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Effect of Disintegrants on Prolongation of Tablet Disintegration Induced by Immersion in Xanthan Gum-Containing Thickening Solution: Contribution of Disintegrant Interactions with Disintegration Fluids

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In clinical practice, a thickening solution is frequently used to allow easy swallowing of tablets by patients suffering from dysphagia. This study investigated the effect of the thickening solution on tablet disintegration. Model tablets containing different disintegrants were prepared and their disintegration times (DTs) measured using standard methods. We also performed an additional disintegration test on the model tablets after immersing them for 1 min in thickening solution containing xanthan gum (XTG-SOL) ("modified disintegration test"). The DTs of the test tablets were substantially prolonged by immersion in XTG-SOL. Furthermore, the effect of the XTG-SOL on the DTs differed depending on the type of disintegrant contained in the tablets. To investigate in more detail this prolongation of tablet disintegration, we examined the contribution of tablet properties to their DTs. The properties analyzed included contact angle, T_2 relaxation time, wetting time, and water absorption ratio. The contributions of these properties to the DTs were analyzed using multiple regression analysis. This analysis clarified that the tablet properties affecting DTs changed after immersion in XTG-SOL: wetting time significantly affected the DTs measured in the normal disintegration test, while T_2 was crucial for the DTs of tablets immersed in XTG-SOL. These findings provide valuable information for design of tablet formulations, and for clinical medication management for older patients with dysphagia.

Key words thickening solution; xanthan gum; disintegrant; disintegration time; T_2 relaxation time

Introduction

Dysphagia is defined as an inefficiency in the process of swallowing food, liquid, or saliva from the oral cavity to the stomach. As the age of the population increases, the number of patients with swallowing difficulties is increasing steadily. Dysphagia is known to be triggered by dementia, head and neck cancers, head injury, neuromuscular disorders, and stroke.[1–3] It is known that thickening food and drink helps people with dysphagia to swallow and hence reduces the risk of aspiration. Various thickening agents have been used for this purpose. Currently, the thickening agents available on the market are classified into three categories: starch-, guar gum-, and xanthan gum (XTG)-based thickening agents. The thickening effects of these agents are affected by various factors including the type of thickening agent, the solute in which they are present,[1,4,5] pH,[6] and the salt concentration.[7] XTG-based thickening agents are the product most recently developed to improve therapeutic performance; they are able to thicken a wide range of liquids at different temperatures while maintaining stable viscosity. Thus, XTG has become the most commonly used thickening agent.

Thickening agents are also used for medication management in older patients with dysphagia. Patients' medicines are usually administered after immersion in thickening solution rather than with tap water. One survey reported that 35 of 42 (83.3%) nursing facilities used a thickening solution for administering medication.[8] However, previous studies reported that thickening agents could decrease the intestinal absorption of drugs, weakening the therapeutic effects of some pharmaceutical products[9–12] including magnesium oxide,[9] mitiglinide,[10] voglibose,[11] acetaminophen,[12] sodium valproate,[12] carbamazepine.[12]

There is a possibility that the decrease in intestinal drug absorption accompanying coadministration of tablets with thickening solution is caused by a delay in tablet disintegration. Tablet disintegration is generally considered the first stage in the bioavailability cascade that includes drug release and absorption from the gastrointestinal tract, leading to the desired therapeutic effects. Recently, we investigated the influence of thickening agents on the disintegration of different types of tablets, including uncoated tablets, orally disintegrating (OD) tablets, and film-coated tablets.[13] In addition to the normal disintegration test, a disintegration test was conducted on tablets that had been immersed in thickening solution containing xanthan gum (XTG-SOL) for 1 min. That experiment showed that uncoated tablets and OD tablets had significantly longer disintegration times (DTs) after immersion in XTG-SOL, while no significant difference was observed for film-coated tablets. However, apart from this study, there are few reports concerning this issue.

We consider that further investigation of the effect of thickening agents on the disintegration properties of tablets will provide insights into the design of tablet formulations and clinical medication management using a thickening solution

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in patients with dysphagia, by, for example, enhancing the technical knowledge required to select appropriate ingredients when designing tablet formulations. It would also provide valuable information allowing medical workers to predict medical risks related to this issue. Hence, the purpose of this study was to perform a detailed investigation of the prolongation of tablet disintegration induced by immersion in XTG-SOL. Based on the assumption that tablet formulation has a significant impact on the prolongation of disintegration, we tested model tablets containing different disintegrants, the excipient most crucial for tablet disintegration. After preparation of the model tablets, their disintegration was examined using both a normal disintegration test and a disintegration test after immersing the tables in XTG-SOL for 1 min ("modified disintegration test"). We also examined other tablet properties to gain further understanding of the effects of XTG-SOL treatment. The results of the study identified that disintegration behavior observed in the modified test was distinct from that in the normal disintegration test.

