Regular Article

Ease of Taking and Palatability of Fixed-Dose Orally Disintegrating Mitiglinide/Voglibose Tablets

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Fixed-dose combination (FDC) medicines containing two or more active pharmaceutical ingredients (APIs) in a single dosage form have been reported to improve patient adherence to a greater extent than single dosages of individual components (ICs). Orally disintegrating tablets (ODTs) are easier to swallow than conventional tablets. The aim of this study was to elucidate the clinical pharmaceutical characteristics of taking a FDC-ODT and two IC-ODTs. We prepared three ODTs containing mitiglinide, voglibose, and mitiglinide/voglibose and three corresponding placebo ODTs and performed 2 independent clinical trials with 13 healthy subjects (mean age, 23.4 ± 1.6 years). One trial evaluated the ease of taking tablets and the amount of water required for taking the tablets; placebo ODTs were used in order to avoid administering APIs. The other trial evaluated the bitterness, sweetness and overall palatability of ODTs containing APIs during disintegration and after spitting out. Ease and taste were evaluated using both a visual analog scale (VAS) and a verbal rating scale (VRS). The results of the VAS and VRS evaluation indicated that FDC-ODT could ease tablet intake unlike IC-ODTs. In addition, FDC-ODT reduced the amount of water required for tablet intake in contrast to IC-ODTs. Taste evaluation results did not reveal any difference between FDC-ODT and IC-ODTs, except for the sweetness score after spitting out. In conclusion, FDC-ODT is easy to take and can help improve patient adherence.

Key words orally disintegrating tablet; fixed-dose combination; palatability; mitiglinide; voglibose

Introduction

Orally disintegrating tablets (ODTs) are easily swallowed by patients with dysphagia and elderly patients and improve patient adherence. ODTs are designed to disintegrate with saliva in the absence of water,^{1,2)} allowing patients to take medication anywhere; this is one advantage for patients with lifestyle-related diseases (e.g., type 2 diabetes mellitus and hypertension). Changing from conventional tablets to ODTs has been reported to result in improved pharmacotherapy adherence and enhanced drug efficacy.³⁾

Patients are often administered multidrug therapy, consisting of a number of therapeutic drugs taken simultaneously.⁴⁾ Fixed-dose combination (FDC) tablets combine two or more active pharmaceutical ingredients (APIs) into a single tablet⁵⁾; some studies have reported that FDC decreases the risk of non-compliance to a greater extent than the two individual components (ICs).⁶⁾ A number of similar studies examining oral antidiabetic therapy have suggested that patients taking an FDC had higher adherence than those taking ICs^{7,8)} and that adherence was improved by switching from IC to FDC.^{9,10)} Thus, ODTs containing two or more APIs (fixed-dose combination orally disintegrating tablet, FDC-ODTs) possess the advantages of both FDC and ODT and have the potential to further improve patient adherence.

Mitiglinide is a rapid- and short-acting insulin secretagogue and voglibose is an agent for improving postprandial hyperglycemia.^{11–13)} Conventional tablets and ODTs of both drugs are commercially available and are used for oral anti-

diabetic therapy. Both are taken immediately before meals for the treatment of postprandial hyperglycemia.¹⁴⁾ Some patients are prescribed both drugs and take them simultaneously. GLUBES, a mitiglinide/voglibose FDC tablet (Kissei Pharmaceutical Co., Ltd., Nagano, Japan), has been approved for the treatment of type 2 diabetes mellitus in Japan¹⁵⁾; however, no mitiglinide/voglibose FDC-ODT is marketed. Mitiglinide/voglibose FDC-ODT is expected to improve patient adherence to take medicines which are administered just before meal, since the FDC-ODT may reduce the issues with medication, such as needing water, taking multiple tablets, and difficulty to swallowing.

The clinical pharmaceuticals (e.g., disintegration time and palatability) of FDC-ODTs and some individual component orally disintegrating tablets (IC-ODTs) may be different. The purpose of this study was to elucidate the clinical pharmaceutical characteristics, including disintegration time, ease of taking (swallowing) tablets, amount of water required for taking tablets, and the taste, of an FDC-ODT and two IC-ODTs.

