



Research article

Effect of food thickener and jelly wafer on the pharmacokinetics of levofloxacin orally disintegrating tablets



Takashi Tomita^{a,b,*}, Akiko Yamaguchi^c, Naoe Nishimura^c, Hidekazu Goto^b, Kenji Sumiya^d, Ryo Arakawa^e, Tadashi Yoshida^f, Hidehisa Tachiki^c, Yukinao Kohda^{b,g}, Kenzo Kudo^a

^a Department of Clinical Pharmaceutics and Pharmacy Practice, School of Pharmacy, Iwate Medical University, 2-1-1, Nishitokuta, Yahabacho, Shiawgun, Iwate, 028-3694, Japan

^b Department of Pharmacy, Hospital Bando, 411 Kutsukake, Bando, Ibaraki, 306-0515, Japan

^c TOWA Pharmaceutical Co., Ltd., Kyoto Analytical Science Center, Kyoto Research Park KISTIC #202, 134, Chudoji Minami-machi, Shimogyo-ku, Kyoto, Kyoto, 600-8813, Japan

^d Faculty of Pharmacy, Iwaki Meisei University, 5-5-1 Chuodai Iino, Iwaki, Fukushima, 970-8551, Japan

^e The Nisshin OilliO Group, Ltd., Central Research Laboratory, 1 Shinnori-cho, Isogo-ku, Yokohama 235-8558, Japan

^f Department of Internal Medicine, Hospital Bando, 411 Kutsukake, Bando, Ibaraki, 306-0515 Japan

^g Faculty of Health Sciences, Tsukuba International University, 6-20-1 Manabe, Tsuchiura, Ibaraki, 300-0051, Japan

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ABSTRACT

This study was designed to determine the effects of a food thickener and deglutition aid jelly for oral administration, jelly wafer, on the pharmacokinetics of levofloxacin orally disintegrating tablets. With an increase in immersion time, the disintegration time of levofloxacin orally disintegrating tablets immersed in food thickener was prolonged, whereas that of the tablets immersed in jelly wafer was shortened. The dissolution behavior of non-immersed levofloxacin orally disintegrating tablets was not similar to that of tablets immersed in food thickener, but was similar to that of tablets immersed in jelly wafer. The time to reach the maximum systemic levofloxacin concentration was the same for non-immersed orally disintegrating tablets and tablets immersed in food thickener and jelly wafer. Moreover, there was no significant difference in the maximum concentration after administration between non-immersed orally disintegrating tablets and tablets immersed in food thickener or jelly wafer. These findings suggest that drugs with a high bioavailability, such as levofloxacin, enter the systemic circulation even when administered with a food thickener or jelly wafer.

1. Introduction

Food thickeners (FTs) are food products that aid in swallowing and used by elderly patients and those with impaired eating and swallowing abilities. FTs are used for patients with dysphagia to reduce the speed of passage of food through the pharynx, and thereby, prevent accidental aspiration [1, 2]. Symptoms associated with dysphagia vary depending on the patient, and therefore, it is considered ideal to adjust the physical properties of FTs per individual needs [3]. FTs are classified based on the type of thickening component they contain, including starch, guar gum, and xanthan gum (XG; first, second, and third generations, respectively). Currently, XG FTs are the standard FT, preferred for their minimal flavor and odor and the ability to adjust viscosity within a short period. Their usefulness is not limited to just food as they are also used for administering oral medications such as tablets [4, 5]. However, undisintegrated

tablets have been observed in the stool of patients who were orally administered magnesium oxide tablets immersed in FTs [6]. Furthermore, FTs have been shown to affect the disintegration and dissolution of magnesium oxide tablets [7, 8], thereby reducing their laxative effects. In addition, the hyperglycemia-alleviating effect of voglibose orally disintegrating (OD) tablets, which rapidly disintegrate and dissolve, was reduced by FTs [9]. Therefore, in this study, we examined the effects of an XG-based FT and deglutition aid jelly for oral administration (jelly wafer, JW), which are commonly used in medical and nursing facilities, on the pharmacokinetics of levofloxacin (LVFX) orally disintegrating (LVFX-ODs) tablets. Agar is the main ingredient in JW, and xanthan gum is added as a gelling component to prepare a gelatin-like product. LVFX hemihydrate is a pale yellow to yellow-white crystalline compound or crystal powder that is highly, slightly, and not soluble in acetic acid (100%), water and methanol, and ethanol (99.5%), respectively. The

* Corresponding author.

E-mail address: tatomita@iwate-med.ac.jp (T. Tomita).

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characteristics of LVFX-OD tablets are as follows: diameter, 16.0 mm; thickness, 6.9 mm; weight, 1400 mg; hardness, 143 N (14.6 kg); additives, crystalline cellulose, sodium croscarmellose, D-mannitol, and crystalline cellulose; binder, hydroxypropyl cellulose; and lubricant, magnesium stearate. LVFX is a quinolone antibacterial agent with a concentration-dependent antibacterial action, and therefore, any decrease in its maximum plasma levels achieved could affect its ability to alleviate infection. Furthermore, during recent years, the increased frequency of use and dose of LVFX has led to serious issues such as the emergence of LVFX-resistant bacterial strains. Research based on pharmacokinetic–pharmacodynamic theories indicate that increasing the dose of LVFX, a concentration-dependent antimicrobial agent, would increase the maximum concentration in blood, and thereby, enhance the bactericidal action and suppress the emergence of resistant bacteria [10]. Therefore, in Japan, high-dose preparations of LVFX (500 and 250 mg) were approved in 2009, and the treatment regime was changed from conventional oral administration of 100 mg three times a day (TID) to a once daily oral dose of 500 mg.

