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Original Article

Effect of xanthan gum as a thickener in widely-used food thickeners on the disintegration of rapidly-disintegrating tablets

Takashi Tomita, PhD,[1,2] Takahiro Fukui, UG,[1] Sayaka Takanohashi, UG,[1] Hidekazu Goto, BS,[2] Tadashi Yoshida, MD, PhD,[3] Kenji Sumiya, PhD,[4] Yukinao Kohda, PhD,[2,5] Kenzo Kudo, PhD[1]

[1]Department of Clinical Pharmaceutics and Pharmacy Practice, School of Pharmacy, Iwate Medical University, Shiwagun, Iwate, Japan
[2]Department of Pharmacy, Hospital Bando, Bando, Ibaraki, Japan
[3]Department of Internal Medicine, Hospital Bando, Bando, Ibaraki, Japan
[4]Faculty of Pharmacy, Iwaki Meisei University, Iwaki, Fukushima, Japan
[5]Faculty of Health Sciences, Tsukuba International University, Tsuchiura, Ibaraki, Japan

ABSTRACT

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Objective: We studied the impact of xanthan gum (XTG) as a thickener in widely-used food thickeners on the disintegration of rapidly-disintegrating tablets.

Methods: We used 0.2%, 0.4%, 0.6%, and 0.8% (w/v) aqueous solutions of XTG (XTG-Sol) for the study. The rapidly-disintegrating tablet used was magnesium oxide tablet (M-Tab). M-Tabs were immersed in XTG-Sol for 1, 5, and 10 min and then subjected to disintegration tests (purified water).

Results: The results obtained revealed that the longer the immersion time in 0.6% or 0.8% XTG-Sol, the longer the disintegration time of the M-Tabs. All the M-Tabs disintegrated in the 0.2% XTG-Sol. Additionally, when the immersion time was 5 or 10 min, the M-Tabs disintegrated in the 0.4% XTG-Sol.

Conclusion: The disintegration of the rapidly-disintegrating tablets was affected by XTG and was dependent on its concentration and the immersion time. Thus, care is needed when swallowing tablets with thickened food products containing XTG.

Key words: xanthan gum, food thickener, magnesium oxide, rapidly-disintegrating tablet, disintegration test

Correspondence: Takashi Tomita, PhD
Department of Clinical Pharmaceutics and Pharmacy Practice, School of Pharmacy, Iwate Medical University, 2–1–1, Nishitokuta, Yahabacho, Shiwagun, Iwate 028–3694, Japan.
E-mail: tatomita@iwate-med.ac.jp
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Introduction

In medical institutions and nursing homes, food thickeners (FTs), which are used to assist the swallowing of foods, are widely used to prevent aspiration when patients and occupants consume food and water [1–3]. The usefulness of FTs as a swallowing aid has been studied extensively in the field of dysphagia [4,5]. In contrast, FTs are also used to assist drug consumption in patients with dysphagia, but there have been few pharmacological studies on the influence of FTs on pharmacokinetics. Thus, special attention should be paid to the effects of thickened food products on their pharmacokinetics [6]. In recent years, undisintegrated tablets have been observed in the feces of patients administered rapidly-disintegrating tablets immersed in FTs that contained xanthan gum (XTG)-based thickening agents, suggesting that FTs affect the disintegration of tablets [7]. Furthermore, it has been reported that XTG-based FTs, which are widely used in medical facilities and nursing homes, affect the disintegration and dissolution of rapidly-disintegrating tablets and orally-disintegrating tablets [8–11].

Therefore, in this study, we investigated the effects of XTG as a thickener in widely-used FTs on the disintegration of rapidly-disintegrating tablets. We also report here our findings on the effects of thickened food products with the same concentration of XTG on the disintegration of rapidly-disintegrating tablets.

Methods

1. Disintegration test

(1) Materials

The rapidly-disintegrating magnesium oxide tablets used in this study were Magmitt®Tab. 330 mg (M-Tab)

made by Kyowa Chemical Industry Co., Ltd., Kagawa, Japan. Xanthan gum (XTG, MP Biomedicals, Inc-Wako Pure Chemical Industries, Ltd., Osaka, Japan), a food thickener, was used in the form of XTG solution (XTG-Sol). "Tsururinko Quickly" (TsuruQ, Clinico Co., Ltd., Tokyo, Japan) containing XTG was used as a thickened food product.

