Application of mini ODTs and coin-shaped ODTs with high performance excipients for pediatric preparation

1. Introduction

There is strong clinical need for pediatric formulations from healthcare professionals and caregivers since the number of available pediatric formulation is limited. Currently oral administration is the main route of administration for pediatric formulations in the market. For development of pediatric oral administration, “acceptability” of “formulation” and “handling” should mainly be considered. Particularly, the formulation is the most important because it includes palatability (e.g., taste, smell and texture) and swallowability (e.g., size and shape). These two factors determine suitability for ~~of~~ taking medications to children (Fig. 1).

Fig. 1 Factors required for pediatric formulations

In European countries, liquid dosage forms such as syrups and suspensions are widely used as oral administrations for children. Although liquid dosage forms can be taken from the neonatal period, there are several issues. Their storage conditions and shelf-life are constrained compared with those of solid formulations. As one bottle covers the amount of medication for the number of days, it is necessary for caregivers to measure the liquid, deriving difficulty to administer a single dose accurately.[1)] In view of these considerations, solid dosage forms have been studied as pediatric preparations recent years.

There are a variety of solid dosage forms, such as tablets, capsules and powders. Among these, orally disintegrating tablet (ODT), is a dosage form that is designed to improve swallowability of conventional tablet for increased medication adherence. ODTs disintegrate in the oral cavity within 30 seconds by saliva, which is suitable for patients with dysphagia. Advantages of ODTs include their safety (they prevent aspiration), convenience (any time and place), and reliability (they prevent medication refusal). However, it might be considered that rapid disintegratability of conventional ODT is not enough for pediatric use. This article discusses distinctive dosage forms in order to improve the acceptability of pediatric formulations from a perspective of excipient manufacturers.

2. Overview and characteristics of co-processed excipients for ODTs

GRANFILLER-D and HiSORAD are co-processed excipients composed of several pharmaceutical excipients that comply with USP-NF, EP, and JP. They are produced with proprietary granulation methods.[2, 3)] Their characteristics are indicated in Fig. 2.

Both products provide advantages such as enhancing performance of ODT, reducing development time, and simplifying manufacturing process. Using these co-processed excipients, we developed ODTs which shape are suitable for pediatric use.

Fig. 2 Daicel co-processed excipients for ODT

3. Mini ODTs

(1) What are mini ODTs?

Fig. 3 Mini ODTs

As the entrance to esophagus is narrow in children, it may be difficult for them to swallow even a regular-size tablet 6 to 10 mm in diameter. Mini tablets, which are miniaturized tablets approximately 2 to 4 mm in diameter, are considered to provide improved acceptability. According to Klingmann et al., children between 6 months and 6 years of age tend to prefer mini-tablets to syrup.[4] Moreover, by adjusting the number of tablets, the dose can be controlled according to weight and age of a pediatric patient in the growth period. To further improve the swallowability of mini-tablets, mini ODTs have been developed.

(2) Preparation and evaluation of mini ODTs

Mini ODTs were prepared using GRANFILLER-D and HiSORAD. Paracetamol pellet that coated for bitterness masking were used as a model API. The composition of the tablets and the tableting conditions is provided in Table 1. After simple mixing of the components without any special preprocessing, tableting was performed by a rotary tablet press (model 102i, Fette Compacting). Compactability was good with the coefficient of variation (CV) for tablet weight of ≤ 1.2%. Both tablets achieved a disintegration time of < 3 seconds, which exhibited sufficient hardness and friability for any mini-tablet measuring devices. Thus, it can be noted that both GRANFILLER-D and HiSORAD are suitable co-processed excipients for manufacturing mini ODTs.

Table 1 Mini ODT (placebo) performance

	GRANFILLER-D	HiSORAD
Tablet hardness [mm]	2.6	2.6
Disintegration time [s]	3	2
Tablet hardness [N]	15	15
Friability [%]	0.13	0.05

Components of ODT :
Paracetamol (9.8%) + GRANFILLER-D/HiSORAD(88.2%)
+ Sodium Stearyl Fumarate (2.0%)
Tablet shape : 15 mg, ϕ2.5 mm, R3.5
Tableting condition : Rotary press 40 rpm, Open-Feeder
Compression force : 3.7 kN

4. Coin-shaped ODTs

Fig. 4 Imprinted coin-shaped ODTs

The following is a discussion of the coin-shaped ODT as a special dosage form also suitable for children. Coin-shaped ODTs are large in diameter, at approximately 14 mm, and thin, with a thickness of ≤ 1 mm (Fig. 4). Because of their large surface area, they have the ability to disintegrate very rapidly. The coin-shaped ODTs described in this article were produced with GRANFILLER-D. The composition of the tablets and the tableting conditions are provided in Table 2.