LVFX tablets in the market include film-coated tablets (to mask the unpleasant flavor of the active ingredient) and orally disintegrating tablets, and research has shown that the disintegration time of orally disintegrating tablets can be extended by immersion in FT [9]. Accordingly, in the present study, we focused on orally disintegrating tablets. In 2014, a report on the status of FT use issued by the Japan Health and Nutrition Food Association, a research organization that focuses on the application of certain food additives, found that 97% of the 922 facilities using FTs investigated were medical or nursing care facilities. For this study, we determined that orally disintegrating tablets, which are highly likely to be taken by patients using FT or JW, are appropriate, considering that such tablets are commonly administered to patients with dysphagia and elderly individuals.

Current research suggests that the disintegration and solubility of drugs in the tablet form are reduced when the therapeutic effect is related to the pharmaceutical maximum blood concentration (C_{max}), as is the case with LVFX. Disintegration and solubility are particularly affected when orally disintegrating tablets are taken with FTs, which can diminish drug efficacy. Moreover, decreased C_{max} of LVFX-OD tablets taken with FT could lead to antibiotic-resistant bacterial infection. However, it is currently unknown whether LVFX C_{max} is affected when the LVFX-OD tablets are administered with FT or JW. Therefore, this is an important clinical question that should be clarified.

In the present study, we examined the effect of FT and JW on the disintegration and solubility of LVFX-OD tablet using the disintegration and dissolution tests outlined in the Japanese Pharmacopoeia (JP). Using a cross-over design, in which a single oral dose of LVFX-OD tablet immersed in FT or JW was administered to healthy adults, we compared the changes in LVFX C_{max} in both the disintegration and dissolution tests to examine the effect of difference in disintegration and solubility on the C_{max} .

2. Materials and methods

2.1. Materials

The model agent, 500 mg LVFX-OD tablet (TOWA) was obtained from Towa Pharmaceutical Co., Ltd. (Osaka, Japan; serial number: B015). An XG product called Tsururinko Quickly was obtained from Clinico Co., Ltd. (Tokyo, Japan) as the FT. However, information on XG added to Tsururinko Quickly is not publicly available due to corporate confidentiality concerns (Clinico Co., Ltd.) A JW developed by Ryu Kakusan Co., Ltd. (Tokyo, Japan) was used.

2.2. Methods

2.2.1. Disintegration test

FT was prepared at concentrations of 1.5% and 3.0% (w/v) according

to the manufacturer's directions [11]. The JW was already in a jellied state. After immersing the LVFX-OD tablets in FT samples prepared at the above concentrations or JW for 1 and 10 min, the disintegration test was immediately performed according to the JP guidelines [12] using the disintegration tester NT-40H (Toyama Sangyo Co., Ltd., Osaka, Japan) under the following conditions: test liquid: purified water, temperature: 37 ± 2 °C, and auxiliary discs: not used. The disintegration time of non-immersed LVFX-OD tablets was used as the control.

During the disintegration test, 12 LVFX-OD tablets were immersed (six tablets each immersed for 1 and 10 min) in 1.5% or 3.0% (w/v) FT or JW solution. Six LVFX-OD tablets not immersed in any solution were used as the control.

2.2.2. Dissolution test

FT was prepared at a concentration of 1.5% (w/v) according to the manufacturer's directions [11]. The JW was already in a jellied state. After immersing LVFX-OD tablets in 1.5% FT for 10 min (LVFX-ODims/ft) or in JW for 10 min (LVFX-ODims/jw), the dissolution test was conducted according to the procedure outlined in the JP [13]. Non-immersed LVFX-OD tablets were used as the control. We performed the dissolution test using an eight-shaft dissolution tester (DT-810 tablet dissolution tester; JASCO Corp., Tokyo, Japan) with distilled water and the first (pH 1.2) and second (pH 6.8) fluids as the dissolution test solutions using the paddle method at 50 rpm with eight vessels. The first fluid (pH 1.2) was prepared by dissolving 2.0 g of sodium chloride in 7.0 mL of hydrochloric acid and water to a final volume of 1000 mL to obtain the final solution. The second fluid (pH 6.8) was prepared by dissolving 3.40 g of potassium dihydrogen phosphate and 3.55 g of anhydrous disodium hydrogen phosphate in water to a volume of 1000 mL. Then, 1000 mL of water (1000 mL) was added to obtain the final sample solution. Sampling times were 0, 5, 10, 15, 30, 45, 60, 90, and 120 min and the samples were filtered using a membrane filter (0.45 μ m pore size; Millex®; Merck KGaA Japan, Tokyo, Japan) to remove any insoluble excipients. Approximately 20 mL of LVFX sample was obtained from each dissolution tester vessel and filtered. Then, 2 mL of the filtrate was placed in a 100-mL volumetric flask and the volume was made up to 100 mL with dissolution medium. The absorbance of the sample and standard solutions was measured at 289 nm, using the dissolution medium as the control. The UV spectrum of LVFX was recorded using a double beam UV-Visible spectrophotometer (UV mini-1240; Shimadzu Corp., Kyoto, Japan) in the range of 200–400 nm. The wavelength of maximum absorption was found to be 289 nm for solvent, which complied with the Pharmacopoeia standard.

