream-like consistency.

FIGURE 2

Comparison of disintegration times of high-hardness ODTs



Note: Flat, 8-millimeter-diameter tablets of 250 milligrams made on a rotary tablet press from blend of ODT excipient (99.5 percent) and magnesium stearate (0.5 percent).

suggests that the excipient's particles function as the water-intake route regardless of tablet porosity and the amount of API. Even when the ODTs contained poorly water soluble APIs (e.g., ethenzamide and acetaminophen) they exhibited excellent hardness-disintegration properties at doses of 50 to 70 percent (Figure 3).

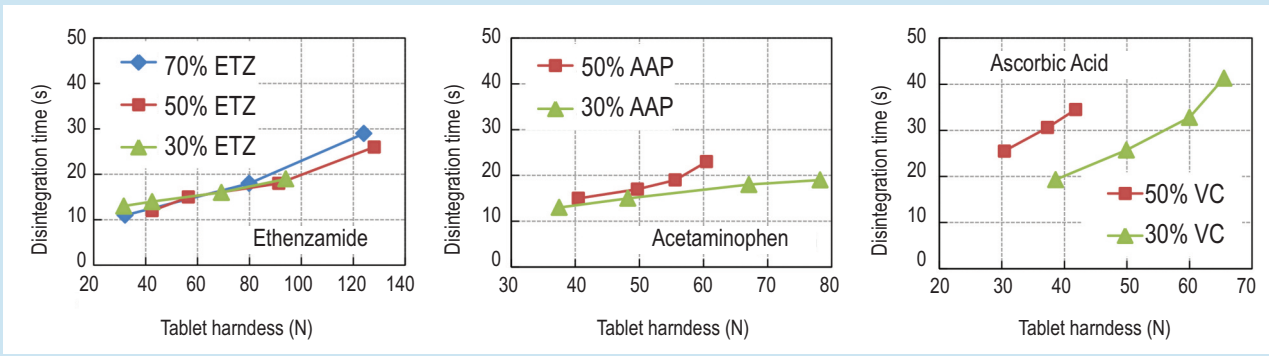
Disintegration time. For this test, Granfiller-D GNF-D211 and 6 to 18 milligrams of a model API were tableted into 60-milligram, 6-millimeter-diameter ODTs with a hardness of 20 to 30 newtons. Oral disintegration time was 4 to 6 seconds and friability was less than 0.3 percent. No chipping or cracking was observed when the ODTs were removed from a press-through blister (Figure 4).

Stress-strain. Many ODTs made using conventional excipients show a clear fracture point when compression force is applied in the radial direction. ODTs made using Granfiller-D, however, show gradual distortion just before reaching the fracture point (Figure 5). They also exhibit a restorative force, meaning that the distortion is reversible before the fracture point is reached. These stress-strain characteristics may reduce the occurrence of breakage and chipping of ODTs, even when they are manufactured at low compression force.

Stability outside the package. To

FIGURE 3

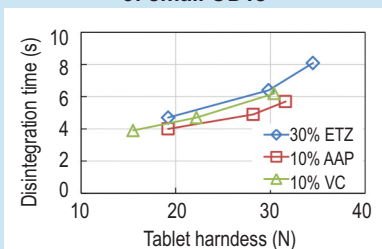
Evaluation of high dose capacity



Note: Flat, 8-millimeter-diameter tablets of 250 milligrams

FIGURE 4

Disintegration performance of small ODTs



Note: Flat, 6-millimeter-diameter tablets of 60 milligrams

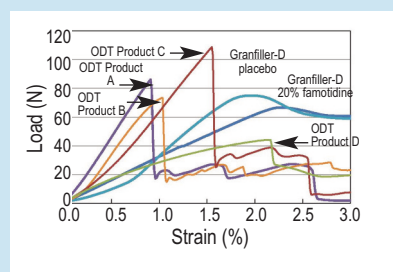
test the storage stability of placebo ODTs made using Granfiller-D (GNF-D211), the tablets remained unpackaged at 25°C and 75 percent relative humidity for 3 months. After 1 month, hardness decreased by about 30 per-

cent, but no change was observed thereafter. Nor was a change observed in the disintegration time after 3 months. Over the same period, tablet weight increased by 1 to 2 percent, and thickness increased by 2 to 3 percent (Figure 6).

Flowability, mixing characteristics, and content uniformity. The particles of many direct-compression excipients are spherical or nearly spherical and therefore have very high flowability. Granfiller-D particles, however, are nonspherical and irregularly shaped; the excipient's angle of repose is about 41 degrees, which exceeds the 30 degrees that is typical of ODT excipients whose particles are more spherical. Granfiller-D nonetheless has sufficient dynamic flowability for practical use and can be tableted on presses

FIGURE 5

Comparison of ODT flexibility



equipped with force-fed and open feeders. In one case, a 38-station tablet press equipped with a force-fed feeder and operating at 100 rpm was also used. It showed stable compression force, with a coefficient of variation (CV) of 3.6



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percent when tableting GNF-D211 and a CV of 3.5 percent when GNF-D215 was used. Tablet weight CV was 0.44 percent for GNF-D211 and 0.63 percent for GNF-D215.

It is well known that blending improves when the size of the particles in the excipient and API is equivalent. Yet Granfiller-D blends well with APIs whose particles are smaller than the those of the excipient due to their non-spherical, irregular shape (Figure 7). This was demonstrated by

testing the content uniformity of ODTs containing just 1 percent of ibuprofen. Four samples of ibuprofen, each with a different median particle diameter—135, 34, 14, and 7 microns—were blended with Granfiller-D GNF-D215. The CV of the API content in the resulting ODTs was 2.4, 2.8, 2.0, and 3.3 percent, respectively.

Conclusions

Granfiller-D, a coprocessed excipi-

FIGURE 6

Stability of placebo ODTs

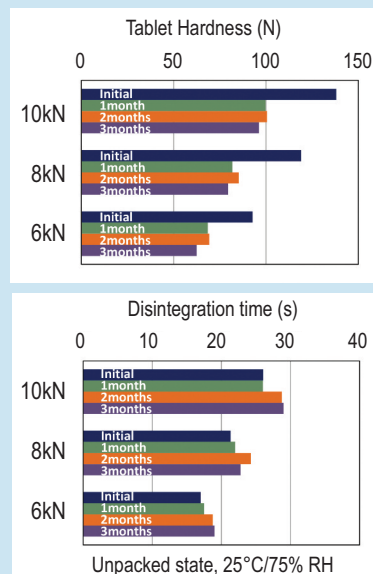
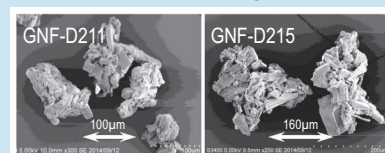


FIGURE 7

Particle shape



ent for directly compressing ODTs, uses a novel granulation method to combine existing excipients. The principal benefit is a water intake route that is not compromised by high compression force. In addition, the excipient is easy to use and simplifies ODT formulation. It also offers you a platform to design sophisticated formulations with modified API particles. T&C

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3. Hiramura, T. and Okabayashi, T. ODT excipient Granfiller-D. Pharm Tech Japan, 735(2015).

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