GRANFILLER-D™-Water Absorption Behavior and Disintegration Mechanism-

1. Introduction

In the formulation design of conventional orally disintegrating tablets (ODTs) by direct compression, disintegratablity often reduces when active pharmaceutical ingredient (API) content is high. Since API tends to block the gap between particles in tablets, which is considered to be the main water absorption pathway, water is prevented from reaching disintegrants. In contrast, GRANFILLER-D[1)] (GNF), Daicel's co-processed excipient (CPE) for ODTs, shows excellent disintegration performance even in case of high-dose APIs.

Table 1 Examples of ODTs with GNF containing high-dose APIs

Content of ETZ	0%		30%		50%	
Compression force [kN]	6	7	9	5	7	5
Tablet hardness [N]	80	69	94	57	91	80
Disintegration time [s]	15	16	19	15	18	18

GNF-D211＋ETZ＋light anhydrous silicic acid (LASA) (1%)＋MgSt (0.5-1.5%)
250 mg, Φ8 mm, Flat beveled edge
Tablet hardness : Measured by electronic hardness tester (Avg. of n＝10)
Disintegration time : Measured by JP general test method (Avg. of n＝6)

As shown in Table 1, ODTs prepared with GNF had both practical tablet hardness and short disintegration time within 30 seconds even at 70% of ethenzamide (ETZ) content. Rapid disintegration was observed although the gap inside of the tablet was reduced by ETZ which is fine particle and water-insoluble. It was suggested that GNF seems to have another water absorption pathway besides the gap between particles. Here we make a hypothesis that GNF particles themselves have a water conducting function as shown in Fig. 1. In this study, we observed its water absorption behavior in disintegrating tablets and verified this hypothesis while making a comparison with other CPEs for ODT.

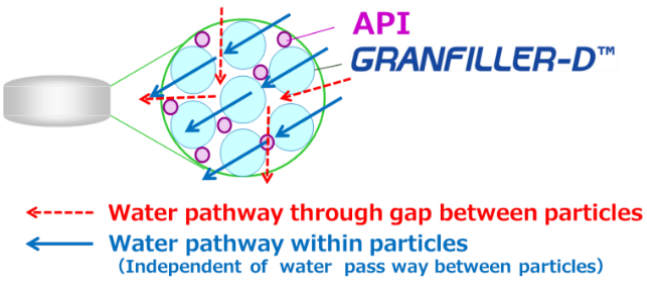

Fig. 1 Hypothesis of water absorption pathway for GNF

2. Methods

(1) Water absorption and disintegration behavior

Tablet samples with GNF as well as other CPEs for ODT were prepared to observe their water absorption behavior by following condition; 35 mg, ϕ6 mm, Flat shape (Excipient (100 %)). These tablets were fixed vertically by sponge on filter paper and remotely applied 10% Sodium bromide (NaBr) solution. Once the solution had been penetrated from the bottom of the tablet through filter paper, we observed the water absorption behavior every 20 milliseconds in real-time (Fig 2 (a)).

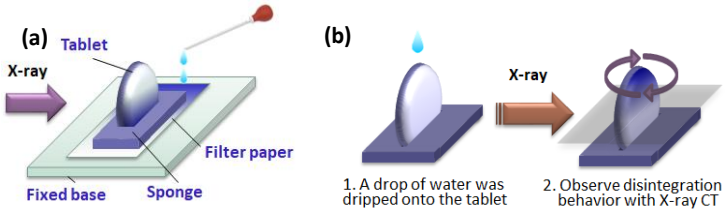

Fig.2 (a) Water absorption observation system
(b) Observation of initial disintegration behavior

We analyzed the initial state of disintegration behavior through observing the boundary between wet and dry sections inside the tablet by using X-ray CT, immediately after dripping a drop of water onto the top of the tablet as well as previous sample (Fig. 2 (b)).

(2) Effect of porosity on disintegration time

Tablet samples were prepared using each CPE including GNF by the following condition; ϕ9 mm, 250 mg (Excipient (99 %) + Mg-St (1%)). The porosity ε of the tablets was calculated based on helium pycnometric density ρ_{true} measurements of each component and the apparent density of the tablets $\rho_{apparent}$, as in accordance with the Eq. (1):

(1) $$\epsilon(\%) = \left(1 - \frac{\rho_{apparent}}{\rho_{true}}\right) \cdot 100$$

$\rho_{apparent}$:Apparent density of tablets
ρ_{true} :Density of each component

Disintegration time was measured by Ph. Eur. 10.