(2) Preparation of XTG solutions

The XTG-Sol was prepared at concentrations that were broadly equivalent to "extremely thick", "moderately thick", and "mildly thick" based on the Japanese Dysphagia Diet 2013 by the JSDR dysphagia diet committee (JDD2013). That is, four concentrations of XTG-Sol (%, w/v) were prepared: 0.2%, 0.4%, 0.6%, and 0.8%. XTG was completely dissolved in purified water warmed to approximately 50°C and returned to room temperature before use in the tests.

(3) Preparation of TsuruQ solution

TsuruQ (approximately 30% XTG content) was manipulated during preparation such that the concentration of XTG (%, w/v) was approximately equivalent to 0.2%, 0.4%, 0.6%, and 0.8%; that is, four concentrations of TsuruQ solution (TsuruQ-sol) (%, w/v) were prepared: 0.7%, 1.3%, 2.0%, and 2.7%. As in the case of XTG-Sol, TsuruQ was completely dissolved in purified water warmed to approximately 50°C and returned to room temperature before use in the tests.

(4) Disintegration test

The M-Tabs were immersed in XTG-Sol and Tsuru Q-sol at each concentration and were allowed to stand for 1 min, 5 min, and 10 min (each of the 18 M-Tabs was immersed for each duration). We then immediately removed the M-Tab and performed the disintegration tests in accordance with the method described in the Japanese Pharmacopoeia. Each M-Tab was subjected to the disintegration test (each of the 18 M-Tabs was subjected to the disintegration test for each immersion time). In the tests, we used a disintegration tester (NT-40H; Toyama Sangyo Co., Ltd., Osaka) and purified water (temperature, 37±2°C) as the test liquid, but did not use a disk. Using purified water as the test solution in the disintegration test as in the previous studies [8, 10,11], the reproducibility of the test was examined by comparing these results with those of the previous studies.

2. Line Spread Test (LST) of XTG-Sol and TsuruQ-sol

In accordance with JDD2013, we measured various concentrations of XTG-Sol and TsuruQ-sol by using a plastic measuring plate in an LST. Briefly, we injected XTG solution or XTG-Sol and TsuruQ-sol (20 mL) into a metal ring (30 mm diameter), lifted the ring after 30 s, and measured the distance (in mm) that the samples traveled after 60 s. The mean (n = 3) in six directions was defined as the LST value.

3. Swelling and disintegration of M-Tabs immersed in XTG-Sol and TsuruQ-sol

M-Tabs were immersed and allowed to stand in the prepared concentrations of XTG-Sol and TsuruQ-sol. The states of swelling and disintegration of M-Tab were observed after 1 min, 5 min, and 10 min.

The swelling status of the M-Tabs after immersion, compared to that of non-immersed M-Tabs, was defined as follows: (i) M-Tabs without notable changes in the side surfaces of the tablets after immersion were classified as "not swollen"; (ii) M-Tabs with slight swelling and without any fissures on the side surfaces of the tablets were classified as "slightly swollen"; (iii) M-Tabs with swelling and fissures that did not reach the center of the side surfaces of the tablets were classified as "moderately swollen"; and (iv) M-Tabs with swelling and fissures reaching the center of the side surfaces of the tablets were classified as "completely swollen" (Figure 1).

The disintegration status of M-tabs after immersion, compared to that of non-immersed M-Tabs, was defined as follows: (i) M-Tabs without notable changes in the surface of the tablets after immersion were classified as "not disintegrated"; (ii) M-Tabs with slight fissures on the surface of the tablets were classified as "slightly disintegrated"; (iii) M-Tabs with fissures over the entire surface of the tablets were classified as "moderately disintegrated"; and (iv) M-Tabs completely disintegrated with the original surface of the tablets unrecognizable were classified as "completely disintegrated" (Figure 1).

4. Statistical analysis

The Kruskal-Wallis test was used to compare the LST values and the disintegration time of the M-Tabs between XTG-Sol and TsuruQ-sol. The test was performed by using IBM SPSS Statistics 25 (IBM Japan, Tokyo, Japan). p-values < 0.05 indicated statistical significance.

Results

1. LST of XTG-Sol and TsuruQ-sol

The (mean of the) LST values of XTG-Sol and TsuruQ-sol were as follows: (i) the LST values were 44.7−32.1 (Table 1), respectively, when the XTG-Sol concentration was in the range of 0.2−0.8% (%, w/v); and (ii) the LST values were 46.7−33.7 (Table 2), respectively, when the TsuruQ-sol concentration was in the range of 0.7−2.7% (%, w/v).