Experimental

Materials Mitiglinide ODTs (10mg, GLUFAST ODTs (GF-ODT), Kissei Pharmaceutical Co., Ltd.) and voglibose ODTs (0.2mg, BASEN ODTs (BS-ODT), Takeda Pharmaceutical Co., Ltd., Osaka, Japan) were purchased and used. The mitiglinide/voglibose FDC-ODT (GB-ODT) was manufactured in a shape similar to that of GF-ODT. Placebo GF-ODTs, BS-ODTs and GB-ODTs, which did not contain

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mitiglinide, voglibose, or either, respectively (pGF-ODT, pBS-ODT and pGB-ODT), were manufactured. GB-ODT and placebo ODTs (pGF-ODT, pBS-ODT and pGB-ODT) were donated by Kissei Pharmaceutical Co., Ltd.

The diameter and thickness of the placebo ODTs were designed to be similar to the corresponding API-containing ODTs and the weight and hardness of the placebo ODTs were determined to ensure that the *in vitro* disintegration time of the ODTs was similar to that of the corresponding ODTs (Table 1).

Measurement of Tablet Characteristics of ODTs Thickness and weight of the ODTs with APIs (GF-ODT, BS-ODT, and GB-ODT) and the placebo ODTs (pGF-ODT, pBS-ODT, and pGB-ODT) were measured. Hardness of the ODTs was determined using a load cell-type tablet hardness tester (PC-30; Okada Seiko Co., Ltd., Tokyo, Japan). The *in vitro* disintegration time of the ODTs was measured using Tricorptester (Okada Seiko Co., Ltd.), as described previously.¹⁶⁾

Trial 1: Ease of Intake of Tablets and the Amount of Water Required for Taking the Tablets The subjects in this clinical trial included 13 healthy adults (8 men and 5 women; age, 23.0 ± 0.86 years, mean $\pm$ standard deviation (S.D.)). We performed a two-phase randomized crossover trial, which consisted of a phase of taking a pGF-ODT and a pBS-ODT (a total of two tablets) simultaneously (IC-ODTs phase) and a phase of taking a pGB-ODT (FDC-ODT phase). The study protocol was approved by the Ethics Committee of the University of Shizuoka and the subjects participated in the trial after providing written informed consent.

The amount of water required for taking the ODTs was measured as previously described.¹⁷⁾ Subjects were asked to consume both a pGF-ODT and a pBS-ODT together or only a pGB-ODT with drinking water after these tablets had disintegrated in their oral cavity. Subjects freely filled a cup with water from a 500-mL bottle and then drank the minimum volume of water required to consume the ODTs. After drinking the water, they were asked to evaluate the ease of taking the ODTs using a visual analogue scale (VAS) with the most

difficult sensation of taking a tablet marked at 100 mm.¹⁸⁾ The subjects rinsed their oral cavity with 120 mL of water and then evaluated ease of intake using a four-point verbal rating scale (VRS): 1 = very difficult to swallow, 2 = slightly difficult to swallow, 3 = slightly easy to swallow, 4 = very easy to swallow. They were given a 10-min interval before the next phase. The amount of water was measured using the weight of the cup and bottle.

Trial 2: Palatability and Clinical Disintegration Time of ODTs The subjects in this clinical trial included 13 healthy adults (8 men and 5 women; age, 23.4 ± 1.6 years, mean $\pm$ S.D.). We performed a two-phase randomized crossover trial, which consists of an IC-ODTs phase including a GF-ODT and a BS-ODT and an FDC-ODT phase including a GB-ODT. The study protocol was approved by the Ethics Committee of Hamamatsu University School of Medicine and the subjects participated in the trial after providing written informed consent.

The subjects placed each ODT in their mouth and allowed the ODT to disintegrate. Subsequently, the bitterness, sweetness and overall palatability of the ODTs were evaluated using a VAS (first evaluation).^{19–23)} Bitterness VAS scores of 0 and 100 indicate “none” and “very bitter,” sweetness scores of 0 and 100 indicate “none” and “very sweet,” and overall palatability VAS scores of 0 and 100 indicate “bad” and “good,” respectively. In parallel with the VAS evaluation, the clinical disintegration time was measured using a stopwatch. After the remnants of each ODT were removed, the subjects immediately completed another VAS evaluation (second evaluation). Subsequently, the subjects rinsed their oral cavity with 120 mL of water and evaluated preferability using a five-point VRS: 1 = very non-preferable, 2 = non-preferable, 3 = neither, 4 = preferable, 5 = very preferable.²⁴⁾ Subjects were given a 15-min interval before testing the next tablets.