3. Results and discussion

(1) Water absorption and disintegration behavior

Wet section was observed as dark color in the X-ray images. In case of tablet with GNF, water absorption was proceeded smoothly and homogeneously (Fig. 3). On the other hand, cracks occurred first and then water absorption via the cracks

was observed in the tablet with other CPE. Water absorption was conducted by repeating this behavior.

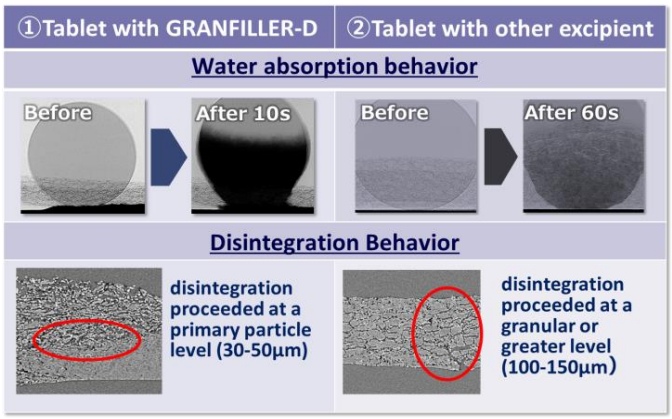

Fig. 3 Image of water absorption and disintegration

Next, the boundary between wet and dry sections of tablets was observed using X-ray CT. Tablet with GNF was found that wet section disintegrated into 30-50 μm particles so that fine disintegration proceeded directly at a primary particle level rather than at a granulated aggregate level, while the disintegration in tablet with other CPE disintegrated into 100-150 μm particles being close to or greater than granular (block disintegration). From these results, it can be assumed that tablet with GNF has a fine water pathway besides gaps between particles.

(2) Effect of porosity on disintegration time

The relation between porosity and disintegration time of ODTs with various CPEs was investigated by M. Kokott, *et al.*[2] These disintegration profiles for the tested excipients are plotted in Fig. 4. Although all samples showed rapid disintegration in the high porosity regions, it was found that disintegration time of tablets with other CPEs remarkably increased as porosity decreased. On the other hand, tablet with GNF maintains short disintegration time being less than 30 seconds over a wide range of porosity. Therefore, GNF particles themselves seem to function as a water absorption pathway besides the gap. In addition, the disintegration of tablet with GNF is hardly affected by the compression force. ODTs with GNF are easily adjusted their tablet hardness in tableting process because there is little concern that disintegration is affected by compression force.

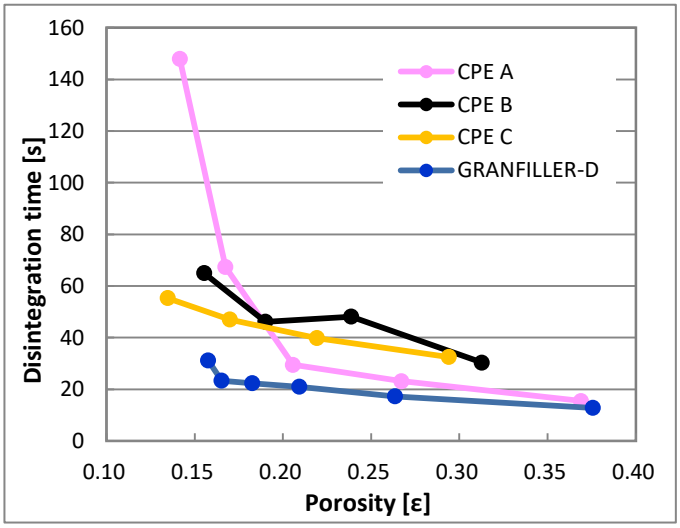

Fig.4 Effect of porosity on disintegration time

4. Conclusion

These investigations revealed that ODTs with GNF showed distinctive smooth and homogeneous water absorption behavior disintegrating directly at a primary particle level. Additionally, GNF particles themselves function as a water absorption pathway. We assume that this is the reason why GNF shows excellent disintegration even with high API content or high tableting pressures. GNF is a versatile excipient that shows high performance even in complex formulations and it has been adapted to several marketed products. We hope to contribute to expand patient centric drugs through providing GNF.

5. Acknowledgements

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6. References

1) T. Hiramura, *et al.*, Tablet & Capsules, 37 (2016)
2) M. Kokott, *et al.,* European Journal of Pharmaceutics and Biopharmaceutics, 168, 122 (2021)

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