Experimental

Materials The disintegrants contained in the model tablets in this study are summarized in Table 1. Corn starch (CS) was was provided by Nihon Shokuhin Kako (Tokyo, Japan). Carmellose (CMC) [NS-300® (NS)] and carmellose calcium (CMC-Ca) [ECG®-505 (ECG)] were was provided by Gotoku Chemical (Tokyo, Japan). Low-substituted hydroxypropyl celluloses (L-HPC®) [LH-21] was provided by Shin-Etsu Chemical (Tokyo, Japan). Sodium starch glycolate [Glycolys® (GLY)] was provided by Roquette Japan (Tokyo, Japan). Crospovidone type A [Kollidon® CL-F (KO)] was provided by BASF Japan (Tokyo, Japan), while crospovidone type B [Polyplasdon™ XL-10 (PP)] was provided by ISP Technologies (Ashland, KY, U.S.A.). Mannitol (Partec® M200) was provided by Merck Millipore (Billerica, MA, U.S.A.). Microcrystalline cellulose (MCC) (Ceolus® UF-F711) was provided by Asahi Kasei Chemicals (Tokyo, Japan). Magnesium stearate (Mg-St) was provided by Taihei Chemical Industrial (Osaka, Japan). XTG (ECO-GUM®) as a food thickening agent was provided by DSP Gokyo Food & Chemical Co., Ltd. (Tokyo, Japan).

Preparation of Model Tablets Model tablets consisting of 85% mannitol (used as filler), 9% MCC (used as binder), 5% disintegrant, and 1% Mg-St (used as lubricant) were prepared using the direct compression method. Designated amounts of each powder except for the lubricant were added into a polyethylene bag and mixed for 3 min. Subsequently, Mg-St was added to the mixture, and blended with the mixture in a polyethylene bag for 1 min. The final blend (170 mg) was compressed at 4 kN into a tablet, 8 mm in diameter, using a rotary tablet press (Kikusui, Kyoto, Japan).

Table 1. Disintegrants Tested in This Study

Product name	Abbreviation	Common name
Corn starch	CS	Corn starch
ECG®-505	ECG	Carmellose calcium (CMC-Ca)
Glycolys®	GLY	Sodium starch glycolate
Kollidon® CL-F	KO	Crospovidone type A
L-HPC ®LH-21	L21	Low-substituted hydroxypropyl celluloses
NS-300®	NS	Carmellose (CMC)
Polyplasdon™ XL-10	PP	Crospovidone type B

Disintegration Test The disintegration test was carried out using a disintegration testing apparatus (NT-60H, Toyama Sangyo, Osaka, Japan) and the first fluid used for the disintegration test was JP17 (as test medium) at 37 ± 2 °C. DT was defined as the time required for the complete disappearance of a tablet or its particles from the tester net. As well as the normal disintegration test, we performed a disintegration test of the tablets immersed in XTG-SOL. Full details of the modified disintegration test were reported previously.[13] In brief, the XTG-SOL was prepared by dissolving a designated amount of XTG in purified water at a concentration of 0.9% (w/v). The XTG-SOL was classified as "extremely thick" as defined in the Japanese Dysphagia Diet 2013 published by the Japanese Society of Dysphagia Rehabilitation (JSDR) dysphagia diet committee.[14] Afterwards, each tablet was immersed in 10 g of XTG-SOL for 1 min because the majority of patients took the tablets within 1 min after immersed in thickening solution.[8] and then the DT was measured by the method described previously. The difference in DTs measured in the two tests was calculated as the prolongation of the DTs.

Measurement of Contact Angle The contact angles of water against the tablets were determined using the sessile drop method. Flat tablets with a diameter of 8 mm were prepared according to the formulation described above. The measurement was performed using a contact angle system (DropMaster 700; Kyowa Interface Science, Saitama, Japan). Using a microsyringe, a drop of water (2 μL) was dispensed onto the tablet surface. The contact angle of the water drop was recorded at 1000 ms using an internal camera.

