Original Article

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Preparation and evaluation of gelling granules to improve oral administration

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Summary **We investigated the preparation of oral granules that are solid when stored and that will swell and gel *via* water absorption, to address problems experienced by patients when taking medication. Important physical properties of gelling granules include elasticity that is normally smooth, quick water absorption and swelling properties that allow easy swallowing. We selected gelatin (GEL), succinylated gelatin (SUC-GEL) and ι-carrageenan (CAR) as matrix polymers that can undergo gelation at room temperature or at cold temperatures. Saccharide and polyethylene glycol (PEG) were added to prepare the experimental granules. The best matrix gelling granule was SUC-GEL. When xylitol (XYL), sorbitol (SOR) and maltitol (MAL) were added, elasticity was improved, and PEG improved the granule's water absorption behavior, which is an important element involved in gelation. The best granules were prepared by selecting SUC-GEL as the matrix and adding a small amount of PEG and XYL in amounts equal to that of SUC-GEL.**

Keywords: Polymer, gelling granules, succinylated gelatin, saccharide, polyethylene glycol

1. Introduction

Oral preparations are widely used, and they are an important type of formulation in pharmacotherapy. Any issue that the patient has when they take their medication affects the curative effect by reducing the patient's compliance or adherence. Tablets are the most preferred form of oral preparations, and they are frequently used because of their handling convenience. However, there are several problems with taking tablets, which can cause difficulties for infants and patients with difficulties swallowing (*1-4*). Therefore, powder, granules, dry syrups, and syrup are often given to these patients. These formulations cause resistance that results from discomfort when taking the medicine, because they can spread and residue can remain in the mouth or feel rough. Addressing these problems that might lead to improvement of the curative effect and quality of life (QOL) for the patient. To date, a jelly preparation (*5-7*), orally disintegrating tablets (*8-11*) and an oral film preparation have been developed to improvement administration. However, the content of these preparations is constant, similar to tablets, which represents a difficulty for children or elderly people who need to adjust the dose. We aimed to determine a new, adjustable preparation with granules that will help improve patient compliance. We targeted properties such as a solid form when stored and the ability to swell and gel quickly by absorbing water for comfortable swallowing. There are many reports of preparations that gel and swell by absorbing water (*12,13*). However, this feature has not often been reported to help improve the patient's experience when they take medication (*14,15*), and there have been no previous reports that have involved the use of granules. In this study, we focus on the properties of xelogel, which changes to hydrogel when water is added, and we investigated gelling granules that are dry until the patient drinks it with water.

2. Materials and Methods

2.1. *Materials*

Acetaminophen (AA) was purchased from Sigma-Aldrich (St. Louis, MO., USA) as model drug. Gelatin (GEL, Japanese Pharmacopoeia (*21*),Tokyo, Japan)

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was obtained from Nacalai Tesque (Kyoto, Japan) and succinylated gelatin (SUC-GEL) was obtained from Higuchi (Tokyo, Japan). ι-Carrageenan (CAR) was obtained from Sigma-Aldrich as a polymer. Sorbitol (SOR) and maltitol (MAL) were obtained from Towa Chemical Industry Co., Ltd. (Tokyo, Japan), and xylitol (XYL), mannitol (MAN) and polyethylene glycol (PEG) were obtained from Nacalai Tesque. Magnesium stearate (stMg) was obtained from Wako Pure Chemical Industries, Ltd. (Osaka, Japan) to be used as the hydrophobic powder material upon which granules were prepared.

2.2. *Granule preparation*

Polymer and AA were dissolved in water solution at 60-70°C in a hot water bath. Using a micropipette, the solution was dropped onto stMg and allowed to spread all over the tray. The granules were then dried in a refrigerator. We obtained the granules by removing excess stMg. Formulation of several granules prepared was shown in Table 1-4.

2.3. *Granule evaluation*

Granules of 1-2 mm were selected for further testing.

2.3.1. *Granule strength*

The granule strength was measured using a rheometer (Sun Scientific Co. Ltd., Tokyo, Japan). Using an adapter that was 10 mm in diameter, granules were placed on the sample table, which placed them under pressure by raising the sample table at a speed 15 mm/min. Thus, the displacement and load were obtained (n = 5).