The LST values of 0.4% XTG-Sol (LST: 37.6), 0.6% XTG-Sol (LST: 34.3), and 0.8% XTG-Sol (LST: 32.1) fell under the "mildly thick", "moderately thick", and "extremely thick" categories, respectively, according to JDD2013. Likewise, those for 1.3% TsuruQ-sol (LST: 40.2), 2.0% TsuruQ-sol (LST: 37.8), and 2.7% TsuruQ-sol (LST: 33.7) fell under the "mildly thick", "moderately thick", and "extremely

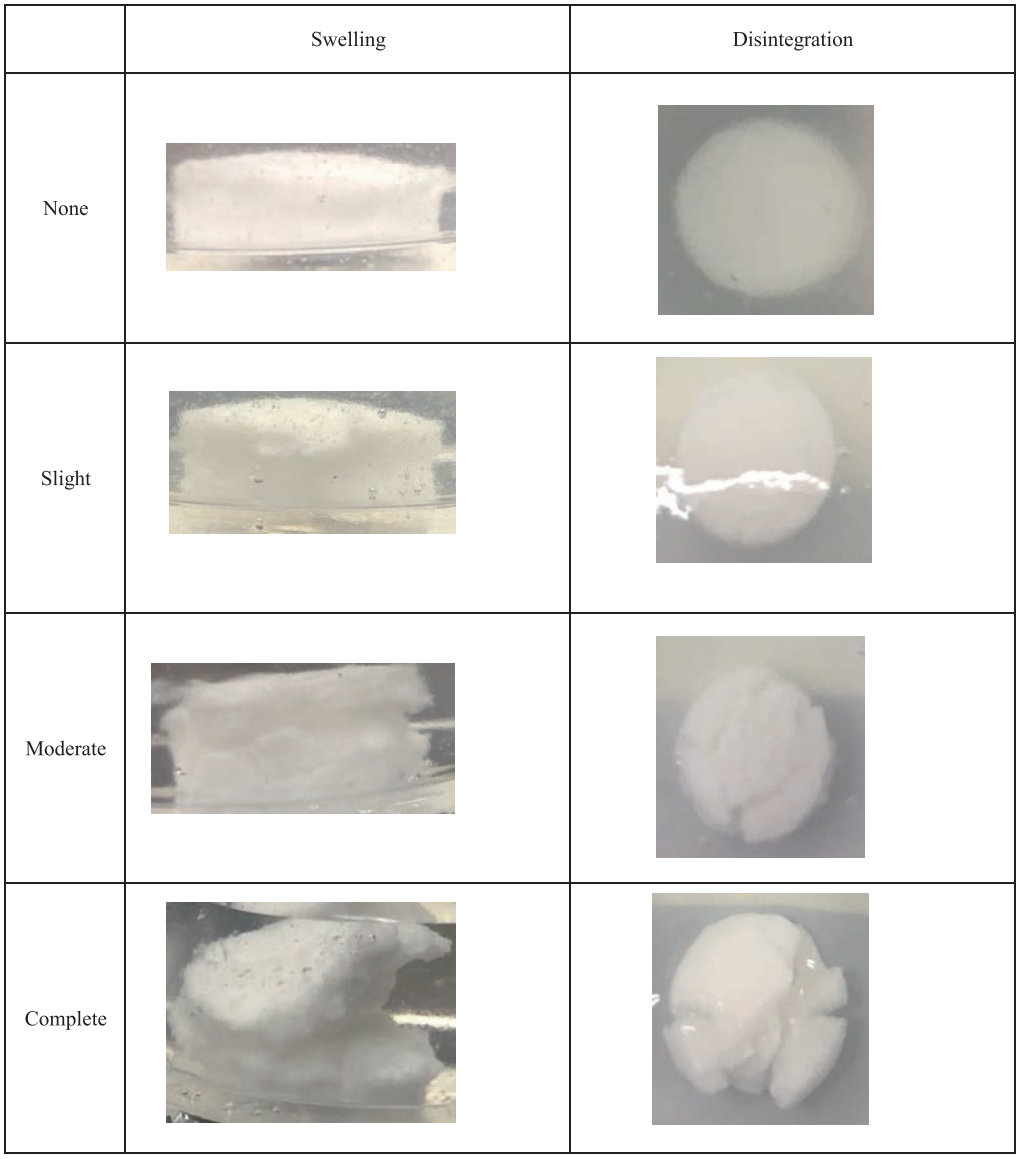

Figure 1. Swelling and disintegration status of rapidly-disintegrating magnesium oxide tablets.

thick" categories, respectively. On the other hand, those for 0.2% XTG-Sol (LST: 44.7) and 0.7% TsuruQ-sol (LST: 46.7) did not fall under the specified values (30−43).