To evaluate the dissolution behavior of the test samples (LVFX-ODims/ft and LVFX-ODims/jw) relative to that of the standard (LVFX-OD), we determined the f_2 function using the “Partial Revision to the Guidelines for Bioequivalence Testing for Generic Drugs” (February 29, 2012, Notification No. 0229-10 of PFSB) recommended by the Ministry of Health, Labour and Welfare. The dissolution test result of the standard prepared using purified water was used as the control; the test result was considered compliant when the mean dissolution rate of the standard preparation at 15–30 min after the start of the test was 85% or more. Accordingly, a test sample with a mean dissolution rate within $\pm 15\%$ of the standard preparation at two time points (when the mean dissolution rate of the standard preparation was 60% and 85%) was considered to have a similar dissolution behavior to that of the standard preparation. Alternatively, if the value of the f_2 function was ≥ 42 , the standard and test preparations were considered similar. The dissolution behavior was interpreted by comparing the results of the dissolution test using the first and second fluids with those of the standard preparation. Accordingly, when the mean dissolution rate of the standard preparation within 15 min of the start of the test was $\geq 85\%$ and that of the test preparation within 15 min of the start of the test was $\pm 15\%$ of the mean dissolution rate of the standard preparation, the dissolution behavior of the standard and test preparations was considered to be similar.

In addition, dissolution test was performed by placing six tablets

soaked in either 1.5% (w/v) FT or JW, or six non-immersed LVFX-OD tablets in distilled water, dissolution test liquid 1, and dissolution test liquid 2.

2.2.3. Oral administration test

The subjects for this study were four healthy Japanese adult men with a mean age of 42 (range, 29–57) years. They had no history of drug allergies and no signs or symptoms of infectious disease, and were not using oral antibacterial agents or antibiotics and deemed suitable based on clinical tests. Prior to the oral administration test, the subjects were explained the purpose and procedure of the test in detail, and then written consent was obtained. In accordance with the Declaration of Helsinki, all subjects received verbal and written explanations concerning the protection of their rights, the fact that their participation was voluntary and that they could withdraw at any time, the specifics of the research, and the potential health effects. Only subjects who signed the informed consent form underwent the oral administration test. The test protocol was approved by the Ethics Committee of Seifukai Hospital BANDO (approval number H28-4-27).

Non-immersed LVFX-OD tablets were used as the control product, while LVFX-ODims/ft and LVFX-ODims/jw (the condition under which the disintegration time was most prolonged, Table 1) were the investigational products. The subjects were administered the investigational and control products using a 2×2 crossover method. All subjects were administered test regimens after a drug-free period of at least 7 days (rationale: elimination half-life after administration of a single 500 mg LVFX-OD dose to healthy adult subjects was 6.866 ± 0.768 h). The test required the subjects to fast for at least 10 h before oral administration of LVFX-OD, LVFX-ODims/jw, and LVFX-ODims/ft with 150 mL of water after pre-administration blood sampling. The intake of alcoholic beverages, grapefruit juice, and caffeine-containing beverages was prohibited for 2 days prior to the start of the test. In addition, as the concomitant use of LVFX with aluminum- and magnesium-containing antacids or iron preparations affects LVFX absorption, tap water with low electrolyte content was used. The subjects remained in the standing or sitting position from the start to the end of the test.

Blood was sampled to measure the plasma level of LVFX immediately before and after oral administration, and at 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, and 180 min. Specifically, 13 blood samples were collected from each healthy adult participant in accordance with the administration test protocol. A dedicated physician inserted a venous catheter and a dedicated nurse collected blood samples under the instruction of the physician. The blood samples were collected in sodium heparin-containing vacuum collection tubes and immediately placed in an ice bath. Plasma obtained by centrifuging ($1200 \times g$, 10 min) the blood was aliquoted into polypropylene storage containers and frozen at -20°C (protected from light).

2.2.4. Measurement of plasma LVFX concentration

After mixing 300 μL of acetonitrile solution containing 10.0 $\mu\text{g/mL}$ norfloxacin as the internal standard with 300 μL of plasma, the solution was centrifuged at $10600 \times g$ for 10 min at 4°C and the supernatant was separated. Then, 300 μL of water was added to 150 μL of the supernatant, and the mixture was filtered using Whatman Mini-UniPrep (0.45 μm ; J.G Finneran Associates, Inc., USA). Subsequently, 25 μL of this filtrate was

subjected to high-performance liquid chromatography (HPLC) to measure the concentration of LVFX. The conditions for HPLC analysis were as follows: column, Cadenza CD-C18 column (4.6 mm $\times$ 150 mm, 3 μm ; Imtakt Corp., Kyoto, Japan); mobile phase, 10 mM phosphate buffer solution containing 2% trimethylamine (pH 7.0)/acetonitrile = 85:15 (v/v); and flow rate, 1.0 mL/min. The measurements were taken at excitation and emission wavelengths of 292 and 494 nm, respectively, using Shimadzu, RF-10AXL fluorescence detector (Shimadzu Corp.). The retention times based on these conditions were 3.5 and 10 min for norfloxacin and LVFX. In addition, the C_{max} was defined as the maximum plasma LVFX concentration at 180 min after oral administration and T_{max} was defined as the time required to reach the C_{max} .

2.2.5. Measurement of tablet hardness

After immersing LVFX-OD in 15 mL of FT or WT for 1, 5, or 10 min, we measured the hardness of LVFX-ODims/ft or LVFX-ODims/jw ($n = 5$) recovered from FT or WT with a spatula. As the control, the hardness of non-immersed LVFX-OD ($n = 5$) was measured. The Kiya hardness tester was used to measure the hardness of LVFX-ODims/ft, LVFX-ODims/jw, and LVFX-OD.

2.2.6. Statistical analysis

The disintegration time and C_{max} between the groups were compared using the Dunnett T3 test using IBM statistical package for the social sciences (SPSS) statistics 25 (IBM Japan, Tokyo) software. The results with a p value of <0.05 were regarded as significantly different.

