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Enhanced Versatility of a Novel Coating Methods of Fine Particles for Time-Saving

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PURPOSE

In the previous study, we introduced a new powder layering technology as a time-saving method to solve the issue of the enormous amount of time required for fine particle coating. In the past, we selected Acetaminophen (APAP), which is a water-soluble API, as the API to be layered.

In this study, we used Ethenzamide (EZ), which is less soluble in water, as a model API to confirm the versatility of the powder layering method.

METHODS

Table 1 Coating formulation

Ingredients			Formulation (%)
Core		NONPAREIL-MM(80) (Mannitol-MCC spherical particle)	50.4
API layer	**Powder**	Ethenzamide (EZ)	15.1
		Light Anhydrous Silicic Acid (AD-101)	0.5
	Binder	Hydroxypropyl Cellulose (HPC-SSL)	0.4
Functional coating layer	**Powder**	Aminoalkyl Methacrylate Copolymer E (Eudragit E PO)	26.6
		Magnesium Stearate	3.3
		Light Silicic Anhydride (AD-101)	0.3
	Binder	Triethyl Citrate (CITROFLEX 2(SC-60), TEC)	3.4
		Polyoxyethylene Sorbitan Monooleate (Tween 80)	0.1

NONPAREIL-MM(80)(NP-MM(80), Freund Corp.) was used as starter pellets. The particle size distribution of NP-MM(80) had the following details : D_{10}= 60 µm, D_{50}= 79 µm, D_{90}= 107 µm. The granulation experiment was carried out using a high shear granulator (GM-MULTI, Freund Corp.)(Fig. 1).

For API layering, Hydroxypropyl Cellulose (HPC-SSL, NISSO SHOJI CO., LTD.) 3 wt% aqueous solution was used as the binding solution. Ethenzamide (EZ) was selected as a model API. The mixed powder of EZ and AD-101 was added into six times while spraying the binding solution to prepare EZ 30% layered pellets. After EZ layering with GM-MULTI, it was dried using of the fluidized bed granulation coating device (FLO-5M, Freund Corp.) to obtain EZ 30% layered pellets.

For polymer layering, Triethyl Citrate (CITROFLEX 2(SC-60), TEC) 15 wt% aqueous solution was used as the binding solution.
An aminoalkyl methacrylate copolymer E (Eudragit E PO) was chosen as the taste masking polymer. Similar to API layering, a mixed powder of polymer, magnesium stearate, and AD-101 was added into eight times at 5% each to drug layered pellets, and the TEC solution was sprayed to prepare E PO 40% layered pellets. The product was then produced by heating the Jacketed Bowl to raise the product temperature to approximately 50℃ for curing inside the GM-MULTI.

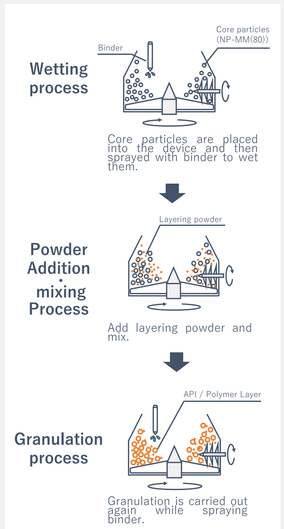


Fig 1 : Schematic of drug and polymer layering

RESULTS

Comparison of coating times

Powder layering was possible with poorly water soluble EZ, under the same conditions as APAP, and the time for 30% layering was 21 minutes. Polymer layering was also possible for the API-layered pellets, and the time required for polymer layering was 26 minutes, and a total of 83 minutes including the curing time in the granulator.

Table2. Comparison of APAP and EZ coating time

	API Layering		Polymer Layering	
	APAP	EZ	APAP	EZ
Coating Amount (%)	30		40	
Required Time (+curing)	31 min	21 min	21 min (+71 min)	26 min (+57 min)

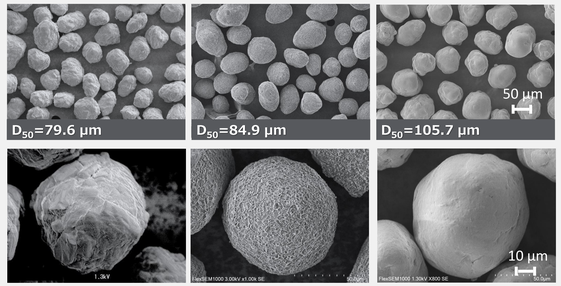


Fig2. SEM image showing coaing particles using powder coating method.
(Left : NP-MM(80) ,Center : EZ 30% layered pellets, Right : E PO 40% layered pellets)

Dissolution test results

Regarding the dissolution rate, the API-layered pellets increased in the early stages of dissolution, whereas the dissolution rate of the polymer-layered pellets 1 minute after the start of dissolution was 2.6%, which was less than 10% to be confirmed sufficient masking(Fig. 3).

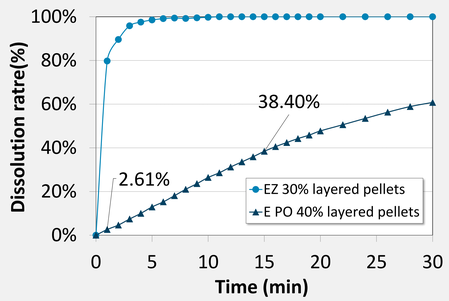


Fig3. Dissolution rate of EZ 30% layered pellets and E PO 40% layered pellets

Evaluation of drug content uniformity

It was acceptable that the drug content uniformity of EZ 30% layered pellets and E PO 40% layered pellets by powder coating . The data for these pellets were acceptable content relative standard deviations (RSDs)(Table3).

Table3. Drug content uniformity of particles by powder coating

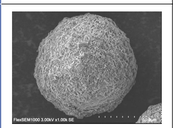
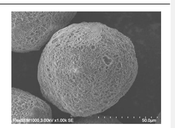
	EZ Layering	Polymer Layering
Average drug content (%)	98.4	101.3
content RSD	0.93	1.25

Powder Layering Applications

In addition, we assume that there is API what is more difficult to layer, we tried adding mannitol powder as a water-soluble excipient or spraying it during API layering.

As a result, it was found that the API content of API-layered pellets could be further increased by adding water-soluble excipients to the layering powder or binder(Table4).

Table4. Drug content in particles by adding water-soluble excipients

	Powder Addition*1	Binder Addition*2
Average drug content (%)	100.6	99.1
content RSD	1.11	1.34
SEM image		

*1 : 25% mannitol was added to the layering powder.
*2 : Mannitol was added to the binder at 20% and dissolved.

CONCLUSIONS

The novel coating method introduced in the previous study is a solution to the issue of the time required for fine particle coating. In order to apply this to a wider range of APIs, we focused on the water solubility of the API and conducted an investigation.

- Powder layering was possible even when the API to be layered was changed to EZ, which is poorly soluble in water.
- In this study, API layering was completed in 21 minutes, and polymer layering in 83 minutes.
- The initial dissolution rate was less than 3%, confirming that masking performance was maintained.
- There were no problems with the drug content in the granules, which was around 100%.
- Furthermore, the addition of water-soluble excipients can assist trap of poorly water-soluble API into the core particles, which is expected to improve the laminating efficiency of API.

From the above, we suppose that powder layering using a high shear granulator may be a more versatile method for solving the issues of fine particle coating.

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