Measurement of T_2 Relaxation Time Using Time-Domain NMR (TD-NMR) Test samples were prepared by dispersing each tablet in purified water at 25%. Immediately after vortexing the sample, the T_2 of the suspension was measured by TD-NMR using a Bruker minispec mq20 (Bruker BioSpin, Billerica, MA, U.S.A.) at a ^{1}H frequency of 20 MHz at 25 °C. The TD-NMR used is a benchtop instrument that is specific for measurement of the ^{1}H-NMR relaxation (*i.e.*, T_1 and T_2 relaxations). Unlike a high-resolution NMR, TD-NMR does not acquire an NMR spectrum, but it enables easy and rapid measurement of the NMR relaxation times of the samples. The Carr–Purcell–Meiboom–Gill (CPMG) pulse sequence was employed for the measurement of T_2 relaxation time. The acquisition parameters were as follows: number of scans = 8, number of dummy scans = 4, recycle delay = 10 s, time between each pulse (τ spacing) = 0.25 ms, data points = 4000. Calculation of T_2 was performed using the TD-NMR Analyze Software (Bruker BioSpin). The measurement of T_2 was performed in triplicate.

Measurement of Wetting Time and Water Absorption Ratio A piece of paper towel folded twice was placed in a small culture dish (5.5 cm internal diameter) containing 6 mL of purified water. A model tablet was placed carefully in the center of the dish. The time required for the water to cover the entire surface of the tablet was designated the wetting time (WT). The water absorption ratio (AR) for the tablets, a variable describing how much water is retained in the tablet when the wetting process is complete, was calculated as follows:

$$\mathrm{AR} = (W_a - W_b)/W_b$$

where W_a is the weight after wetting and W_b is the weight

before wetting.

Data Analysis The experimental data were analyzed using the statistical software JMP Pro15 (SAS Institute, Lane Cove, Australia). Multiple regression analysis applying a least-squares assessment was conducted to design the multiple regression equations that determined the significance of the effects of tablet properties on the DTs.

Results and Discussion

DTs and Other Tablet Properties The model tablets containing different disintegrants were prepared and their disintegration properties were examined. All of the tablets in the present study were pressed with the same tableting pressure (4 kN), and there are no differences in the diameter, thickness and hardness of the tablets. The mean values (minimum–maximum) values were 8.06 mm (8.04–8.07 mm) and 3.2 mm (3.21–3.24 mm) and 45 N (41–48 N), respectively. In addition to the normal disintegration test, a "modified disintegration test" of the test tablets was conducted after their immersion in XTG-SOL. The test disintegrants included corn starch (CS), NS-300 (NS), ECG-505 (ECG), Glycolys (GLY), LH-21 (L21), Kollidon CL-F (KO) and Polyplasdon XL-10 (PP) (Table 1). These are commonly used for manufacturing commercial tablets. CS is the most traditional disintegrant. ECG and NS belong to the same carmellose (CMC) group members, CMC-Ca and CMC. GLY and L21 are sodium starch glycolate and low-substituted hydroxypropyl cellulose (L-HPC). KO and PP are different commercial grades of crospovidone having different particle sizes; they are commonly used for OD tablets because of their high disintegration ability.

From the normal disintegration test, the longest and shortest DTs were observed in CS- and KO-containing tablets: 47.7 ± 5.0 and 10.7 ± 0.6 s, respectively (Table 2). The rank order of the values was consistent with those reported previously.[15] From the modified disintegration test, it was obvious that DT was extended by immersion in XTG-SOL. The DTs measured from the modified test were much longer than those from the normal test, ranging from 104 ± 23 s (KO-containing tablet) to 515 ± 184 s (ECG-containing tablet). We note that the DTs measured from the two disintegration tests were only weakly correlated with each other ($r = 0.431$). This suggests that the disintegration behaviors of the model tablets were changed by immersion in XTG-SOL. For example, in the case of GLY-containing tablets, although a relatively long DT was observed in the normal disintegration test, the DT became proportionally shorter after immersion in XTG-SOL. By contrast, for the ECG-containing tablet, a proportionally shorter DT was observed in the normal disintegration test, while it had the longest DT in the modified disintegration test. We next calculated the extent of prolongation of the DTs to identify the effect of XTG-SOL treatment on each model tablet. As shown in Fig. 1, the extent of prolongation clearly fluctuated depending on the type of disintegrant. For example, the DTs of CS- and ECG-containing tablets were obviously extended by immersion in XTG-SOL, while the prolongation of DTs for crospovidone (KO and PP)-containing tablets was much shorter than those of the other tablets.