3. Results

3.1. Disintegration test

The median disintegration time of LVFX-OD (control) was 27.0 s. The median disintegration time of LVFX-OD immersed in 1.5% (w/v) FT for 1 and 10 min was 61.0 and 435.5 s, respectively ($p < 0.001$ vs. control). The median disintegration time of LVFX-OD immersed in 3.0% (w/v) FT for 1 and 10 min was 65.0 and 312.0 s ($p < 0.001$ vs. control). The median disintegration time of LVFX-OD immersed in JW for 1 and 10 min was 35.0 and 9.0 s, respectively ($p < 0.001$ vs. control, Table 1).

3.2. Dissolution test

The results of the dissolution test are shown in Fig. 1. When purified water was used as the test solution, the mean dissolution rate of LVFX-OD at 30 min after the start of the test was $98.6\% \pm 0.6\%$. The mean dissolution rate of LVFX-ODims/jw at 10 ($46.4\% \pm 2.3\%$) and 15 ($72.2\% \pm 3.5\%$) min after the start of the dissolution test, were within $\pm 15\%$ of the mean dissolution rate of LVFX-OD (10 and 15 min: $60.2\% \pm 4.8\%$ and $81.0\% \pm 3.1\%$, respectively). However, the mean dissolution rate of LVFX-ODims/ft at 10 and 15 min ($3.3\% \pm 1.5\%$ and $11.6\% \pm 4.7\%$, respectively) was out of this range. Furthermore, the f_2 values of LVFX-OD and LVFX-ODims/ft calculated using the mean dissolution rate at three time points, viz., 15, 30, and 45 min after the start of the dissolution test, was 11.2, while that of LVFX-OD and LVFX-ODims/jw was 58.9.

When the first fluid (pH 1.2) was used for the JP dissolution test, the mean dissolution rate of LVFX-OD at 5 min after the start of the test was

Table 1
Effects of food thickener and jelly-wafer immersing on disintegration of levofloxacin orally-disintegrating tablet.

	Disintegration time (s)							
	non immersing		1 min immersing			10 min immersing		
	Median a	Range	Median b	Range	(b / a)	Median c	Range	(c / a)
Food thickener								
1.5 (w/v%)	27.0	27.0–27.0	61.0	54.0–65.0	(2.3)	435.5	412.0–536.0	(16.1)
3.0 (w/v%)	27.0	27.0–27.0	65.0	52.0–65.0	(2.4)	312.0	195.0–608.0	(11.6)
Jelly-wafer	27.0	27.0–27.0	35.0	35.0–39.0	(1.3)	9.0	9.0–9.0	(0.3)

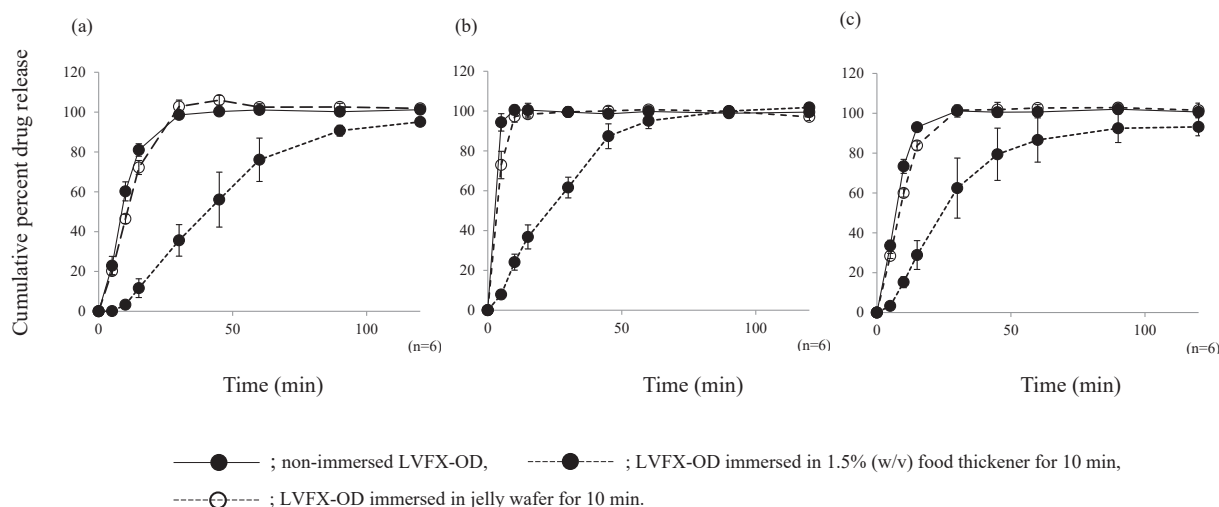


Fig. 1. In vitro dissolution profile of levofloxacin orally disintegrating tablet (LVFX-OD) in (a) distilled water, (b) Japanese Pharmacopoeia (JP) first fluid for dissolution test (pH 1.2), and (c) JP second fluid for the dissolution test (pH 6.8). The symbols in the figure (closed circle, opened circle) and the dotted line represent the mean, while the vertical solid lines represent the standard deviation.

94.4% $\pm$ 4.3%. Interestingly, the mean dissolution rate of LVFX-ODims/jw at 15 min after the start of the dissolution test (98.4% $\pm$ 1.9%) was within the $\pm$ 15% range of the mean dissolution rate of LVFX-OD (100.5% $\pm$ 3.4%), whereas that of LVFX-ODims/ft (36.8% $\pm$ 6.0%) was outside this range.