The LST values of 0.4% XTG-Sol (LST: 37.6), 0.6% XTG-Sol (LST: 34.3), and 0.8% XTG-Sol (LST: 32.1) were significantly lower than that of 0.2% XTG-Sol (LST: 44.7) (Table 1). The LST values of 2.0% TsuruQ-sol (LST: 37.8) and 2.7% TsuruQ-sol (LST: 33.7) were significantly lower than that of 0.7% TsuruQ-sol (LST: 46.7) (Table 2). In addition, the LST values of 0.6% XTG-Sol (LST: 34.3) and 0.8% XTG-Sol (LST: 32.1) were significantly lower than that of 0.4% XTG-Sol (LST: 37.6) (Table 1). The LST value of 2.7% TsuruQ-sol (LST: 33.7) was significantly lower than that of 1.3% TsuruQ-sol (LST: 40.2) (Table 2).

2. Swelling and disintegration of M-Tabs immersed in XTG-Sol and TsuruQ-sol

The M-Tabs immersed in 0.8% XTG-Sol (LST: 32.1) neither swelled nor disintegrated, regardless of the duration of immersion (Table 1). The M-Tabs immersed in 2.7% TsuruQ-sol (LST: 33.7) swelled slightly with an increase in immersion time but did not disintegrate (Table 2). By contrast, the M-Tabs immersed in 0.2% XTG-Sol (LST: 44.7) and 0.7% TsuruQ-sol (LST: 46.7) completely swelled and disintegrated during immersion, regardless of the immersion time (Table 1, Table 2). Thus, the higher the LST values of XTG-Sol and TsuruQ-sol, the higher the tendency of the immersed M-Tabs to swell and disintegrate.

Table 1. Status of rapidly-disintegrating magnesium oxide tablets in xanthan gum solution.

Xanthan gum concentration (%, w/v)	LST (mm, mean ± S.D.) (times = 3)	Immersion time (min)	Swelling (n = each 18 tablets)	Disintegration (n = each 18 tablets)	Disintegration time (s) Median (n = each 18 tablets, times = 18)	Range
–	–	no immersion	–	–	7	7–7
0.2	44.7±3.3	1	Complete: 18 tabs	Complete: 18 tabs	–	–
		5	Complete: 18 tabs	Complete: 18 tabs	–	–
		10	Complete: 18 tabs	Complete: 18 tabs	–	–
0.4	37.6±2.8 [a]	1	None: 16 tabs Slight: 2 tabs	None: 18 tabs	159 [d]	80–265
		5	Moderate: 14 tabs Slight: 4 tabs	Slight: 13 tabs Moderate: 4 tabs	–	–
		10	Complete: 15 tabs Moderate: 3 tabs	Moderate: 15 tabs Complete: 3 tabs	–	–
0.6	34.3±2.1 [a, b]	1	None: 18 tabs	None: 18 tabs	143 [d]	96–257
		5	Slight: 12 tabs None: 6 tabs	None: 18 tabs	440 [d, e]	311–590
		10	Moderate: 13 tabs Slight: 5 tabs	None: 18 tabs	506 [d, e, f]	387–625
0.8	32.1±2.3 [a, c]	1	None: 18 tabs	None: 18 tabs	146 [d]	95–246
		5	None: 18 tabs	None: 18 tabs	517 [d, e]	286–766
		10	None: 18 tabs	None: 18 tabs	536 [d, e]	351–818

Kruskal-Wallis test: [a] $p < 0.001$ vs 0.2 (%, w/v), [b] $p = 0.011$ vs 0.4 (%, w/v), [c] $p < 0.001$ vs 0.4 (%, w/v), [d] $p < 0.001$ vs non immersion, [e] $p < 0.001$ vs 1 min immersion, [f] $p = 0.024$ vs 5 min immersion.

–: Not applicable

Table 2. Status of rapidly-disintegrating magnesium oxide tablets in thickened food products.

