Study on Applicability of ODTs with Co-processed Excipient to Continuous Manufacturing Process

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1. Introduction

"Continuous Manufacturing (CM)" is a manufacturing method in which raw or blended materials are continuously charged to the processing line, and products are continuously discharged throughout the duration of the process. CM can yield required quantities of products with desired quality at a required time by continuous process operation. In addition, CM has the following advantages[1]:

- ✔ Less unit operations in CM process may reduce human and system errors.
- ✔ There are no scale-up issues, since the bench-scale is the same as the commercial scale in CM.
- ✔ Saving space for equipment makes it easier to install and transfer manufacturing sites.
- ✔ It can be expected to reduce the cost of manufacturing and storage because it can timely control the product quantity on demand.
- ✔ Reliable and high-quality FDF products can be produced with more advanced development methods (PAT tool etc.).

Thus, CM method is of great significance from the perspective of manufacturing operations, medical professionals and patients.

There are 2 types of processes for solid dosage forms that can be applied to CM: dry and wet granulation processes. Compared to wet granulation process, dry granulation process can be shorter, deriving to cost reduction of manufacturing and equipment. In this study, we verified applicability of orally disintegrating tablets (ODTs) to CM. We produced ODTs with our co-processed excipient, which is "HiSORAD", by applying dry granulation process. Co-processed excipients seem to be suitable to CM as they can reduce numbers of control parameters required to maintain appropriate quality.

2. Apparatus and Method

2-1 Dry Granulation Process

The whole experimental flow is shown in Fig.1 and compositions of granules are shown in Table 1. HiSORAD HSR-D03 (HSR)[2] was used as filler, ethenzamide (ETZ) was chosen as model API and Sodium Stearyl Fumarate (SSF) was used as lubricant.

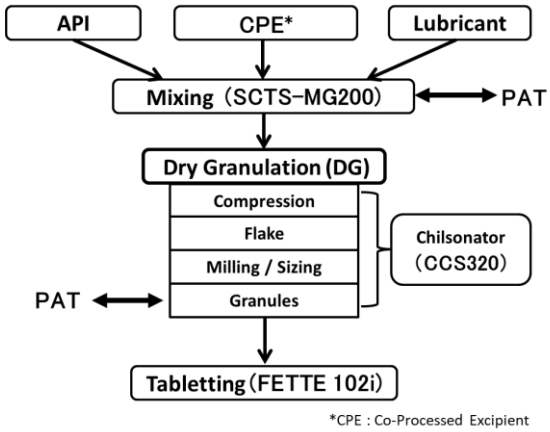


Fig. 1 Experimental flow

Table 1 Compositions of granules

	Composition (%)		
	ETZ	HSR	SSF
HSR-5	5	94	1
HSR-10	10	89	1
HSR-30	30	69	1

For mixing raw materials in dry granulation (DG) process, a mixer which was developed for CM (Material mixing unit; SCTS-MG200, Powrex) was applied. The mixer can maintain the quality of the mixture by controlling the mixing endpoint with real-time monitoring by NIR

sensor (PNIR-R17, Powrex).

The dry granulator (Chilsonator; CCS320, IDEX(Powrex)) is shown in Fig.2. This simple and compact granulator can continuously produce granules for tableting in a closed system.

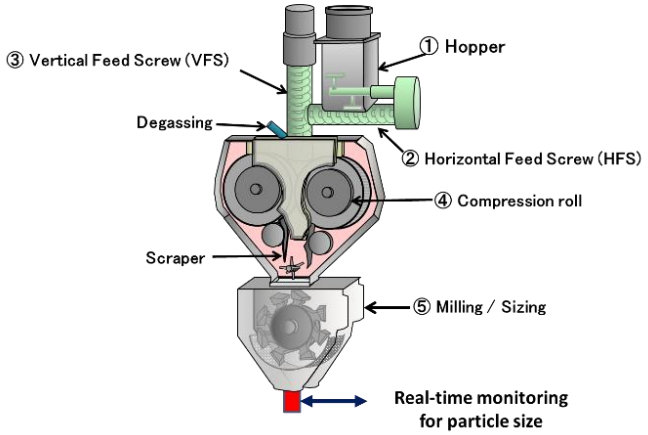


Fig. 2 Outline of dry granulator

The particle size analyzer with real-time monitoring (Parsum, Malvern Panalytical) was applied as PAT tool. Detailed conditions of mixing and dry granulation are shown in Table 2.

