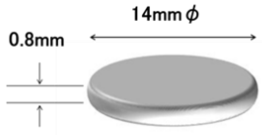
Coin-Shaped Orally Disintegrating Tablets (ODTs) Prepared by Direct Compression Using GRANFILLER-D

■ INTRODUCTION

Orally disintegrating tablets (ODTs) prepared by lyophilization such as Zydis® disperse almost instantly in the oral cavity but their preparation requires special manufacturing equipment and packaging. Here we describe the preparation of unique coin-shaped ODTs (Figure 1) by direct compression using GRANFILLER-D and the evaluation of their characteristic properties.



[Figure 1] Coin-shaped ODT

■ METHODS

1. Preparation of samples

ODTs were prepared by a dry compression process (a) using GRANFILLER-D. Commercially available lyophilized ODTs (b) were used as references (Table 1).

2. Evaluation of mechanical strength

Mechanical strength was evaluated using three methods.

2-1 Tablet hardness

The hardness of ODTs was measured using a KHT-40 digital harness tester from Fujiwara Scientific Company Co., Ltd.

2-2 Friability

The friability of ODTs was measured in accordance with a pharmacopoeia test method.

2-3 Drop test

Fifty each of ODTs were dropped from a height of 1 m onto a stainless plate and the number of fractured tablets was counted.

3. Evaluation of disintegration time and behavior

The disintegration times of ODTs were evaluated by three methods: a pharmacopoeia test method, an oral disintegration test (in vivo) and a measuring device for oral disintegration, Toricopetester from OKADA SEIKO CO.,LTD. (in vitro)

4. Evaluation of handling properties

The handling properties of ODT preparations were evaluated as follows.

4-1 Contact with an ultra-low volume of water

A water droplet (1 µL) was placed on individual tablets (a) and (b) and surface changes were observed.

4-2 Stability of unpackaged ODTs

ODTs were exposed to 40°C/75%RH for 1 day, and the appearance, hardness and oral disintegration time (in vitro) were evaluated.

5. Masking of bitter taste

Active pharmaceutical ingredient (API) particles are often coated to mask bitter taste. While coating APIs is unlikely to be compatible with lyophilization, we applied coated APIs to dry compression coin-shaped ODTs.

[Table 1] Samples used in this study

Sample	Composition	API (dose in a tablet)	Process	Weight & Size
(a)-Placebo	GNF-D211*(99.5%)+ Mg-St (0.5%)	none	Dry Compression Rotary Press	150 mg, Φ14 mm, Th0.8 mm
(a)-βCD	GNF-D211 (59.5%) + β-CD (40%) + Mg Stearate (0.5%)	none		
(a)-30% ETZ	GNF-D211 (68.7%) + Etenzamide (30%) + Light anhydrous silicic acid (1.0%) + Mg Stearate (0.3%)	Ethenzamide (45 mg)		
(a)-10% AAP	GNF-D211 (88.3%) + Acetaminophen (10%) + Light anhydrous silicic acid (1.0%) + Mg Stearate (0.7%)	Acetaminophen (15mg)		
(a)-cAAP	GNF-D211(72.2%) + Acetaminophen(5.0%)+Celphere/Eudragit RL30D(22.3%)+Mg-St(0.5%)	Acetaminophen (7.5 mg)		
(b)-Loratadine	(Existing Product)	Loratadine (10 mg)	Lyophilization	27 mg, Φ12.5 mm, Th2.4 mm
(b)-Aripiprazole	(Existing Product)	Aripiprazole (12 mg)		35mg, Φ14mm, Th3mm
(b)-CPM-SHH	(Existing Product)	Chlorpheniramine maleate (2 mg), Scopolamine hydrobromide hydrate (0.25 mg)		22mg, Φ11.5mm, Th3mm

* GNF-D211 : GRANFILLER-D (GNF-D211)

■ RESULTS

1. Hardness, Friability, Drop Test and Disintegration Time

Dry compression coin-shaped ODTs (a) containing GRANFILLER-D (GNF-D211) were sufficiently hard to withstand handling (20-28 N), had adequate friability

(0.05-0.31%), and disintegrated rapidly (3-5 sec). Lyophilized ODT (b) disintegrated even faster (Table 2).