Food thickener concentration (30% xanthan gum content) (%, w/v)	Xanthan gum concentration (%, w/v)	LST (mm, mean ± S.D.) (times = 3)	Immersion time (min)	Swelling (n = each 18 tablets)	Disintegration (n = each 18 tablets)	Disintegration time (s) Median (n = each 18 tablets, times = 18)	Range
–	–	–	no immersion	–	–	7	7–7
0.7	0.2	46.7±7.4	1	Complete: 18 tabs	Complete: 18 tabs	–	–
			5	Complete: 18 tabs	Complete: 18 tabs	–	–
			10	Complete: 18 tabs	Complete: 18 tabs	–	–
1.3	0.4	40.2±2.1	1	Moderate: 12 tabs Slight: 6 tabs	None: 16 tabs Slight: 2 tabs	290 [d]	157–550
			5	Complete: 13 tabs Moderate: 5 tabs	Moderate: 18 tabs	–	–
			10	Complete: 15 tabs Moderate: 3 tabs	Moderate: 16 tabs Complete: 2 tabs	–	–
2.0	0.6	37.8±3.3 [a]	1	None: 16 tabs Slight: 2 tabs	None: 16 tabs Slight: 2 tabs	233 [d]	130–432
			5	Moderate: 13 tabs Slight: 5 tabs	None: 16 tabs Slight: 2 tabs	576 [d, e]	348–738
			10	Moderate: 18 tabs	None: 15 tabs Slight: 3 tabs	563 [d, e]	390–795
2.7	0.8	33.7±3.2 [b, c]	1	None: 18 tabs	None: 18 tabs	283 [d]	140–541
			5	Slight: 16 tabs None: 2 tabs	None: 17 tabs Slight: 1 tab	605 [d, e]	453–989
			10	Slight: 15 tabs None: 3 tabs	None: 17 tabs Slight: 1 tab	682 [d, e]	399–872

Kruskal-Wallis test: [a] $p = 0.03$ vs 0.7 (%, w/v), [b] $p < 0.001$ vs 0.7 (%, w/v), [c] $p < 0.001$ vs 1.3 (%, w/v), [d] $p < 0.001$ vs non immersion, [e] $p < 0.001$ vs 1 min immersion.

–: Not applicable

3. Disintegration test of M-Tabs immersed in XTG-Sol and TsuruQ-sol

The (median of the) disintegration time of the M-Tabs, which were immersed in 0.8% XTG-Sol (LST: 32.1), increased to 146, 517, and 536 s as the immersion time increased to 1, 5, and 10 min. The (median of the) disintegration time of the M-Tabs, which were immersed in 2.7% TsuruQ-sol (LST: 33.7), increased to 283, 605, and 682 s as the immersion time increased to 1, 5, and 10 min.

Likewise, the (median of the) disintegration time of the M-Tabs, which were immersed in 0.6% XTG-Sol (LST: 34.3), increased to 143, 440, and 506 s as the immersion time increased to 1, 5, and 10 min (Table 1). The (median of the) disintegration time of the M-Tabs, which were immersed in 2.0% TsuruQ-sol (LST: 37.8), increased to 233, 576, and 563 s as the immersion time increased to 1, 5, and 10 min (Table 2).

Thus, it was observed that, in the case of XTG-Sol and TsuruQ-sol with lower LST values, the longer the immersion time, the longer the disintegration time of the M-Tabs.

When the M-Tabs were immersed in 0.2% XTG-Sol (LST: 44.7) or 0.7% TsuruQ-sol (LST: 46.7), all the M-Tabs in the 0.2% XTG-Sol disintegrated regardless of the immersion time. Thus, the 0.2% XTG-Sol was not used in the disintegration test. Likewise, when the M-Tabs were immersed in 0.4% XTG-Sol (LST: 37.6) or 1.3% TsuruQ-sol (LST: 40.2) for 5 or 10 min, all the M-Tabs disintegrated regardless of the immersion time. Thus, the 0.4% XTG-Sol (LST: 37.6) and 1.3% TsuruQ-sol (LST: 40.2) were not used in the disintegration test (Tables 1 and 2).

