The bitterness-masking effect of β-Cyclodextrin in the formulation of ODTs using Granfiller-D

1. Introduction

Improving medication adherence is an important aspect of patient-centric pharmaceutical development. Patients and healthcare providers are looking for routes of administration or dosage forms that are easy to take. Orally disintegrating tablets (ODTs) are one of the most popular dosage forms for improving medication adherence. ODTs disintegrate in the oral cavity within 30 seconds without water so that patients with dysphagia can also swallow tablets easily.

Fig.1 Functions required for ODTs

To produce ODTs, rapid disintegration is required under sufficient tablet hardness. Additionally, as ODTs taken without water remain in the mouth while they are disintegrating, palatability is more important compared to when regular tablets taken with water. Active pharmaceutical ingredients (APIs) which have an unpleasant or bitter taste decrease medication adherence. Therefore, taste masking is one of the most important issues in manufacturing ODTs.

There are three types of bitterness masking methods: physical, organoleptic and chemical masking. While physical and organoleptic masking methods are the mainstream in marketed formulations, chemical masking has different advantages. It is the simplest method with fewer steps and at lower cost than the others. The main technique used in chemical masking is conducted with cyclodextrins (CDs) due to their complex-forming ability[1)].

In this paper, we report the preparation of ODTs including CD-masked APIs with practical ODT performance.

2. Methods

(1) Preparation of β-CD/ Mitiglinide complex

Mitiglinide Ca (MIT) was selected as a bitter API. The complex was prepared by the kneading method with composition of β-CD : MIT = 4 mol : 1 mol. As a result, 13.5% of the API was contained in the finished β-CD/MIT complex, which was normalized to 12 wt% based on water content.

(2) Preparation of ODTs

GRANFILLER-D GNF-D211[2)] (GNF) was selected as filler. ODTs were prepared with mixing the API complex, GNF and Sodium stearyl fumarate (SSF) as lubricant, then by tableting. All the ingredients were of pharmaceutical grade. The composition of ODTs is shown in Table 1.

Table 1 Composition of ODTs

	Sample 1	Sample 2
GNF	57.8%	57.8%
β-CD	41.7%	-
β-CD/MIT *	-	41.7%
SSF	0.50%	0.50%

* 10 mg as API content
200 mg, Φ8 mm Flat beveled edge

3. Results and discussion

(1) Chemical property of β-CD/MIT complex

Differential scanning calorimetry (DSC) thermograms of each sample are illustrated in Fig. 2. MIT showed sharp peaks at 179–185 °C and 201 °C, attributed to Mitiglinide Ca・$2H_2O$ and Mitiglinide Ca respectively. Since these peaks disappeared in β-CD/MIT complex obtained by the method in 2-(1), the inclusion of MIT was considered to be successful. Furthermore, an organoleptic evaluation indicated that bitterness of naked-MIT disappeared in the β-CD/MIT complex.

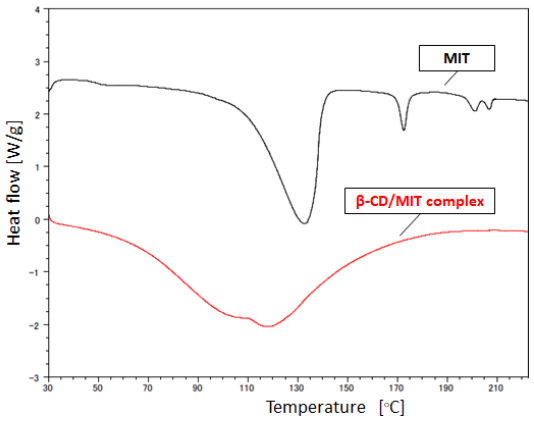

Fig. 2 DSC thermograms of samples

(2) ODT performance

The tablet performance is shown in Table 2.

Table 2 Performance of ODTs

	Tablet hardness [N]	Disintegration time [s]	D/H*
Sample 1	70	16	0.23
Sample 2	71	20	0.28
Originator's drug**	50	18	0.36

Sample 2 and original drug have the same amount of API, 10 mg.
Compression force: 3 kN (sample 1), 5 kN (sample 2)
* D/H = Disintegration time/Tablet hardness
** 200 mg, Φ8 mm

Sample 1 showed sufficient tablet hardness and excellent disintegration even after 41.7 % β-CD was included. It was found that β-CD did not affect the ODT performance when it was used with GNF. It is known that two water penetration pathways exist for ODTs produced with GNF; one uses gaps between particles and the other draws water inside particles [3]. The latter contributes ODT's disintegration in case of high content β-CD. Sample 2 showed similar performance in terms of disintegration time and tablet hardness compared with Sample 1. There was no difference in ODTs performance whether or not MIT was included. Furthermore, Sample 2 showed similar disintegration time with higher tablet hardness than the originator's drug. It is clear that Sample 2 showed better ODT performance than the originator's drug when we compare D/H value.

(3) Hygroscopic stability

The result of hygroscopic stability test stored at 25℃/75%RH (no packaging) is shown in Fig. 3. Tablet hardness of originator's drug significantly decreased to 20 N on day 7. On the other hand, Sample 2 (this study) showed higher tablet hardness at the initial and maintained better hardness than the originator's drug (45 N on day 7), despite the same disintegratability (13 s on day 7). It is considered that high interparticle binding force between β-CD and GNF contributes to keeping tablet hardness under the hygroscopic condition.

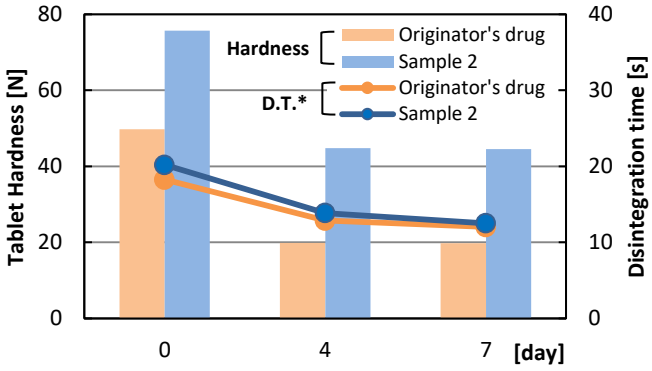

Fig.3 Hygroscopic stability

* D.T. = Disintegration time

4. Conclusion

ODTs with β-CD and GNF achieved practical bitterness masking, sufficient tablet hardness and rapid disintegration. Although further studies are needed, it is assumed that β-CD can be used for bitterness masking for poorly soluble APIs such as MIT. Combining bitterness masking by β-CD and ODTs production by GNF enable to reduce the number of steps in manufacturing processes for ODTs. Therefore, the combination of β-CD and GNF appears to be one of the best solutions for manufacturing palatable ODTs.

5. References

1) J. Szejtli, et al., EUR. J. PHARM. BIOPHARM., 61 (2005) 115-125
2) T. Hiramura, et al., Tablet & Capsules, March 2016, 37.
3)https://www.europeanpharmaceuticalreview.com/whitepaper/125290/application-note-disintegration-property-of-odts-with-co-processed-excipients/

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