Why not choose DC co-processed excipients in your ODT formulation?

■ Introduction

Direct compression (DC) is the simplest process to manufacture tablets. The advantage of DC is that the simplicity of the manufacturing process can reduce manufacturing costs and manufacturing time. In addition, DC is applicable to those APIs which are sensitive to water and heat, since it does not include wet processes. On the other hand, we often encounter challenges, such as tableting trouble, tablet weight fluctuation, and difficulty in maintaining content uniformity, as the powder properties of raw materials directly affect the DC process. Co-processed excipients (CPEs) are applicable to DC and can overcome such challenges that are difficult to solve with simply mixed powders. In this article we introduce a recent study conducted by the research team at Heinrich Heine University demonstrating the advantages of CPEs in comparison to physically mixed powders of the same composition as CPEs.[1)]

■ Raw materials

Daicel's CPEs, HiSORAD® HSR-D03 (HSR) and GRANFILLER-D® GNF-D211 (GNF) are designed for orally disintegrating tablets (ODTs), which perform fast disintegration under practical tablet hardness. Raw materials of each excipient are shown in Table 1. The physical mixture of GRANFILLER-D was composed of the raw materials of GNF. The physical mixture of HISORAD® was composed of the raw materials of HSR.

Table 1 Raw materials

Product name	Component
GNF	D-Mannitol, Microcrystalline Cellulose, Carmellose, Crospovidone
HSR	D-Mannitol, Microcrystalline Cellulose, Croscarmellose sodium

■ Flowability

Flowability of powders is important for DC since the flowability affects many operations such as storage, discharge, transport, mixing, and feed. Here we evaluated flowability with Carr's flowability Index determined from compressibility, different angle of reposes, and cohesion or uniformity coefficient with a powder tester (Fig.1 (a)). Carr's index classifies the flowability based on the behavior of 2,800 dry materials. Additionally, the flowability was also analyzed by the shear test method, which is based on the frictional properties of particles (Fig.1 (b)).

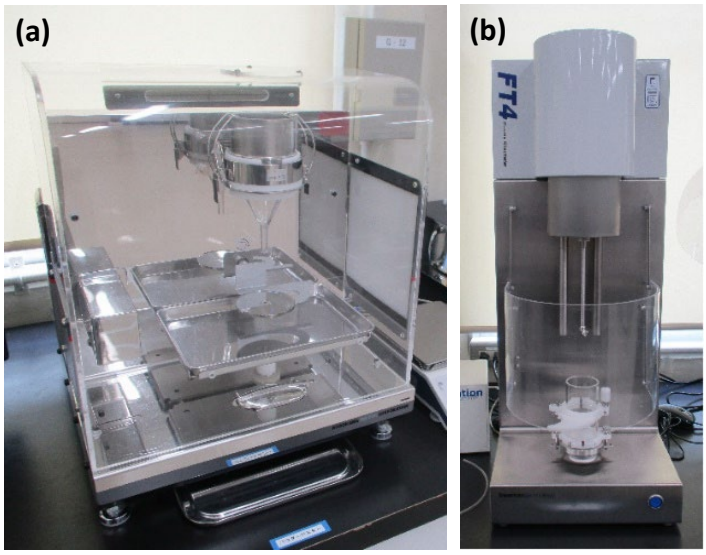

Fig. 1 Equipment

(a) Powder Characteristics Tester PT-X, Hosokawa Micron Corporation
(b) FT4 Powder Rheometer, Freeman technology

Table 2 Flowability

(a) Flowability of GNF and Physical mixture of GNF

Item	Physical mixture		GNF	
	Result	Point	Result	Point
Angle of repose [°]	49	12	41	17
Compressibility [%]	40	2	32	9.5
Angle of spatula [°]	60	15	49	16
Cohesion [%]	19	12	-	-
Uniformity coefficient	-	-	2.3	23
Carr's flowability index	-	**41**	-	**65.5**
Cohesion [kPa]	0.73		0.16	
Angle of internal friction [°]	40.2		36.9	
Flow factor	6.5		25.8	

(b) Flowability of HSR and physical mixture of HSR

Item	Physical mixture		HSR	
	Result	Point	Result	Point
Angle of repose [°]	45	15	41	17
Compressibility [%]	39	2	30	12
Angle of spatula [°]	59	16	47	16
Cohesion [%]	12	12	-	-
Uniformity coefficient	-	-	2.5	23
Carr's flowability index	-	**45**	-	**68**
Cohesion [kPa]	0.64		0.37	
Angle of internal friction [°]	40.1		35.7	
Flow factor	6.5		11.1	

Each color represents degree of flowability determined from points.

Excellent	Good	Fair	Passable	Poor	Very poor	Extremely poor

Table 2 shows the experimental results of flowability. To determine Carr's index, the cohesion is measured for physical mixtures, while the coefficient of uniformity is measured for CPEs. CPEs show better flowability compared to physical mixtures in all evaluations. It is attributed to the reduction of fine powder due to granulation of CPEs.