2.3.2. *Water absorption test*

Granule water absorption behavior was evaluated by measuring the increase in granule weight when the granules were placed in a mesh basket after contact with a known amount of purified water. The increased weight ratio was obtain by measuring the amount of water absorption every 30 sec (n = 5).

2.3.3. *Dissolution study*

The paddle method, using the JP 16 dissolution apparatus (Toyama Sangyo Co. Ltd., Osaka, Japan), was used in this experiment. The dissolution medium was 900 mL purified water at 37°C, with a stirring rate of 100 rpm. At appropriate time intervals, a quantity of samples were withdrawn and replaced with the same volume of purified water. These samples were diluted with purified water as needed. AA concentrations were determined using UV spectrophotometry (Shimadzu Co., Kyoto, Japan) at a wavelength of 244 nm (n = 3).

Table 1. Formulation of granules prepared with polymer and saccharides

Material	GEL/MAN	GEL/XYL	GEL/SOR	GEL/MAL	SUC-GEL/MAN	SUC-GEL/XYL	SUC-GEL/SOR	SUC-GEL/MAL	CAR/MAN	CAR/XYL	CAR/SOR	CAR/MAL
Acetaminophen (g)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	0.5	0.5	0.5	0.5
Gelatin (g)	5.0	5.0	5.0	5.0	-	-	-	-	-	-	-	-
Succinylated gelatin (g)	-	-	-	-	5.0	5.0	5.0	5.0	-	-	-	-
ι-Carrageenan (g)	-	-	-	-	-	-	-	-	1.0	1.0	1.0	1.0
Mannitol (g)	5.0	-	-	-	5.0	-	-	-	1.0	-	-	-
Xylitol (g)	-	5.0	-	-	-	5.0	-	-	-	1.0	-	-
Sorbitol (g)	-	-	5.0	-	-	-	5.0	-	-	-	1.0	-
Maltitol (g)	-	-	-	5.0	-	-	-	5.0	-	-	-	1.0
Water (mL)	q.s.											
Total (mL)	100											

Values are given as volume per 100 mL. AA concentration of granules was prepared as a 20% (200 mg/g). q.s., quantum sufficiat; AA, acetaminophen; GEL, gelatin; SUC-GEL, succinylated gelatin; CAR, ι-carrageenan; MAN, mannitol; XYL, xylitol; SOR, sorbitol; MAL, maltitol.

Table 2. Formulation of granules prepared with CAR and SUC-GEL and saccharides

Material	GrA	GrB	GrA/XYL	GrA/MAL	GrB/XYL	GrB/MAL
Acetaminophen (g)	1.25	1.25	2.5	2.5	2.5	2.5
Succinylated gelatin (g)	4.5	4.0	4.5	4.5	4.0	4.0
ι-Carrageenan (g)	0.5	1.0	0.5	0.5	1.0	1.0
Xylitol (g)	-	-	5.0	-	5.0	-
Maltitol (g)	-	-	-	5.0	-	5.0
Water (mL)				q.s.		
Total (mL)				100		

Values are given as volume per 100 mL. AA concentration of granules was prepared as a 20% (200 mg/g). q.s., quantum sufficiat; AA, acetaminophen; CAR, ι-carrageenan; SUC-GEL, succinylated gelatin; XYL, xylitol; MAL, maltitol.

Table 3. Formulation of granules prepared with CAR and SUC-GEL and saccharides

Sample	Acetaminophen (g)	Succinylated gelatin (g)	Polyethylene glycol-400 (mL)	Xylitol (g)	Water (mL)	Total (mL)
SUC-GEL/PEG(1)	1.5	5.0	1.0	-		
SUC-GEL/PEG(2)	1.8	5.0	2.0	-		
SUC-GEL/PEG(3)	2.1	5.0	3.0	-	q.s.	100
SUC-GEL/PEG(10)	4.1	5.0	10.0	-		
SUC-GEL/XYL	2.5	5.0	-	5.0		

Values are given as volume per 100 mL. AA concentration of granules was prepared as a 20% (200 mg/g). q.s., quantum sufficiat; AA, acetaminophen; SUC-GEL, succinylated gelatin; PEG, polyethylene glycol-400; XYL, xylitol.