Statistical Analysis All data are presented as mean $\pm$ S.D. Statistical analysis was performed using the paired *t*-test with Bonferroni correction with GraphPad Prism ver.5.02 (GraphPad software, Inc., San Diego, CA, U.S.A.). A statisti-

Table 1. GB-ODT, pGB-ODT, GF-ODT, pGF-ODT, BS-ODT, and pBS-ODT Tablet Characteristics

	Diameter (mm)	Thickness (mm)	Weight (mg)	Hardness (N)	<i>In vitro</i> disintegration time (s)
GB-ODT	8.05	3.88 ± 0.02	199.5 ± 1.7	47.0 ± 3.9	21.7 ± 0.8
pGB-ODT	7.55	3.54 ± 0.01	181.4 ± 0.7	35.7 ± 1.5	19.3 ± 0.6
GF-ODT	8.04	3.91 ± 0.02	200.0 ± 0.5	49.7 ± 1.8	18.4 ± 1.2
pGF-ODT	8.06	3.90 ± 0.03	215.3 ± 0.4	75.0 ± 2.4	24.3 ± 2.2
BS-ODT	7.54	2.67 ± 0.01	149.8 ± 0.6	66.4 ± 1.6	28.0 ± 2.4
pBS-ODT	7.53	2.69 ± 0.02	145.3 ± 0.8	92.0 ± 5.4	28.7 ± 0.4

Diameter data are shown as the mean ($n = 3$). Thickness, weight, hardness, and *in vitro* disintegration time data are shown as the mean $\pm$ S.D. ($n = 10$).

Table 2. Four-Point VRS Scores for Ease of Tablet Intake

Phase	Number of subjects scored ($n = 13$)				Mean $\pm$ S.D.	<i>p</i>
	1	2	3	4		
	Very difficult	Slightly difficult	Slightly easy	Very easy		
IC-ODTs	0	2	5	6	3.3 ± 0.8	0.028
FDC-ODT	0	0	2	11	3.8 ± 0.4	

Data represents the number of subjects that scored 1, 2, 3, or 4 in four-point VRS. The mean indicates the ease score of the 13 subjects. The subjects took both a pGF-ODT and a pBS-ODT simultaneously in the IC-ODTs phase and a pGB-ODT in the FDC-ODT phase.

Fig. 1. VAS Score for Ease (a) and Amount of Water Required (b) for Tablet Intake in Trial 1

Each point represents the value of one of the subjects. The horizontal line indicates the mean for the 13 subjects. The subjects took both a pGF-ODT and a pBS-ODT simultaneously in the IC-ODTs phase and a pGB-ODT in the FDC-ODT phase.

Fig. 2. VAS Scores for Bitterness (a), Sweetness (b) and Overall Palatability (c) in the First Evaluation, and for Bitterness (d), Sweetness (e) and Overall Palatability (f) in the Second Evaluation of Trial 2

Each point represents the value of one of the subjects. The horizontal line indicates the mean for the 13 subjects. The subjects took both a GF-ODT and a BS-ODT simultaneously in the IC-ODTs phase and a GB-ODT in the FDC-ODT phase.

cally significant difference was noted at $p < 0.05$.

Results

Tablet Characteristics of ODTs Tablet characteristics of GB-ODT, pGB-ODT, GF-ODT, pGF-ODT, BS-ODT, and pBS-ODT are listed in Table 1. Hardness of the ODTs ranged from 35.7 to 92.0N. The *in vitro* disintegration time of GF-ODT was the shortest (18.4s) and that of pBS-ODT was the

longest (28.7s); however, those of all ODTs tested in this study were within 30s. A good correlation was observed between tablet hardness and *in vitro* disintegration time ($r^2 = 0.7305$, $p = 0.03$).

Ease of Intake of Tablets and the Amount of Water Required for Taking the Tablets In Trial 1, the ease of tablet intake was evaluated and the amount of water required for taking the tablets was measured for a pGF-ODT and a

pBS-ODT simultaneously (IC-ODTs phase) and for a pGB-ODT (FDC-ODT phase; Fig. 1). The ease VAS score for the FDC-ODT phase was significantly lower (62.5%) than for the IC-ODTs phase (7.8 vs. 20.8; $p = 0.010$, Fig. 1a). The mean score significantly increased from 3.3 to 3.8 (IC-ODTs phase and FDC-ODT phase, respectively) in the four-point VRS evaluation of ease of intake ($p = 0.028$, Table 2). The amount of water required for taking the tablets in the IC-ODTs phase and FDC-ODT phase was 22.5 mL and 17.0 mL, respectively. The amount of water for taking an FDC-ODT was decreased by 24.4% compared to that required for taking two IC-ODTs; however, the difference was not significant ($p = 0.155$, Fig. 1b).