When the second fluid (pH 6.8) was used for the JP dissolution test, the mean dissolution rate of LVFX-OD at 15 min after the start of the test was 93.0% $\pm$ 1.4%. Although the mean dissolution rate of LVFX-ODims/jw at 15 min after the start of the dissolution test (83.8% $\pm$ 2.3%) was within the $\pm$ 15% range of the mean dissolution rate of LVFX-OD (93.0% $\pm$ 1.4%), whereas that of LVFX-ODims/ft (28.9% $\pm$ 7.2%) was outside this range.

Based on the JP dissolution test results using purified water, and the first (pH 1.2) and second (pH 6.8) fluids, similarities were observed in the dissolution behavior of LVFX-OD and LVFX-ODims/jw, but not LVFX-OD and LVFX-ODims/ft.

3.3. Oral administration test

Fig. 2 shows the changes in the plasma LVFX concentration after

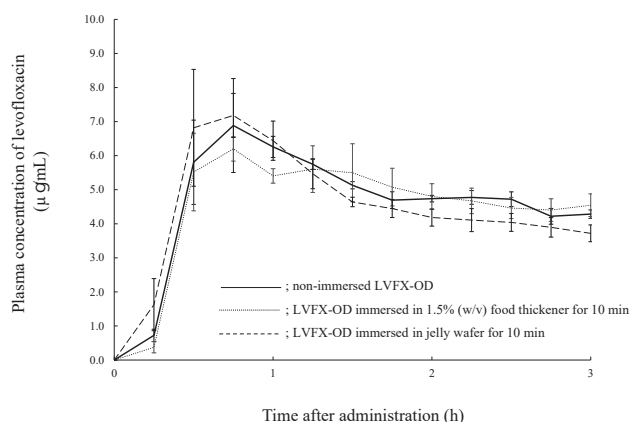


Fig. 2. Effect of levofloxacin orally disintegrating tablet (LVFX-OD) immersed in 1.5% (w/v) food thickener (FT) and jelly-wafer (JW) on the time course of plasma LVFX concentration. The line graph in the figure shows the mean, while the vertical solid lines show the standard deviation.

LVFX-OD, LVFX-ODims/ft, and LVFX-ODims/jw administration. The T_{max} after LVFX-OD, LVFX-ODims/ft, and LVFX-ODims/jw administration was 0.75 h, and there were no significant differences among the three samples. The C_{max} after LVFX-OD administration was 6.884 μ g/mL, whereas that after LVFX-ODims/ft and LVFX-ODims/jw administration was 6.199 and 7.180 μ g/mL, respectively, which indicated that the C_{max} after LVFX-OD administration was 1.1 times higher than that after LVFX-ODims/ft. The C_{max} after LVFX-OD administration was 0.9 times lower than that after LVFX-ODims/jw administration. There were no significant differences in the C_{max} among the three samples ($p = 0.945$, LVFX-OD vs. LVFX-ODims/ft; $p = 0.996$, LVFX-OD vs. LVFX-ODims/jw; and $p = 0.521$, LVFX-ODims/ft vs. LVFX-ODims/jw). Moreover, there was no significant difference in the plasma LVFX concentration between values at 15 and 180 min among the three samples.

The highest difference in the plasma LVFX concentration among the three tested samples was observed at 0.25 h after administration. The plasma LVFX concentration after LVFX-ODims/ft administration at this time point was lower than that after LVFX-OD administration by 0.52 times (0.374 vs. 0.725 μ g/mL, $p = 0.452$). The plasma LVFX concentration after LVFX-ODims/jw administration was higher than that after LVFX-OD administration by 2.24 times (1.626 vs. 0.725 μ g/mL, $p = 0.630$).

In addition, the plasma LVFX concentration after LVFX-ODims administration between 1.5 ($p = 0.959$, LVFX-OD vs. LVFX-ODims/ft; $p = 0.089$, LVFX-OD vs. LVFX-ODims/jw) and 2.0 h ($p = 0.997$, LVFX-OD vs. LVFX-ODims/ft and $p = 0.254$, LVFX-OD vs. LVFX-ODims/jw) was higher than that after LVFX-OD administration. The plasma LVFX concentration after LVFX-ODims administration considerably decreased between 0.75 and 1.0 h, and then remained constant. Moreover, the plasma LVFX concentration after LVFX-OD administration considerably decreased between 0.75 and 1.75 h. During the test period, no hypersensitivity, nausea, or other adverse subjective symptom was observed in the subjects.

3.4. Measurement of tablet hardness

The mean hardness of LVFX-OD tablets was 145 N. The mean hardness of LVFX-OD tablets immediately after immersion in FT, and at 1 and 5 min after immersion were 146, 125, and 86 N, respectively. After 10 min of immersion, tablet hardness was not measurable, indicating that the hardness decreased with increase in immersion time. Similarly, the mean hardness of LVFX-OD tablets immediately after immersion in JW and at 1 min after immersion was 138 and 108 N, respectively; but the

hardness was not measurable at 5 and 10 min after immersion.

4. Discussion

Tomita et al. recently reported that nursing home residents with dysphagia were taking tablets (including orally disintegrating tablets) using approximately 15 mL of FT or JW to prevent aspiration [14]. They also found that the caregivers in several nursing facilities provided assistance to the residents by recovering tablets immersed in FT or JW for around 10 min with a spoon [14]. In this study, we immersed LVFX-OD tablets in 15 mL of FT or JW for 10 min, collected them with a spatula, and orally administered them to healthy adults. The LVFX-OD tablet soaking and administration methods used in this study were the same methods as those employed in several nursing facilities; thus, we believe that the methods replicate the current settings of nursing facilities.