Table 4. Formulation of granules prepared with SUC-GEL and PEG and XYL

Sample	AA (g)	SUC-GEL (g)	PEG (mL)	XYL (g)	Water (mL)	Total (mL)
SUC-GEL/PEG(1)/XYL	2.8	5.0	1.0	5.0	q.s.	100
SUC-GEL/PEG(10)/XYL	5.3	5.0	10.0	5.0		

Values are given as volume per 100 mL. AA concentration of granules was prepared as a 20%. AA, acetaminophen; SUC-GEL, succinylated gelatin; PEG, polyethylene glycol-400; XYL, xylitol.

2.3.4. *Statistical analysis*

The results are presented the mean ± standard deviation (S.D.). Statistical differences were analyzed using the Tukey-Kramer test for multiple comparisons, and the level of significance was set at $p < 0.05$.

3. Results

3.1. *Influence of polymer and saccharide type*

Composition of each granule that used a polymer of GEL, SUC-GEL and CAR as the matrix in addition to four saccharides are shown Table 1. The AA content was prepared at 20% (200 mg/g). Concentration of the polymer was 5% (w/v) for the GEL and SUC-GEL, and 1% (w/v) for CAR. These granules were mixed with various saccharides at a ratio of 1:1.

3.1.1. *Granule strength*

A strength test for each polymer yielded a stress-displacement curve (Figure 1). In any polymer containing GEL, SUC-GEL or CAR, granules that contained MAN had the most variation in load because the compression power changed on the stress-displacement curve, which showed that they were inelastic. However, granules containing XYL, SOR or MAL with GEL and SUC-GEL showed little variation. There was no difference observed among the granules, but they showed elasticity. When CAR was used for the matrix, granules elasticity tended to increase with XYL and SOR. Compared to granules using each polymer containing MAL, XYL and SOR without MAN, which had no effect on elasticity, there were no differences in the type of polymer between XYL and SOR (Figure 1). However, granules that contained MAL with GEL and SUC-GEL had a tendency to increase in elasticity.

3.1.2. *Granule water absorption*

Water absorption behavior was shown by a relationship between the square root of time (seconds) and the rate at which weight increased for each polymer (Figure 2). For GEL and SUC-GEL, the difference depended on the type of saccharide. GEL granules showed a tendency to increase the amount of water absorbed when MAL was added. The findings were similar with SUC-GEL granules when XYL was added. The CAR granules showed no difference for the various saccharides. The order of increasing weight ratio compared for each polymer is as follows: CAR > SUC-GEL > GEL. This showed that a large amount of water was absorbed when CAR was used.

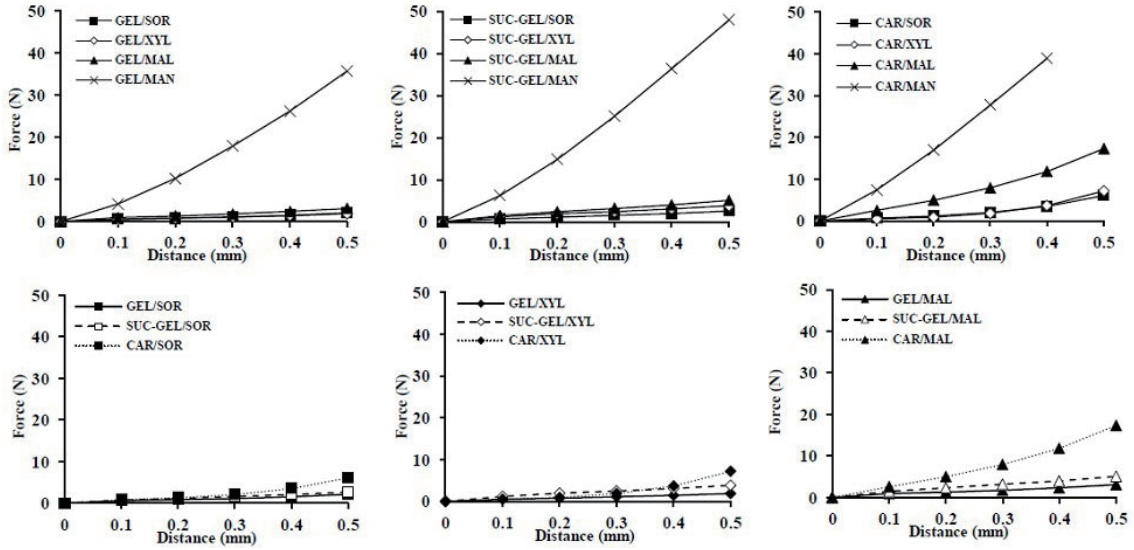

Figure 1. Elasticity of granules prepared with polymer and saccharides.