The disintegration time of the placebo tablets was < 5 seconds. Moreover, they exhibited practical friability values of < 0.5%, and drop tests of 50 tablets detected no cracking or chipping. Although thin tablets are typically fragile in response to external impact, the coin-shaped ODTs with GRANFILLER-D had practical strength that exceeded expectations.

Table 2 Coin-shaped ODTs (placebo) performance

Compression force [kN]	18	24
Tablet hardness [mm]	0.83	0.79
Disintegration time [s]	3	4
Tablet hardness [N]	16	23
Drop test	No Fractured tablets	
Friability [%]	0.40	0.19

Components of ODT : GRANFILLER-D (99.5%) + Mg stearate (0.5%)
Tablet shape : 150 mg, ϕ14 mm, Flat shape
Tableting condition : Rotary press 40 rpm
Drop test : Each of 50 ODTs were dropped from a height of 1m to a stainless plate, and then the number of fractured tablets was counted.

This thin tablet with high strength is derived from the unique mechanical property of GRANFILLER-D (Fig.5).

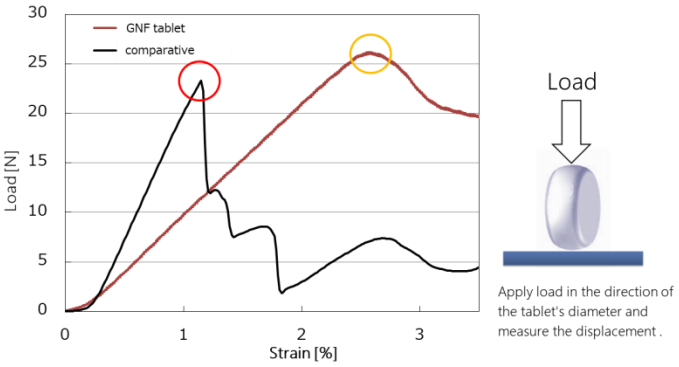

Fig. 5 Mechanical property

With a typical tablet (Reference tablet), a rapid decrease is observed near the breaking point, whereas with the GRANFILLER-D tablet, it is distorted gradually near the break point. This behavior is characteristic of elastic materials. Moreover, coin-shaped ODTs can be applied to a variety of APIs. For all of the formulations shown in Table 3, the disintegration time for the coin-shaped ODT is approximately 6 seconds. Development for manufacturing is currently in progress.

Table 3 Examples of application with various APIs

	Ethenzamide*1	Paracetamol*2	Ascorbic acid*3
Compression force [kN]	18	18	18
Tablet hardness [N]	16	13	13
Disintegration time [s]	6	6	6
Oral disintegration time[s]	6	6	4
Friability [%]	0.98	0.63	0.96

Components of ODT:
*1 GRANFILLER-D (68.7%) + Ethenzamide (30.0%) + Silica, Colloidal Hydrated (1.0%) + Mg stearate (0.3%)
*2 GRANFILLER-D (88.3%) + Paracetamol (10.0%) + Silica, Colloidal Hydrated (1.0%) + Mg stearate (0.7%)
*3 GRANFILLER-D (88.5%) + Ascorbic acid (10.0%) + Silica, Colloidal Hydrated (1.0%) + Mg stearate (0.5%)
Tablet shape : ϕ14 mm, 150 mg, Flat shape
Tableting condition : Rotary press, 10 rpm, Open-Feeder

5. Summary

Mini ODTs and coin-shaped ODTs prepared with GRANFILLER-D and HiSORAD disintegrate in several seconds, indicating excellent disintegratability more than that of conventional ODTs. The tablets provided not only the advantages of ODTs, such as safety, convenience, and reliability, but also a special shape considered suitability to children taking medications.

The Daicel's products enable realizing well balanced property between compactability and disintegratability of ODTs. Furthermore, the distinctive properties also allow tablets to be miniaturized and made thinner. We would be pleased if providing our product could contribute to creating more options for pediatric preparations.

6. 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.

7. References

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