Photographs of LVFX-OD tablets immersed in FT or JW and LVFX-OD tablets alone used in the disintegration test are shown in Fig. 3. The shape of the tablet did not disintegrate when immersed in FT or JW or when LVFX-OD tablets were recovered after soaking in FT or JW.

Tomita et al. reported the results of a questionnaire sent to nursing facilities. They found that 207 residents took tablets immersed in FT or JW; of those, 71 residents were taking 28 different types of orally disintegrating tablets after immersing in FT or JW [14]. The most common orally disintegrating tablets taken by these 71 residents were lansoprazole (n = 19), followed by amlodipine (n = 13) and famotidine (n = 11).

LVFX is a quinolone antibacterial agent introduced in Japan in 1993 and is presently available in over 100 countries and regions worldwide [10]. It is sold in the form of a film-coated tablet that may be taken with water and an OD tablet that may be taken without water.

OD tablets are “tablets that can rapidly dissolve or disintegrate in the oral cavity, and have proper disintegratability,” according to the general rules for preparation in the JP 17th Edition (JP17). However, there are no specific rules for the analysis of OD tablets in the JP17 disintegration test where uncoated tablets, which are rapid release formulations, should disintegrate within 30 s. The median value of the LVFX-OD disintegration time in this study was 27 s, which is rapid and characteristic of OD tablets. In contrast, the disintegration time of LVFX-OD immersed in FT was prolonged by 2.3–16.1 times compared with that of LVFX-OD and tended to prolong with increasing immersion time. The exact mechanism by which the immersed LVFX-OD disintegration time was prolonged remains unknown, but we believe that the high viscosity of FT, which coated the outside of the tablets and slowed the rate of water infiltration into the tablets, may be responsible [7]. The extended disintegration time of LVFX-OD immersed in FT is thought to be due to the less viscous dextrin added to FT. The mechanism underlying the extension of disintegration time by FTs, including FT XG, might involve the following: the less viscous dextrin additively coats the surface of LVFX-OD tablets, thereby reducing the penetration rate of water into the tablet. Agar, the main component of JW, has syneresis properties, and therefore, water may take less time to penetrate LVFX-OD tablets immersed in JW compared with that immersed in FT, which may explain their superior disintegration.

The FT used in this study was XG, a third generation FT used in several facilities (main ingredients: dextrin, XG, calcium lactate, and trisodium citrate) [16]. The mean FT viscosity measured using a type B rotational viscometer (rotation speed, 12 rpm; rotor, No. 3; and measurement time, 60 s; n = 2) was 1275 Pa·s (first measurement, 1270 Pa·s; second measurement, 1280 mPa·s). For hardness measurement, a

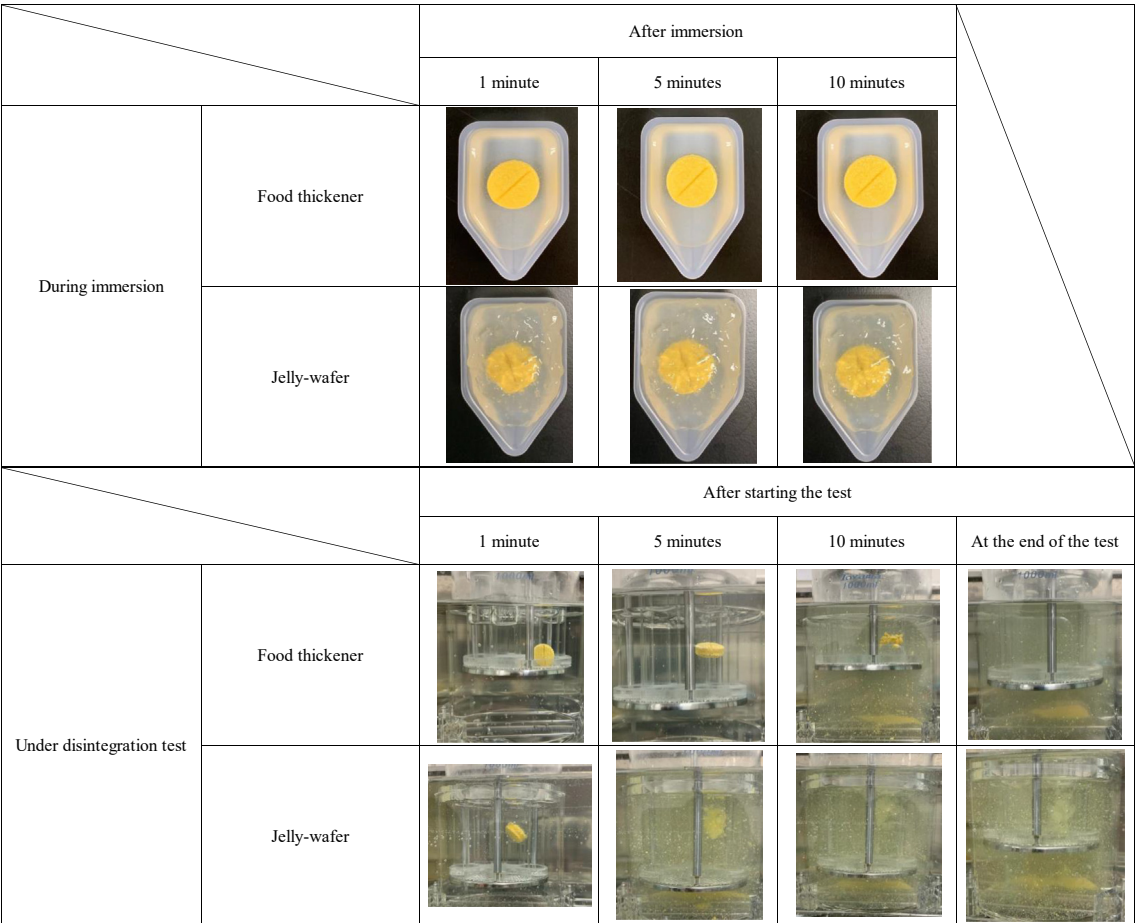


Fig. 3. Disintegration status of levofloxacin orally disintegrating tablets.