Palatability and Clinical Disintegration Time of ODTs
In Trial 2, the VAS scores for bitterness, sweetness and overall palatability in the IC-ODTs phase and the FDC-ODT phase were evaluated (Fig. 2). The differences in the first and second evaluation VAS scores between the IC-ODTs phase and FDC-ODT phase were not significant, except for the sweetness VAS score in the second evaluation. The sweetness VAS score after spitting out the ODT in the FDC-ODT phase was significantly higher than the score in the IC-ODTs phase ($p = 0.012$, Fig. 2e).

Table 3 shows the preferability VRS scores. Two IC-ODTs phase subjects and four FDC-ODT phase subjects answered "preferable" (4 or 5). The mean FDC-ODT phase score for taking a GB-ODT tended to be higher than the IC-ODTs phase score for taking a GF-ODT and a BS-ODT ($p = 0.053$). The clinical disintegration time in the IC-ODTs phase and in the FDC-ODT phase was 27.9 ± 4.5 and 25.3 ± 5.6 s, respectively (Fig. 3).

Discussion

The aim of this study was to clarify the clinical pharmaceutical characteristics of ODTs when taking one FDC-ODT containing both mitiglinide and voglibose and simultaneously taking two ODTs (one mitiglinide ODT and one voglibose ODT). We performed two independent clinical trials. Trial 1 evaluated ease of tablet intake and used placebo ODTs in order to avoid administering APIs to healthy subjects. The shape and tablet characteristics of each placebo were similar to a commercially available mitiglinide ODT and voglibose ODT (GLUFAST and BASEN) and an FDC-ODT containing mitiglinide and voglibose. Trial 2 evaluated palatability and clinical disintegration time using ODTs containing APIs. Subjects disintegrated each ODT, then spat it out to avoid API uptake.

The results of Trial 1 indicated that FDC-ODT significantly decreased the ease of intake VAS score and reduced amount of water required for ODT intake unlike IC-ODTs. The results of the four-point VRS evaluation showed that FDC-ODT

Fig. 3. Clinical Disintegration Time in Trial 2

Each point represents the value of one of the subjects. The horizontal line indicates the mean for the 13 subjects.

intake is easier than IC-ODTs. Taken together, these results suggest that switching from two IC-ODTs to one FDC-ODT can reduce the number of tablets needed to be taken and ease tablet swallowing. A previous study reported that switching from conventional tablets to ODTs reduced the amount of water required for tablet intake and enhanced ease of intake.¹⁷⁾ In addition, a number of studies have suggested that switching from conventional tablets to ODTs significantly improved adherence,^{7,8)} while other studies have suggested that switching from IC to FDC significantly improved adherence.^{25,26)} Bangalore *et al.* examined the influence of FDC on adherence by means of a meta-analysis including nine studies.⁶⁾ The study included 11925 patients receiving FDC treatment and 8317 patients receiving IC treatment; the results suggested that FDC led to a 26% decrease in the risk of non-compliance compared to that caused by IC. Similarly, oral antidiabetic studies showed that adherence was higher in patients administered FDC with type 2 diabetes mellitus than in patients administered ICs, and that switching from ICs to FDC enhanced patient adherence.^{9,10)} As described above, it has been reported that switching to ODT and FDC positively influences patient adherence. This study showed that FDC-ODT intake is easier and requires lesser water than IC-ODTs intake. It is likely that FDC-ODT with the advantages of both FDC and ODT could lead to further improvement of patient adherence. This improvement of adherence can be especially expected for the elderly patient, because polypharmacy is common in medication for elderly patients, resulting in low adherence.²⁷⁾ It would be interesting to examine whether FDC-ODT improves adherence in diabetic patients as well as elderly patients.

Table 3. Five-Point VRS Scores for Preferability

Phase	Number of subjects scored ($n = 13$)					Mean $\pm$ S.D.	p
	1	2	3	4	5		
	Very non-preferable	Non-preferable	Neither	Preferable	Very preferable		
IC-ODTs	1	4	6	2	0	2.7 ± 0.9	0.053
FDC-ODT	0	2	7	4	0	3.2 ± 0.7	

Data represents the number of subjects that scored 1, 2, 3, 4, or 5 in five-point VRS. The mean indicates the ease score for the 13 subjects. The subjects took both a GF-ODT and a BS-ODT simultaneously in the IC-ODTs phase and a GB-ODT in the FDC-ODT phase.