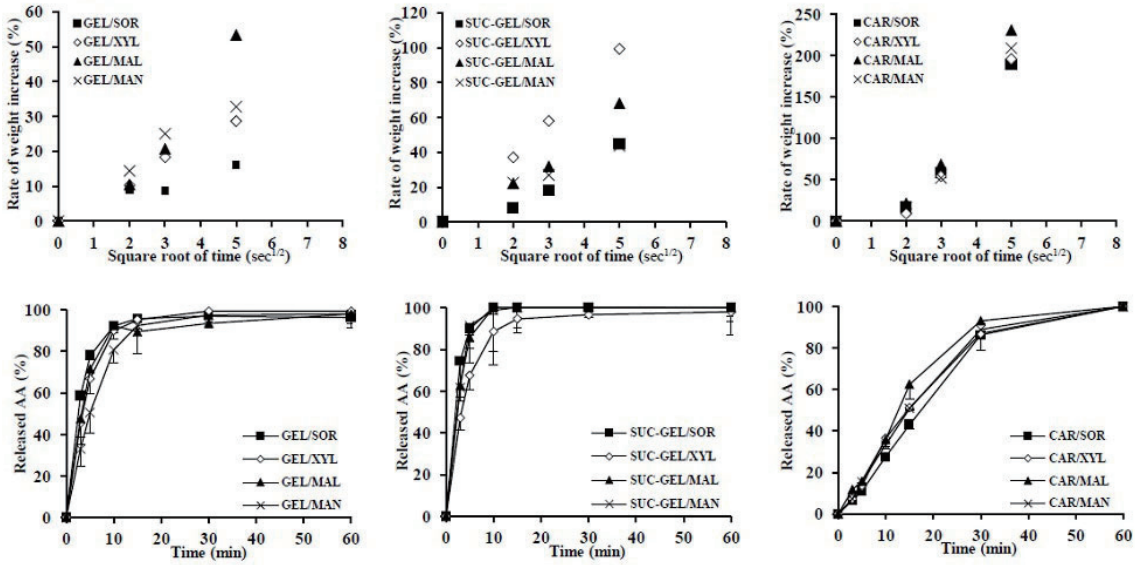

Figure 2. Water absorption and dissolution profiles of granules prepared with polymer and saccharides. Values are mean ± S.D. (n = 3).

The apparent water absorption speed relationship was a straight-line slope with the square root of time (seconds) and the rate of weight increase. Granules with GEL and SUC-GEL had a straight-line relationship (R^2 = 0.896-0.997) and the slope (apparent rate coefficient) was 3.0-18.0 (Table 5). This shows that SUC-GEL with XYL was the fastest (18.0) followed by SUC-GEL with MAL (11.6). CAR showed an apparent rate coefficient of 27.99-33.9, which was apparently larger than GEL and SUC-GEL. However, the straight-line relationship was not shown in any granules that included CAR (R^2 = 0.761-0.805). From Figure 2, there was a small amount of water absorption behavior initially, which increased thereafter.

3.1.3. *Granule dissolution behavior*

Dissolution behavior of AA released from the granules of each polymer is shown Figure 2. There were no differences in the type of saccharides on any polymer. Granules with either GEL or SUC-GEL released 100% of the AA at about 15 min. Granules with CAR showed a gradual dissolution behavior, which had a dissolution rate of 40-60% at 15 min and 100% at 60 min. However, this was slower than that for GEL and SUC-GEL.