Of the M-Tabs immersed in XTG-Sol or TsuruQ-sol, the disintegration time of those used in the disintegration test was significantly longer than that of the non-immersed M-Tabs. In addition, the disintegration time of the M-Tabs immersed in 0.6% XTG-Sol (LST: 34.3), 0.8% XTG-Sol (LST: 32.1), 2.0% TsuruQ-sol (LST: 37.8), or 2.7% TsuruQ-sol (LST: 33.7) for 5 or 10 min was significantly longer than that of those immersed in any of the solutions for 1 min. The disintegration time of the M-Tabs immersed in 0.6% XTG-Sol (LST: 34.3) for 10 min was significantly longer than that of those immersed for 5 min (Tables 1 and 2).

Discussion

FTs are classified as starch types (first generation), guar gum types (second generation), and XTG types (third generation), depending on the thickening agent they contain [4, 5]. The label information on the thickening agents describes them in terms of sauces or dressings with a similar viscosity (e.g., "mayonnaise-like", "French dressing-like", etc.). Because their viscosity after preparation varies depending on the type and amount of thickening agent contained in each product, viscosity comparisons between FTs are difficult. Currently, the Japanese Society of Dysphagia Rehabilitation proposes the use of an LST value correlated with viscosity [12] to standardize the degree of thickening, with the intention of evaluating and adjusting the viscosity between FTs. LST values in the range of 36−43 are classified as "mildly thick" (level 1), those in the range of 32−36 are classified as "moderately thick" (level 2), and those in the range of 30−32 are classified as "extremely thick" (level 3).

This study examined the disintegration properties of M-Tabs immersed in XTG-Sol with different concentrations using an objective measure (i.e., LST value). The results showed that none of the M-Tabs disintegrated in XTG-Sol with lower LST values. On the other hand, the M-Tabs showed disintegration in XTG-Sol with higher LST values. In XTG-Sol with higher viscosity (i.e., lower LST values), XTG forms a mild three-dimensional network structure. In contrast, in XTG-Sol with lower viscosity (i.e., higher LST values), XTG cannot maintain such a structure, leading to the dehydration of the polymer matrix in the XTG-Sol. This may be the reason why the M-Tabs immersed in XTG-Sol with lower viscosity absorb a moderate amount of liquid. The results also showed that the M-Tabs disintegrated in the XTG solution used as FT, and that the disintegration time of the M-Tabs immersed in the XTG-Sol was significantly longer than that of the non-immersed M-Tabs. Third-generation FTs, which contain XTG, are currently used widely in medical institutions and nursing homes, with many products available on the market. In this research, we confirmed that the disintegration time of M-Tabs was prolonged even in aqueous solutions of XTG, which is commonly added to FTs as a thickening agent; therefore, it is suggested that all XTG-based FTs currently on the market may affect the disintegration of rapidly-disintegrating tablets.

The reproducibility of the disintegration test was examined by comparing the results of this study with those of a previous study [8]. A disintegration test was not performed in the previous study because the M-Tabs were immersed in TsuruQ-sol in vitro for 30 min and then the solution was stirred with a glass rod to examine the disintegration status of the M-Tabs. Thus, the current study examined the reproducibility of the test by evaluating the disintegration status of the M-Tabs in TsuruQ-sol and their disintegration time in TsuruQ-sol separately.

As observed in this study, the M-Tabs in the previous study were not subjected to the disintegration test because they disintegrated in mildly thick TsuruQ-sol. Since the disintegration status of the M-Tabs in moderately or extremely thick TsuruQ-sol in this study was equivalent to that in the previous study, M-Tabs after the immersion were used in the disintegration test. Therefore, the reproducibility of the disintegration status of M-Tabs in TsuruQ-sol seems to be sufficient.

In this study, the normality of the distribution of the disintegration time of M-Tabs in TsuruQ-sol with higher viscosity was not rejected while that in TsuruQ-sol with moderate viscosity was rejected. This suggests that the state of the M-Tabs in moderately thick TsuruQ-sol is not always uniform because the viscosity and immersion time of M-Tabs are more likely to be affected by moderately thick TsuruQ-sol than by extremely thick TsuruQ-sol. In addition, the disintegration time of multiple M-Tabs in extremely thick TsuruQ-sol, of which the normality of the distribution was not rejected, was significantly shorter than the median disintegration time and was outside the 95% confidence interval (data not shown).

Thus, the disintegration status of the M-Tabs in TsuruQ-sol was observed with high reproducibility, while the disintegration time was not. The significant results of the Kruskal-Wallis test of the longer disintegration time suggested that high variation in the disintegration time of the M-Tabs was largely due to the viscosity and the immersion time in TsuruQ-sol.