To understand further the effect of XTG-SOL treatment on tablet disintegration, we also investigated the contributions to the DTs of other tablet properties (Table 2), including contact angle, T_2 relaxation time, wetting time, and water absorption ratio, which have been reported to be associated with tablet disintegration.[15–19] Contact angle is commonly used as an index to evaluate the wettability of a tablet by water.[19] The smallest angle was observed for the NS-containing tablets, indicating that these possessed the highest wettability compared with the other model tablets. NS is a representative wicking-type disintegrant. Wicking is defined as the process of liquid entry into the interior of tablets by capillary action. A higher

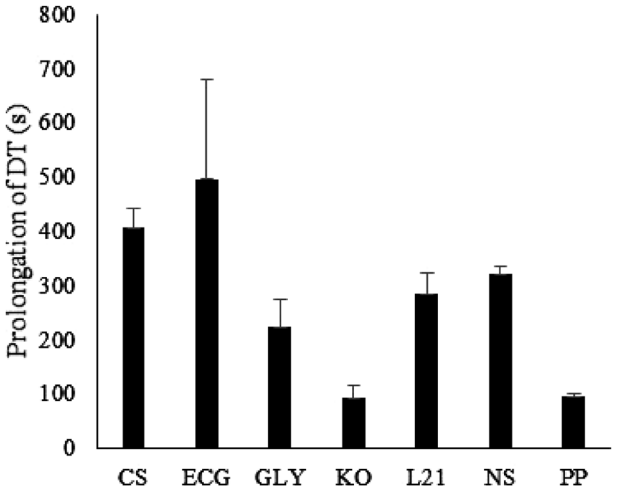

Fig. 1. Prolongation of Tablet Disintegration Times (DTs) Induced by Immersion in XTG-SOL

The Values were Calculated as the Difference between the DTs Measured in the Normal and Modified Disintegration Tests. Each Bar Represents the Mean ± Standard Deviation ($n = 3$). A significant difference test was performed by Tukey–Kramer method. $p < 0.01$ ECG *vs.* KO, ECG *vs.* PP, CS *vs.* KO, CS *vs.* PP. $p < 0.05$ ECG *vs.* GLY, NS *vs.* KO, NS *vs.* PP.

Table 2. Disintegration Times and Other Properties of Tablets

Disintegrants		Disintegration time [s]		Other tablet properties			
		Normal test	Modified test[a]	Contact angle [°]	T_2 relaxation time [ms]	Wetting time[b] [s]	Water absorption ratio[b]
Corn starch	CS	47.7 ± 5.0	457 ± 35	95.8 ± 1.6	732 ± 41	606 ± 4	0.33 ± 0.02
ECG-505	ECG	17.0 ± 2.6	515 ± 184	90.1 ± 6.1	708 ± 44	453 ± 1	0.96 ± 0.06
Glycolys	GLY	30.3 ± 1.2	255 ± 51	85.4 ± 0.5	760 ± 7	456 ± 24	1.69 ± 0.15
Kollidon CL-F	KO	10.7 ± 0.6	104 ± 23	89.8 ± 1.9	963 ± 33	279 ± 33	0.63 ± 0.02
LH21	L21	19.7 ± 0.6	305 ± 38	89.0 ± 4.9	763 ± 44	356 ± 30	0.94 ± 0.02
NS-300	NS	17.7 ± 0.6	339 ± 14	82.9 ± 3.7	705 ± 94	418 ± 53	0.62 ± 0.04
Polyplasdon XL-10	PP	16.0 ± 1.0	114 ± 3	97.3 ± 5.1	976 ± 26	423 ± 37	0.55 ± 0.03

a) The modified distintegration test was carried out after preincubation with XTG-SOL for 1 min. *b*) The values were quoted from the previous study (Onuki Y., *et al.*, *J. Drug Deliv. Sci. Technol.*, **43**, 141–148 (2018)).