3.2. *Effects of mixing polymer and saccharide*

From the results obtained by influencing the type of polymer and saccharide that affected granule elasticity and water absorption behavior, we examined the effect using mixed material of SUC-GEL and CAR to take into consideration both of these benefits. The saccharides selected were XYL and MAL. Composition of each granule is shown Table 2. The concentration of

the polymer solution was 5% (V/W) and the AA content was 20% (200 mg/g).

3.2.1. *Granule strength*

The stress-displacement curve obtained from the strength test is shown Figure 3A). Granule elasticity increases by adding saccharide regardless of the SUC-GEL and CAR mixture ratio. The polymer mixture ratio did not have an effect on elasticity.

3.2.2. Granule water absorption

Weight change in the water absorption test and the relationship between the square root of time (seconds) and the rate of weight increase is shown in Figure 3B).

Table 5. Apparent water absorption rate and linear correlation coefficient of granules prepared with polymer and saccharides

Sample	Apparent water absorption rate (Slope)	Linear correlation coefficient (R^2)
GEL/MAN	6.5	0.953
GEL/XYL	5.3	0.988
GEL/SOR	3.0	0.955
GEL/MAL	8.4	0.900
SUC-GEL/MAN	8.3	0.979
SUC-GEL/XYL	18.0	0.998
SUC-GEL/SOR	7.1	0.896
SUC-GEL/MAL	11.6	0.976
CAR/MAN	- (29.9)	0.766
CAR/XYL	- (28.1)	0.761
CAR/SOR	- (27.9)	0.805
CAR/MAL	- (33.9)	0.800
GrA	- (24.49)	0.798
GrB	- (16.19)	0.735
GrA/XYL	- (28.74)	0.780
GrA/MAL	- (21.67)	0.842
GrB/XYL	- (26.25)	0.796
GrB/MAL	- (16.88)	0.790
SUC-GEL/PEG(1)	58.3	0.987
SUC-GEL/PEG(2)	62.7	0.978
SUC-GEL/PEG(3)	58.0	0.975
SUC-GEL/PEG(10)	54.5	0.995
SUC-GEL/PEG(1)/XYL	56.8	0.990
SUC-GEL/PEG(10)/XYL	65.3	0.978

GEL, gelatin; SUC-GEL, succinylated gelatin; CAR, ι-carrageenan; MAN, mannitol; XYL, xylitol; SOR, sorbitol; MAL, maltitol; PEG, polyethylene glycol.

The slopes are shown in Table 5. There were some differences in the amount of water absorbed by each granule, but these changes were linear (R^2 = 0.735-0.842). The amount of water absorbed was large, but the speed of water absorption was initially slow for the SUC-GEL and CAR mixtures as well as for CAR alone.

3.2.3. *Granule dissolution behavior*

There were no obvious differences between the granules. The dissolution ratio was 30-60% at 15 min and 100% at 30 min. This was the same behavior as for CAR alone (Figure 3C).

3.3. *Effects of adding PEG and XYL*

Based on results from the type of polymer and saccharide, we selected SUC-GEL as the polymer, and investigated effects of adding various amount of PEG that was using as a plasticizer or as a solubilizing agent by comparing it with granules where XYL was added (Table 3).

3.3.1. *Granule strength*

The stress-displacement curve obtained from the granule strength test when the amount of PEG was varied and XYL was added is shown in Figure 4A). Granules that were mixing SUC-GEL with XYL in a ratio of 1:1 (SUC-GEL/XYL) had the highest elasticity. For granules that included PEG, the elasticity increased with an increasing amount of PEG.

3.3.2. *Granule water absorption*

The weight change in of the water absorption test showed a relationship between the square root of time (sec) and the rate of weight increase (Figure 4B). Granules that included PEG absorbed a greater amount of water and also absorbed it more rapid than granules with XYL, but there were no differences amount of PEG. The slope and linearity were obtained as the apparent water absorption speed from the relationship between the square root of time and the rate of weight increase (Table 5). All of the granules have linearity,