Table 2 Conditions of mixing / dry granulating

	Items	Conditions
Mixer	Center blade speed	500 rpm
	Scraper blade speed	60 rpm
Dry granulator	HFS speed	30 rpm
	VFS speed	300 rpm
	Roll speed	7.9 rpm
	Roll force	13.4 kN/cm
	Roll gap	0.5 mm
	Milling speed (Knife rotor)	1000 rpm
	Sizing (Round hole screen)	2 mm

2-2 Tableting

The obtained granules were tableted by the rotary tableting machine (FETTE Compacting 102i). Tableting conditions are described below;

200 mg, ϕ8 mm, R12, 30 rpm of rotary speed, 25 rpm of Stirring feeder, 8-10 kN of compression forces.

3. Results and discussion

3-1 Granule properties

Particle size of each sample is shown in Table 3.

Table 3 Particle size of each sample

sample	Particle size (D_{50})
HSR-5	345 µm
HSR-10	382 µm
HSR-30	385 µm

HSR was able to be granulated into large particle size between 300 to 400 µm. Thus, HSR has good compactability.

In case of CM, “Quality by Design (QbD) approach is important from the perspective of a control strategy for pharmaceutical quality. QbD involves designing the product quality maintained by accurate process control, such as real-time monitoring of physical properties of continuously produced granules. Fig.3 shows an example of the results of real-time monitoring for the particle size distribution (D_{50} and D_{90}) by PAT tool.

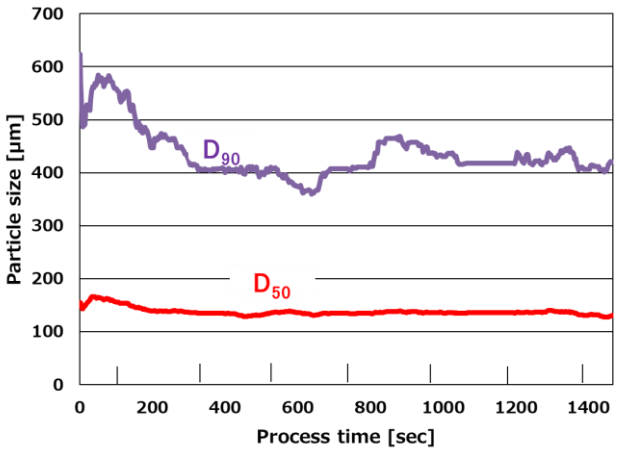


Fig.3 real-time monitoring (HSR-30)

In case of D_{90}, there was large variation of the particle size at the beginning. it came down immediately and fell within a certain range. In case of D_{50}, it stayed within a certain range until the end. Further studies are necessary though, these preliminary studies have

suggested that our co-processed excipient can be applied to CM method.

3-2 Tablet performance

The results of tablet performances are shown in Table 4.

Table 4 Each tablet performance

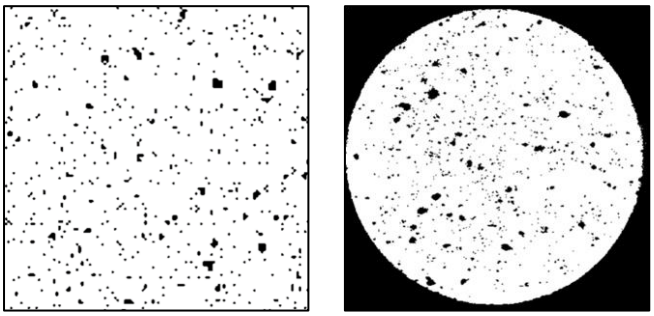
	Comp. Force[kN]	Hardness [N]*1	D.T. [sec]*2	Friability [%]*3
HSR-5	9.7	64	23	0.15
HSR-10	8.6	60	20	0.04
HSR-30	8.4	76	26	0.19

*1 Measured by electronic hardness tester
*2 Measured by JP general test method
*3 Measured by JP general test method

All samples showed sufficient disintegratability and tablet hardness. HSR showed good compactability even at high API dosage and low compression force.

3-3 Content uniformity of API

HSR-5 granule and HSR-5 tablet produced by DG system were measured using a laser raman microscope (RAMANforce, Nanophoton) as PAT tool (Fig.4).



Flake (12mm*12mm) **Tablet (ϕ8mm)**

Fig.4 Imaging of DG System (HSR-5)

It was found that ETZ particle was uniformly dispersed in both granules and the tablet. In conclusion, HSR is expected to have high applicability for DG system in CM since HSR is unlikely to cause separation and segregation of API.

4. Conclusion

Co-processed excipient “HiSORAD” can be applied to the DG system in continuous manufacturing, while maintaining high productivity and high quality of ODTs. Co-processed excipient may be more useful compared to single excipients in terms of quality control in continuous manufacturing.

5. Acknowledgements

The authors are grateful to Dr. Keijirou Terashita, Center President, Osaka Life Science Labo, and POWREX CORPORATION for their technical support given to the experiments.

6. References

1) U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) “Quality Considerations for Continuous Manufacturing Guidance for Industry (Draft guidance)”
2) Y. Suganuma, Tablet & Capsules, September 2020, 50.

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