stainless steel Petri dish (diameter, 40 mm; depth, 15 mm) was filled with JW. The hardness (N/m^2) of JW was measured using a texture analyzer (TA-XT2i; jig: diameter, 20 mm; height, 8 mm; resin, cylindrical; mounting velocity, 10 mm/s; clearance, 5 mm; $n = 3$). The mean hardness of JW was 466 N/m^2 (first measurement, 462 N/m^2 ; second measurement, 468 N/m^2 ; and third measurement, 468 N/m^2). Hardness and viscosity measured using a type B rotational viscometer have a positive correlation [15]; therefore, we converted the viscosity of JW measured using the type B rotational viscometer to hardness using the following conversion formula:

$$\text{Hardness (N/m}^2\text{)} = 0.0436 \times \text{type B viscosity (mPas)} + 130$$

The hardness of JW obtained after conversion was $7706 \text{ mPa} \cdot \text{s}$ ($R^2 = 0.971$).

The disintegration test results showed that the disintegration time of LVFX-OD immersed in JW, which is highly viscous, was shorter than that of LVFX-OD immersed in the less-viscous FT. This may be due to the influence of thickener added to JW and FT. Agar is the thickener in JW, while XG is the thickener in FT. Agar has higher moisture content than that of XG, and tends to remove more water. Due to these properties of agar, water easily entered LVFX-OD tablets immersed in JW compared with that of LVFX-OD tablets immersed in FT. Consequently, the disintegration time of LVFX-OD tablets immersed in highly viscous JW was shorter than that of LVFX-OD tablets immersed in less viscous FT. Furthermore, line spread test (LST) values determined according to the Japanese Society of Dysphagia Rehabilitation's 2013 Classification of Dysphagia Modified Food [16] were 38.0 ± 1.45 and $31.7 \pm 1.62 \text{ mm}$ with 1.5% and 3.0% FT, respectively [9].

The disintegration time of LVFX-OD immersed in JW for 1 min was 1.3 times longer than that of non-immersed LVFX-OD, but that of LVFX-OD immersed for 10 min was 0.3 times shorter than that of non-immersed LVFX-OD. The difference in disintegratability between LVFX-OD immersed in FT and JW may be attributable to the effect of the thickening agents. While FT and JW contain dextrin and agar, respectively, they also contain the thickening agent XG [11]. Because dextrin contained in FT is a weak viscous additive, when LVFX-OD is immersed in FT, the additive effect of XG and dextrin allows FT to cover the tablet better than JW [16]. Therefore, the penetration of water into LVFX-OD tablets immersed in FT could slow down compared with that into LVFX-OD tablets immersed in JW, prolonging the disintegration time [7]. Furthermore, agar has the characteristic of easily separating water, and therefore, tablets covered by agar-containing JW could allow water to penetrate easily compared to tablets covered with FT [17]. Therefore, the penetration rate of water into the tablet is presumed to be greater for LVFX-OD immersed in agar-containing JW than for LVFX-OD immersed in FT. This phenomenon made LVFX-OD immersed in JW to disintegrate in a shorter time than LVFX-OD immersed in FT.

Although we identified similarities in the dissolution behavior of LVFX-OD and LVFX-ODims/jw, there were no similarities between LVFX-OD and LVFX-ODims/ft. The difference in disintegratability of LVFX-ODims/jw and LVFX-ODims/ft can be attributed to this phenomenon. As the disintegration time of LVFX-ODims/jw was shorter than that of LVFX-OD, the dissolution rate of LVFX could be promoted. However, based on the identified similarities in the dissolution behavior of LVFX-OD and LVFX-ODims/jw, we do not consider that the disintegration degree of LVFX-ODims/jw is sufficient to affect its dissolution behavior. Furthermore, because the disintegration time of LVFX-ODims/ft was longer than that of LVFX-OD and there was no observable similarity in the dissolution behavior of LVFX-OD and LVFX-ODims/ft, it is conceivable that the increase in disintegration time of LVFX-ODims/ft decreased the dissolution rate of LVFX.

LVFX and several other superior antibacterial agents have been developed, which have rapidly advanced the treatment of infectious disease [18]. However, improper or biased use has resulted in the appearance of quinolone-resistant *Escherichia coli* and other

drug-resistant bacteria, making bacterial resistance a problem. Resistance to antibacterial agents and their therapeutic effects is closely related to pharmacokinetics. Quinolone antibacterial agents exhibit concentration-dependent bactericidal action, indicating a correlation between inhibition of resistance and the ratio of C_{max} to the minimum inhibitory concentration (MIC, $C_{\text{max}}/\text{MIC}$) [10].