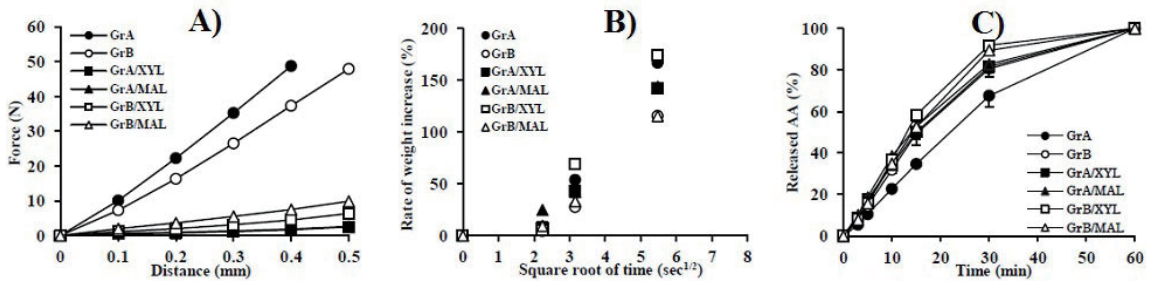

Figure 3. Characteristics of granules prepared with SUC-GEL and CAR and saccharides. A) Elasticity. **B)** Water absorption. **C)** Dissolution profiles. Values are mean ± S.D. (n = 3).

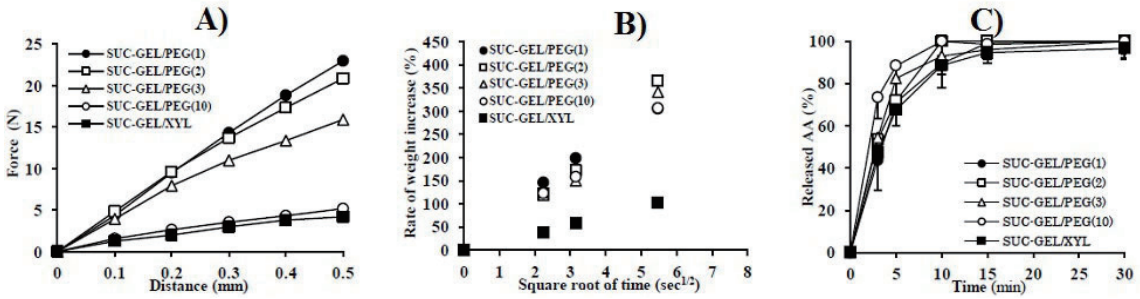

Figure 4. Characteristics of granules prepared with SUC-GEL and PEG or XYL. A) Elasticity. **B)** Water absorption. **C)** Dissolution profiles. Values are mean ± S.D. (n = 3).

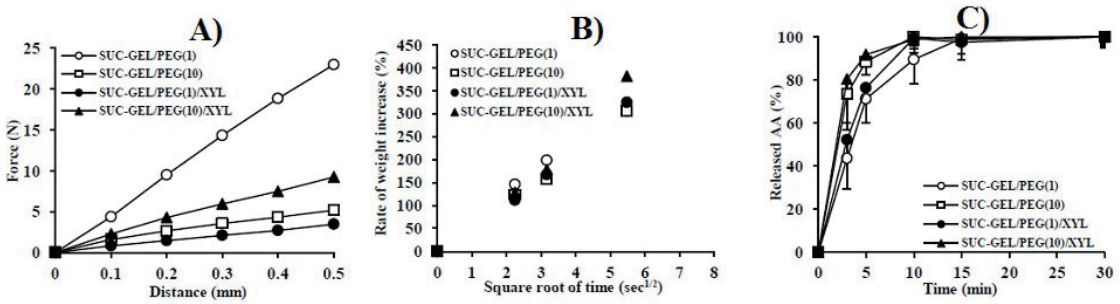

Figure 5. Characteristics of granules prepared with SUC-GEL and PEG and XYL. A) Elasticity. **B)** Water absorption. **C)** Dissolution profiles. Values are mean ± S.D. (n = 3).

and their R^2 value was greater than 0.97. The apparent water absorption speed for SUC-GEL/XYL was 18.0, and granules that included PEG were 54.5-62.7, which shows a high speed regardless of the amount of PEG that was added.

3.3.3. *Granule dissolution behavior*

There were no obvious differences in dissolution for the amount of PEG added, and comparison with granules that included XYL showed no differences. All the granules show a dissolution ratio of about 100% at 15 min (Figure 4C).