It is noteworthy that Carr's index indicates that the flowability of CPEs is "Passable", while the flow factor measured by the shear test method was over 10, representing free-flowing property. It is considered that GNF and HSR have non-spherical shape (Fig.2) and the particles hang on each other in the static flowability measurement such as angles, resulting "Passable" flowability. However, there is no electrostatic adhesion or bridges between particles and the friction is small. Thus, the flow factor measured based on the frictional properties represents free-flowing.

The non-spherical shape was designed to avoid segregation. In the mixture of CPE and APIs, APIs are stuck in CPEs or hung on CPEs, which is able to maintain the content uniformity of APIs in the mixture. GNF and HSR have a reasonable flowability and good content uniformity.

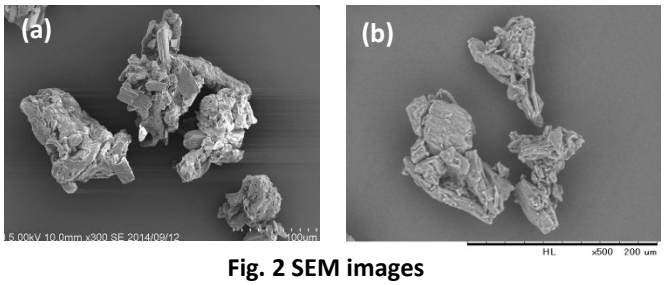

Fig. 2 SEM images
(a) GNF, (b) HSR

■ Tablet performance

Tablet performance was also compared to physical mixtures of the same composition. Fig.3 shows the tensile strength of tablets against the compression pressure. Both CPEs have higher tablet hardness than physical mixtures, indicating better compactability. Both CPEs contain D-mannitol which is often described as a low-compressible excipient, however, the granulation manufacturing process gives the CPEs good compactibility.

The disintegratability was studied as shown in Fig. 4. The CPEs have better disintegratability than physical mixtures especially in the region of higher tensile strength.

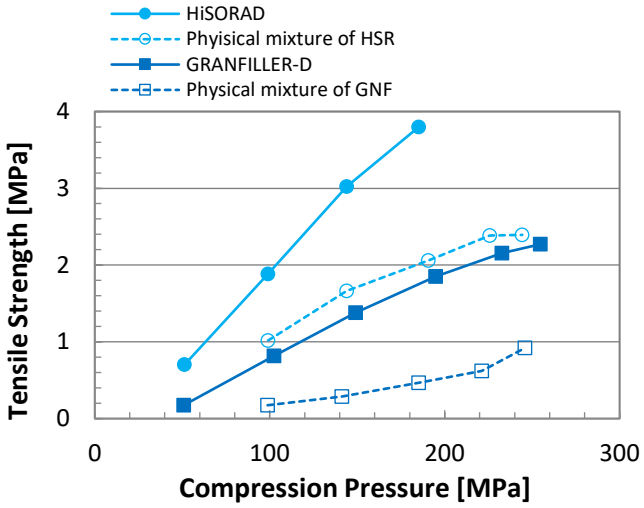

Fig. 3 Comparison of compactability

Composition: GNF/HSR (99.0%) + Mg stearate (1.0%)
Tableting Condition: Single punch tablet press, ϕ11.28 mm, Flat-faced

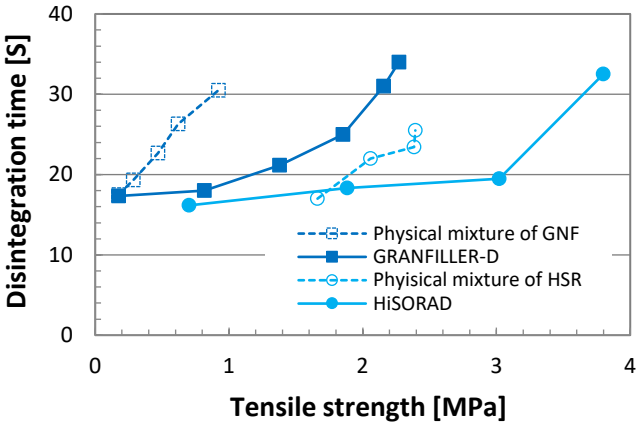

Fig. 4 Comparison of disintegratability

Composition: GNF/HSR (99.0%) + Mg stearate (1.0%)
Tableting Condition: Single punch tablet press, ϕ11.28 mm, Flat-faced

■ Conclusion

The study revealed that GNF and HSR are superior to physical mixtures of the same composition in terms of flowability, compactability and disintegratability which parameters are important to manufacture ODT by DC.

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■ References

1) M. Kokott, *et al., Eur. J. Pharm. Biopharm.*, **168**, 122 (2021)

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