In our previous studies, we revealed that the disintegration time of voglibose OD tablets (a drug that exerts its pharmacological effect in the gastrointestinal tract without being absorbed) [9] and mitiglinide tablets (a rapid-acting drug that exerts its pharmacological effect in a short period) [17] immersed in FT was longer than that of the non-immersed tablets. When healthy adults were orally administered these tablets after immersion in FT, the blood glucose-lowering ability after glucose tolerance was considerably attenuated compared with that of non-immersed tablets [9, 17]. Moreover, the disintegration time of LVFX-ODims/ft was longer than that of LVFX-OD or LVFX-ODims/jw. In addition, although the dissolution rate of LVFX-ODims/ft was lower than that of LVFX-OD and LVFX-ODims/jw, the T_{max} of each tablet measured in a cross-over test where single oral doses of LVFX-OD, LVFX-ODims/ft, and LVFX-ODims/jw were administered to healthy adults was the same, whereas there was no significant difference in their C_{max} values. Therefore, when examining the effect of FT or JW using the blood concentration of a drug as an indicator, instead of the pharmacological effect, even if the drug acts after absorption in the body and is not a rapid-acting drug, it is suggested that the difference in blood concentration is not large enough to detect the effect of FT and JW.

In studies to date, immersion of magnesium oxide, voglibose OD, and mitiglinide tablets in FT attenuated their pharmacological effect [9, 17]. The diameter, thickness, and weight of those tablets ranged from 6.0 to 9.0 mm, 2.0–4.7 mm, and 75–375 mg, respectively, indicating that LVFX-OD tablet (diameter: 16.0 mm, thickness: 6.9 mm, weight: 1,400 mg) is larger than these tablets. Moreover, undissolved magnesium oxide tablets have been reported to be excreted via the stool of a patient administered the drug with FT [6]. Based on the above observations, it can be assumed that when magnesium oxide, voglibose OD, and mitiglinide tablets, which are smaller than LVFX-OD tablets, were orally administered after immersion in FT, the tablet may have remained for a long time in the gastrointestinal tract with the tablet surface covered in FT (undissolved tablet). This likely attenuated the pharmacological effect and led to the excretion of undissolved magnesium oxide tablet [6]. Therefore, the tablet size is an important criterion to determine whether FT affects the pharmacological effect when elderly patients or those with dysphagia take tablets with FT.

We measured the hardness of LVFX-OD, LVFX-ODims/ft, and LVFX-ODims/jw tablets ($n = 5$) using a Kiya hardness tester. In this study, LVFX-OD was immersed in FT or JW for 10 min, and then orally administered to healthy adults. Because the hardness of LVFX-OD tablets at 10 min after immersion in FT or JW was reduced (non-measurable), LVFX-OD tablets (either immersed in FT or JW) taken by healthy adults were possibly crushed by the tongue pressure during chewing and swallowing. Therefore, no significant difference in the LVFX blood concentration could be observed in healthy adults taking LVFX-ODims/ft or LVFX-ODims/jw.

A possible reason why the C_{max} and T_{max} were unaffected by the difference in disintegratability and solubility of LVFX-OD, LVFX-ODims/ft, and LVFX-ODims/jw is the bioavailability of LVFX and tablet size. The bioavailability of LVFX is approximately 99% [18]. Even if the disintegration time is prolonged and dissolution rate is decreased for LVFX-ODims/ft after being immersed in FT, because the LVFX-OD tablet is large, it is presumed that the FT on the tablet surface would fall off because of physical effects such as movement in the gastrointestinal tract. Furthermore, if LVFX-ODims/ft is disintegrated to a certain degree and LVFX is eluted in the upper part of the small intestine where LVFX is absorbed, it would result in a high bioavailability, and therefore, the maximum blood concentration would remain unaffected.

The administration of single oral doses of LVFX-OD, LVFX-ODims/ft,

and LVFX-ODims/jw to healthy adults showed no clear differences in the C_{max} (T_{max} at 45 min after administration), but the blood concentration (0.374 $\mu\text{g/mL}$) at 15 min after the oral administration of LVFX-ODims/ft was 0.52 times lower than that after the administration of LVFX-OD (0.725 $\mu\text{g/mL}$). Furthermore, the maximum blood concentration at 15 min after the oral administration of LVFX-ODims/jw (1.626 $\mu\text{g/mL}$) was 2.24 times higher than that following the administration of LVFX-OD (0.725 $\mu\text{g/mL}$). Moreover, the blood concentration at 15 min after administering LVFX-ODims/ft (0.374 $\mu\text{g/mL}$) was 0.23 times lower than that after administering LVFX-ODims/jw orally (1.626 $\mu\text{g/mL}$). These results revealed that an increase in the disintegration time and a decrease in the dissolution rate of LVFX-OD due to FT, and a decrease in the disintegration time and an increase in the dissolution rate of LVFX-OD due to JW affected the blood concentration of LVFX immediately after administration.

5. Conclusions

The results of the in vitro disintegration and dissolution tests to examine the pharmacokinetics of FT-, JW- and non-immersed LVFX-OD tablets revealed no differences in the C_{max} and T_{max} in vivo. The size of tablet and bioavailability of the drug were considered responsible for this observation. For large tablets, we presumed that drugs with a high bioavailability are not affected by gastrointestinal tract fluids and are rapidly absorbed into the systemic circulation. Therefore, they would be effective even when administered with FT or JW.

Declarations

Author contribution statement

Takashi Tomita, Hidekazu Goto, Kenji Sumiya: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Akiko Yamaguchi, Naoe Nishimura, Ryo Arakawa: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Tadashi Yoshida: Conceived and designed the experiments; Analyzed and interpreted the data.

Hidehisa Tachiki: Conceived and designed the experiments; Wrote the paper.

Yukinao Kohda, Kenzo Kudo: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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Availability of data and materials

All data generated or analyzed during this study are included in this article.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Seifukai Hospital BANDO (approval number H28-4-27). Informed consent was obtained from the volunteers.

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