wettability is known to be important for the wicking rate; thus, this result is considered to be reasonable. The largest contact angle ($97.3 \pm 5.1°$) was observed for the PP-containing tablets. We note that KO, a different commercial grade of crospovidone, showed a smaller contact angle. This is probably related to the difference of distribution of crospovidoine according to the different particle sizes. The T_2 measurement was performed by dispersing suspensions of the tablet powder in water as a test to assess the capacity of tablet powders to interact with water molecules. T_2 is widely used for the evaluation of the molecular mobility of compounds.[20] In the present study, a shorter T_2 was regarded as indicating a stronger interaction of the tablet powder with water molecules. As shown in Table 2, the T_2 values of crospovidone-containing tablets were much longer than those of the other disintegrants. Unlike their contact angles, the T_2 values for KO- and PP-containing tablets were indistinguishable: 963 ± 33 ms and 976 ± 26 ms, respectively. Therefore, T_2 was independent of particle size. The tablets containing the CMC-group disintegrants showed shorter T_2: 705 ± 94 and 708 ± 44 ms for NS- and ECG-containing tablets, respectively. This result suggests that the tablet powders of the crospovidone-containing tablets interacted weakly with water molecules, while those of the CMC-containing tablets bound tightly to water molecules. We previously reported the T_2 values of suspensions of disintegrant powders dispersed in purified water.[15] Although the absolute T_2 values measured from the previous study were overall higher than those from the present study, their T_2 values from the two studies were strongly correlated ($r = 0.899$). Taken together, the difference in T_2 values shown in Table 2 was mainly caused by the difference in the disintegrants contained in the model tablets. The values for wetting time (WT) and water absorption ratio (AR) are cited from our previous study.[15]

WT and AR are regarded as parameters representing the rate of penetration of water through the model tablets and the capacity of the model tablets to retain water, respectively. We also note that these tablet properties listed in Table 2 can be regarded as being independent of each other, because their correlation coefficients were low: the absolute values of the correlation coefficients (r) were 0.463 or less.

Contribution of Tablet Properties to the Disintegration Time To investigate the contribution of the tablet properties to their DTs, multivariable analysis was performed using multiple regression models. Standardized variables were employed for this analysis. The regression models constructed are shown in Tables 3, 4. These regression models appeared to be reliable, because the correlation coefficients between experimental and predicted values were high: correlation coefficients of 0.837 and 0.809 for DTs measured from normal and modified disintegration tests, respectively (Fig. 2). By comparing the p values of the tablet properties as an index of contribution, the crucial tablet properties for DTs were identified (Fig. 3). In the normal disintegration test, WT was demonstrated to have a significant effect on DT ($p < 0.01$). As shown in Fig. 4a, a shorter DT was accompanied by a shorter WT. By contrast, the result from the modified disintegration test showed a sig-

Table 3. Regression Model of Disintegration Times Measured in the Normal Disintegration Test

Terms	Estimate	Standard error[a)]	t-Value	p-Value
Intercept	22.7	1.6	14.2	<0.01
Contact angle	0.7	4.5	0.2	0.8712
T_2 relaxation time	–0.1	4.2	0.0	0.9761
Wetting time	18.4	4.5	4.1	<0.01
Water absorption ratio	1.6	3.4	0.5	0.6485

a) Estimates of standardized regression coefficients and standard errors of the regression model.

Table 4. Regression Model of Disintegration Times Measured in the Modified Disintegration Test

Terms	Estimate	Standard error[a)]	t-Value	p-Value
Intercept	298.4	23.1	12.9	<0.01
Contact angle	106.1	64.6	1.6	0.1198
T_2 relaxation time	–223.4	59.9	–3.7	<0.01
Wetting time	13.2	65.0	0.2	0.8418
Water absorption ratio	–15.0	48.9	–0.3	0.7625

a) Estimates of standardized regression coefficients and standard errors of the regression model.