ODT taste and texture are factors that affect preferability, and preferability in turn affects patient adherence; thus, taste and texture should be considered in the development of ODTs. Trial 2 used ODTs containing APIs and evaluated taste in the IC-ODTs phase and FDC-ODT phase using VAS and five-point VRS. The VAS evaluations showed that there is no difference between the two phases except for the sweetness score after spitting out (Fig. 2). Five-point preferability VRS scores did not differ significantly between FDC-ODT and IC-ODTs; however, preferability for the FDC-ODT tended to be higher than that for the IC-ODTs. We focused on excipients of ODT and tablet weight because there was a possibility that they affected the preferability of ODT. The primary excipients of GF-ODT, BS-ODT, and GB-ODT are listed D-mannitol, corn starch, and crystalline cellulose in their package inserts.^{28,29)} Thus, texture of ingredients hardly affected the preferability of ODTs. On the other hand, preferability is considered dependent on the amount of powder in the oral cavity, because ODTs disintegrate in the oral cavity. In fact, the total amount of IC-ODTs was 350 mg, which is 1.75 times that of the FDC-ODT (200 mg). Therefore, the difference in preferability is attributed to the total amount of ODTs.

In addition, the sweetness VAS score after spitting of FDC-ODT was significantly higher than that of IC-ODTs. Although the reason for this remains unclear, the flavoring agents contained in each IC-ODT may have influenced sweetness. It has been reported that the addition of flavor improves the sweetness of famotidine ODT and amlodipine ODT.^{19,22)} Generally, taste masking is adjusted to a certain target drug during ODT development. When two different ODTs are taken simultaneously, the respective flavoring agents might not be appropriate for drugs other than the target drug, which may greatly worsen palatability. The appropriate flavors for APIs are chosen in the development of FDC-ODT; thus, the preferability of FDC-ODT will be higher than that of IC-ODTs.

Disintegration time is one of the factors affecting palatability. All ODTs used in this study were prepared using D-mannitol as a tablet base and crospovidone as a disintegrant. The *in vitro* disintegration time and hardness were significantly correlated ($r^2 = 0.731$, $p = 0.030$). This suggested that *in vitro* disintegration time and hardness were correlated in ODTs composed of similar ingredients. The Food and Drug Administration (FDA) Guidance for Industry: Orally Disintegrating Tablets recommends an *in vitro* disintegration time of 30 s or less.³⁰⁾ All ODTs evaluated in this study disintegrated within 30 s and met the criteria. On the other hand, measurement of *in vitro* disintegration time in the IC-ODTs phase, in which two ODTs were administered simultaneously, is impossible, although Yoshita *et al.* showed a significant positive correlation between *in vitro* disintegration time measured by using Tricorp tester and clinical disintegration time measured by a clinical trial.¹⁶⁾ Hence, we also measured the clinical disintegration time in this study. The results showed that the clinical disintegration time in the FDC-ODT phase was slightly shorter than that in the IC-ODTs phase. The clinical disintegration time in the IC-ODTs phase, in which a GF-ODT and a BS-ODT were administered simultaneously, was close to the *in vitro* disintegration time of BS-ODT, which was the longest among those of the two ODTs. Additionally, increasing the number of ODTs taken simultaneously increases the absolute amount of the tablet base, and thus affects the disintegra-

tion time of ODTs. Recently, multidrug therapy is used as a standard treatment in most areas of clinical practice, and it is assumed that patients receive some ODTs. Therefore, evaluation of preferability and disintegration time for simultaneous administration of ODTs is important. Preferability and disintegration time must be optimized in the development of FDC-ODTs.

Conclusion

This study demonstrated that the mitiglinide/voglibose FDC-ODT improved palatability and reduced the amount of water required for taking tablets to a greater extent than the two IC-ODTs (mitiglinide ODT and a voglibose ODT). Many patients with diabetes mellitus take two or more medicines daily; in these cases, switching from IC to FDC and from conventional tablets to ODTs will be helpful in terms of improving palatability and reducing the amount of water required. Mitiglinide/voglibose FDC-ODT can contribute to enhancing the adherence of patients with diabetes mellitus.

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