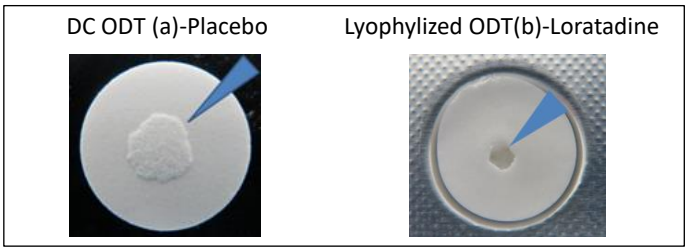
[Table 2] Hardness, Friability, Drop Test and Disintegration Time

Sample	Tablet Hardness (N)	Friability (%)	Drop Test (number of fractured)	Disintegration Time (sec)	Oral Disintegration Time (sec)
(a)-Placebo	28	0.05	0/50	3.6	3.6 (in vivo)
(a)-30% ETZ	22	0.31	3/50	5.2	4.5 (in vivo)
(a)-10% AAP	20	0.27	0/50	5.2	5.2 (in vivo)
(a)-cAAP	20	0.05	0/50	3.1	3.9 (in vivo)
(b)-Loratadine	2	not tested (adhesion)	slightly deformed	<1	1.0 (in vitro)
(b)-Aripiprazole	2	not tested (adhesion)	slightly deformed	<1	1.4 (in vitro)
(b)-CPM-SHH	3	not tested (adhesion)	slightly deformed	<1	0.9 (in vitro)

2. Handling properties

2-1 Contact with an ultra-low volume of water

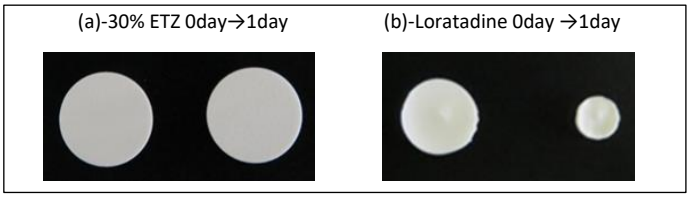
When an ultra-low volume of water (1 µL) was placed on a tablet, a dry compression (a)-Placebo tablet maintained their strength and could be removed from their packaging although the surface had swollen. In contrast, lyophylized ODTs (b)-Loratadine easily deformed and developed a hole (Figure 2).



[Figure 2] Contact with an ultra-low volume of water

2-2 Stability of unpackaged ODTs

After 1 day at 40 °C/75%RH, no change was observed in appearance of dry compression ODTs (a)-Placebo whereas lyophylized ODTs (c)-Loratadine deformed significantly (Figure 3). The hardness of dry compression ODT (a)-Placebo decreased after 1 day but its disintegration time was unchanged whereas the disintegration time of lyophylized ODTs (b)-Loratadine was significantly prolonged (Table 3).



[Figure 3] Stability of unpackaged ODTs

[Table 3] Stability of unpackaged ODTs

	Hardness / 0 day (N)	Disintegration Time / 0 day (sec)	Hardness / 1 day (N)	Disintegration Time / 1 day (sec)	Type of OD tablet
(a)-Placebo	16	3.3	6	4.2	Dry compression
(a)-30% ETZ	23	6.0	16	7.2	Dry compression
(b)-Loratadine	2	1	not tested	187	Lyophylized
(b)-Aripiprazole	2	1	not tested	62	Lyophylized

3. Masking of bitter taste

Despite the increase in API particle volume due to coating to mask bitter taste, we succeeded in forming coin-shaped ODT (a)-cAAP by dry compression. This method is easily applied in dry tableting processes and thus is an advantage over the lyophilization processes. β-CD, which is sometimes used in the lyophilization process instead of coating, also applied to the coin-shaped ODTs, and showed good results (Table 4).

[Table 4] Masking the bitter taste of OD tablets formed by dry compression

Sample	Tablet Hardness (N)	Friability (%)	API or Masking agent	Weight & Size	Disintegration Time (sec)	Oral Disintegration Time (sec)
(a)-βCD	19	0.24	β-CD (60 mg)	150 mg, Φ14 mm, Th0.8 mm	2.7	3.2
(a)-cAAP	20	0.05	AAP (7.5 mg)	150 mg, Φ14 mm, Th0.8 mm	3.1	3.9

■ CONCLUSION

Coin-shaped ODTs containing GRANFILLER-D were formed by a direct compression process and exhibited rapid oral disintegration comparable to that of lyophilized OD tablets. The tablets were only 0.8 mm thick yet adequately withstood external impact.

The coin-shaped ODTs disintegrated orally in about 3 seconds and could be useful both for patients who typically refuse their medication and for pediatric applications.

Compared with lyophilized tablets, coin-shaped ODTs can be manufactured using a direct compression process. Therefore this approach may find application to a wide range of drug products. Masking bitterness by coating APIs is easier to achieve using the dry compression method compared to lyophilization and thus this tablet form could help improve medication adherence.

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