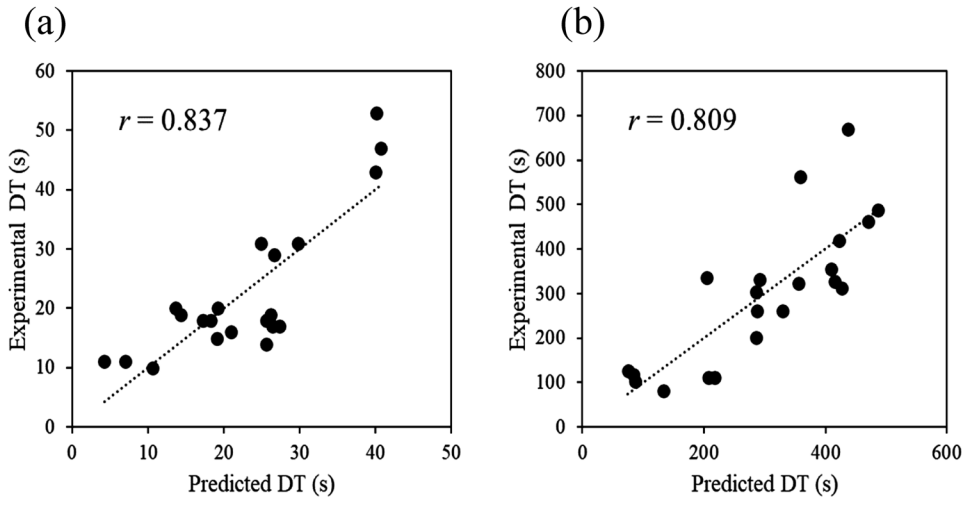

Fig. 2. Scatterplots of Experimental *vs.* Predicted Values Modeled by Multiple Regression

Disintegration Times (DTs) measured in (a) normal and (b) modified disintegration tests.

nificant effect of T_2 ($p < 0.01$): a shorter DT was derived from the tablets having longer T_2 (Fig. 4b). In addition, there was no significant influence of WT.

To date, various mechanisms have been proposed to explain the disintegration of tablets. These include swelling of particles, exothermic wicking reactions, particle deformation recovery, and particle repulsion.[21–23] The associations between these mechanisms are complex. Tablet disintegration progresses according to the distribution and penetration of outside water through the tablet. Thus, relative studies frequently investigate WT to investigate the penetration behavior of fluids though the tablet.[16–18] For example, Hooper *et al.* conducted a comparative study of the disintegration properties of commercial tablets, and found a close correlation between WT and DT for most tablets tested.[18] The present study also found a significant contribution of WT in the normal disintegration test. Thus, as far as the normal disintegration test is concerned, the penetration behavior of water though the tablet is crucial for disintegration of the model tablets. By contrast, the crucial factors in the modified disintegration test obviously differed from those of the normal disintegration test: the most significant factor was T_2, while no contribution of WT was observed. Thus, this indicates that the disintegration behavior of the model tablets was changed by their immersion in XTG-SOL. In the modified disintegration test, the interaction with water of the disintegrant contained in a tablet had a significant impact on its disintegration behavior.

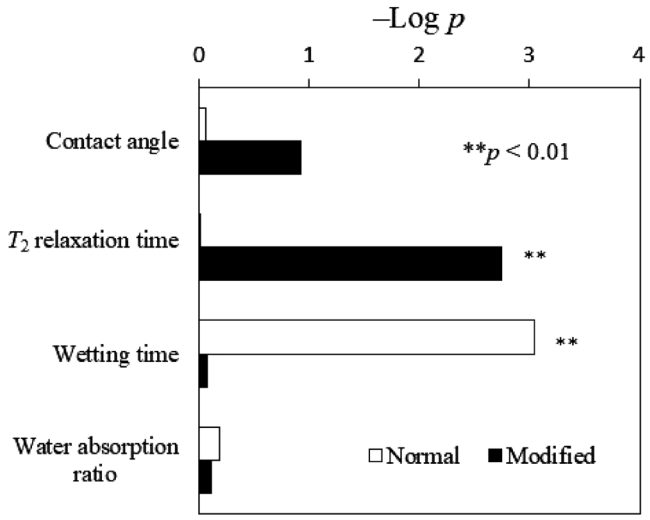

Fig. 3. Contribution of Tablet Properties to DTs Measured in the Normal and Modified Disintegration Tests Clarified by Multiple Regression Analysis

One possible explanation for this result is as follows. As soon as the disintegration test is started, the tablet surface allows interaction with water molecules in the disintegration fluid. The water molecules interacting with the tablet surface are likely to be much more restricted than the bulk water molecules. Furthermore, based on the results for T_2 values (Table 2), the water molecule mobility appears to change according to the type of disintegrant contained in the tablet. For example, water interacting with the crospovidone-containing tablet possesses high molecular mobility, while the CMC group (NS and ECG) allows tight interactions with water molecules. We assume that the water interacting with the disintegrant can serve as an obstacle to the distribution of bulk water within the tablet, and the strength of this obstacle depends on the intensity of the interaction: water more highly restricted by the disintegrant inhibits the distribution of bulk water in the tablet. However, in the normal disintegration test, no significant contribution of T_2 was observed. That is probably because the amount of bulk water that was distributed to the tablet was very large compared with the amount of disintegrant, meaning that the effect was difficult to identify. By contrast, in the modified disintegration test, the amount of bulk water located close to the tablet surface was very limited, because the water in XTG-SOL is mostly restricted by XTG. Thus, depending on its environment, the disintegrant in the tablet can exert a significant effect on the distribution of water near disintegrant, resulting in an effect on the distribution at the tablet surface.. Consistent with this proposed mechanism, we detected a significant contribution of T_2 in the modified test but not in the normal disintegration test. Because crospovidones interact weakly with water molecules, meaning that the water has higher molecular mobility, the water was relatively easily distributed in these tablets even in the viscous surroundings of XTG-SOL, resulting in little prolongation of DT.