As in previous studies [8,10,11], the disintegration time of the M-Tabs was significantly longer in the case of (i) immersion in TsuruQ-sol with lower LST values; and (ii) longer immersion in TsuruQ-sol than otherwise. Likewise, the disintegration time of the M-Tabs was significantly longer in the case of (i) immersion in XTG-Sol with lower LST values; and (ii) longer immersion in XTG-Sol than otherwise. Generally, for tablets to disintegrate, it is most important that water penetrates into the tablets; the disintegrant added to the tablets absorbs the water that has entered the tablet and causes the tablet to disintegrate. Although the exact mechanism that prolonged the time of disintegration of M-Tabs immersed in XTG-Sol and TsuruQ-sol is unclear, because XTG is a thickening agent and has a high viscosity, lower LST values resulted in more XTG coverage on the outside of the tablet, which reduced the penetration of purified water into the tablet and extended the disintegration time.

When the LST values of TsuruQ-sol and XTG-Sol prepared with equivalent concentrations of XTG were compared, the LST values of TsuruQ-sol were 1.04–1.10 times higher than those of XTG-Sol; therefore, we predicted that the disintegration time of M-Tabs immersed in TsuruQ-sol would be shorter than that of M-Tabs immersed in XTG-Sol at equivalent XTG concentrations. However, we found that the disintegration time of M-Tabs immersed in TsuruQ-sol was 1.11–1.94 times longer than that of M-Tabs immersed in XTG-Sol at equivalent XTG concentrations. The influence of low-viscosity dextrin, which is an additive in TsuruQ, was suggested as a possible cause. For TsuruQ-sol, because the low-viscosity dextrin covers the surface of M-Tabs in addition to the thickening agent XTG, it is conceivable that the speed of penetration of water into the tablet was decreased relative to the XTG-Sol which does not contain dextrin. We considered the possibility that a decrease in the speed of penetration of water into the tablet thereby prolonged the disintegration time of M-Tabs. Furthermore, at the shortest immersion time (1 min), the disintegration time of M-Tabs immersed in TsuruQ-sol was 1.63–1.94 times longer than that of XTG-Sol. Therefore, in FTs that contain viscosity-modifying additives other than XTG, the speed of penetration of water into the tablet is reduced proportionately more over short immersion times, which suggests the possibility that even low-viscosity additives can affect the disintegration of M-Tabs. These results elucidated the need to consider the viscosity of additives other than XTG when using FTs to take drugs.

The results showed that the longer the 0.6% XTG-Sol (LST: 34.3) immersion time, the higher the swelling and disintegration time of the M-Tabs. When tablets are immersed in and swell in water, the viscous XTG-Sol simultaneously penetrates them. Subsequently, not only the viscosity at the surface but also that inside the tablets seems to increase. The larger the swelling of the tablets, the greater the extent of XTG-Sol penetration into the tablets. Thus, a consistent viscosity may be given extensively inside the tablets, making disintegration difficult and the disintegration time longer.

In the case of 0.6% and 0.8% XTG-Sol and 2.0% and 2.7% Tsuru Q-sol, there was no significant difference in the disintegration time of the M-Tabs between the 5 min and 10 min immersion. However, the results showed that the longer the immersion time, the longer the disintegration time. In addition, the disintegration time of the M-Tabs immersed for 5 or 10 min was significantly longer than that of those immersed for 1 min. On the other hand, the comparison of the disintegration time of M-Tabs in 0.6%, 0.8% XTG-Sol or 2.0%, 2.7% TsuruQ-sol for the same immersion time showed a tendency that the higher the concentration of the solutions, the longer the disintegration time. However, this was not statistically significant. These results suggest that the immersion time of the M-Tabs is a factor that more crucially affects the disintegration time of the M-Tabs in XTG-Sol or TsuruQ-sol, than the concentration of the solutions. There are cases in which patients with dysphagia with worsening symptoms swallow M-Tabs with a higher concentration of TsuruQ-sol. In such cases, according to the results, a shorter immersion time can reduce the concentration-related increase in the disintegration time of the M-Tabs.

We have also examined the effects of thickened food products on tablets other than M-Tabs and found that they increase the disintegration time of orally disintegrating tablets [10]. Thus, it is important to use appropriate thickened foods with a low risk of issues related to the disintegration and dissolution of tablets.

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