Another possible mechanism of the effects seen in the modified disintegration test is that the interaction of disintegrant with water also affected the retention of XTG-SOL on the tablet surface. Visual inspection suggested that the XTG-SOL

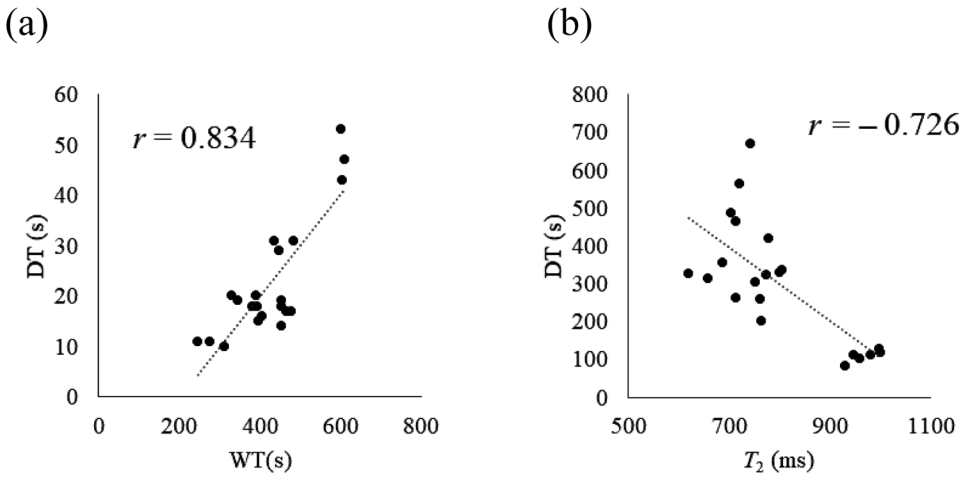

Fig. 4. Relationships between Crucial Tablet Properties and DTs Measured in (a) Normal and (b) Modified Disintegration Tests

covering the tablet surface gradually disappeared over longer experimental periods. The removed XTG-SOL was not dissolved in the disintegration fluid but was swollen by absorbing the disintegration fluid. The tighter interaction of disintegrants with water in XTG-SOL is suggested to prevent removal of XTG-SOL from the tablet surface, leading to a significant prolongation of DT under the modified conditions.

The present study provided enhanced technical knowledge concerning the disintegration properties of tablets coadministered with a thickening solution. Although the precise reason for the changes in DT remain unclear and require further investigation, we believe that these findings would be a valuable contribution to the design of tablet formulations and for clinical medication management using a thickening solution for elderly patients with dysphagia.

Conclusion

The present study investigated the effect of immersion in XTG-SOL on tablet disintegration. The results of the normal and modified disintegration tests confirmed that DTs of tablets were significantly prolonged by their immersion in XTG-SOL and that the extent of prolongation of the DTs differed according to the disintegrants contained in the model tablets. The DTs of crospovidone-containing tablets (KO- and PP-containing tablets) were less affected by XTG-SOL treatment than those of the other tablets. In the second phase of the study, the contribution of tablet properties to DTs was investigated using multiple regression analysis. The results indicated that the mechanism responsible for tablet disintegration was changed by XTG-SOL immersion, because the tablet properties crucial to each DT were clearly different: DTs in the normal disintegration test showed a significant effect of WT, while T_2 significantly affected the DTs of tablets immersed in XTG-SOL. These findings confirmed that the molecular mobility of water existing on the surface of a tablet has a significant impact on its disintegration properties, especially in viscous fluids. The findings offer a profound insight into the design of tablet formulations for use in older patients and for medication administration using a thickening solution for patients with dysphagia.

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