3.4. *Effect of XYL added to granules containing PEG*

When granules with various amounts of PEG and granules that included XYL were compared to SUC-GEL granules that were including 1% [V/V] of PEG (SUC-GEL/PEG (1)) and SUC-GEL granules that were including 10%[V/V] of PEG (SUC-GEL/PEG (10)), which are shown in Table 3, there were differences in elasticity. We investigated adding XYL to these granules (Table 4).

3.4.1. *Granule strength*

SUC-GEL/PEG (1), which had low elasticity, showed an increase in elasticity when XYL was added. However, SUC-GEL/PEG (10) that had high elasticity and adding XYL tended to slightly decrease this elasticity (Figure 5A).

3.4.2. *Granule water absorption*

The relationship between the square root of time (sec) and the rate of weight increase is shown in Figure 5B). There was no obvious difference and all granules showed the same water absorption behavior. Apparent water absorption speed of the granules containing XYL compared to SUC-GEL/PEG (1) and SUC-GEL/PEG (10) was 56.8 and 65.3, respectively, and effect of adding XYL was also not shown (Table 5).

3.4.3. *Granule dissolution behavior*

There were no obvious changes in dissolution behavior when XYL was adding. Any granules showed about 100% dissolution at 15 min (Figure 5C).

4. Discussion

We investigated preparation of orally-administered granules that are solid when stored and that will swell and gel when they absorb water. This research was aimed at addressing problems experienced by patients when taking medications. Required physical properties of gelling granules include elasticity that is normally smooth, and quick water absorption and swelling properties that will allow the granules to be easily swallowed. We prepared the targeted granules by selecting GEL and SUC-GEL and CAR for matrix polymers that can gel at room temperatures or at cold temperatures, and we also included some additives.

Polymer gels used here were physical gels that

formed a three-dimensional unstructured network, and basic dynamic gel properties were known to be different at different gel concentrations and with different additives (*16,17*). We evaluated the additive effects of saccharides and found that granules with a high degree of elasticity can be prepared by adding XYL, SOR and MAL regardless of which polymer is used. However, a combination of CAR and MAL showed a decrease in elasticity compared with the other compositions. Granule elasticity seems to be affected by varying water-retaining properties and these unstructured networks showed elastic properties when XYL or SOR were added, which have a relatively high ability to retain water (*18*). Water absorption behavior was different depending on the type of polymer. GEL and SUC-GEL showed rapid water absorption behavior and variable differences with different saccharides. However, SUC-GEL granules tend to have a faster absorption speed and a larger amount can be absorbed compared with GEL. A combination of SUC-GEL with XYL had the fastest absorption. On the other hand, granules with CAR absorbed a large amount of water but the initial water absorption was slow regardless of the type of saccharide. This shows that CAR was not suitable to prepare the target granules. All granules showed a weight increase, and the polymer might swell and gel because of water absorption. Swelling of polymers generally occurs because a solvent enters and diffuses into the gel. This phenomenon of increasing the cubic volume by absorbing a solvent into a three-dimensional unstructured network made of a polymer compound occurs by placing it in a solution and increasing the crosslink density that causes a decrease in diffusion of the unstructured network and the degree of swelling (*19-21*). The affinity and osmotic pressure are responsible for this infiltration (*22,23*). Therefore, interaction between the unstructured network and the polymer, and the additives, affinity for water and osmotic pressure all affect the water absorption behavior. This happens with AA dissolution behavior. Granules with CAR showed slow dissolution behavior compared with granules with GEL and SUC-GEL, which showed rapid dissolution behavior. Granules with SUC-GEL tend to have a slightly higher initial dissolution ratio than granules with GEL, and this tendency was related to SUC-GEL rapid water absorption behavior.

From these results, it was observed that our granules can be prepared with a matrix of SUC-GEL and XYL or MAL as additives. However, we evaluated the effect of mixing SUC-GEL with CAR to take advantage of CAR's characteristics such as the ability to absorb a large amount of water even though the initial absorption is slow. Adding XYL or MAL to these granules improves their elasticity. However, initial water absorption behavior did not improve because CAR characteristics seemed to be significantly affected. Dissolution behavior was also slow in granules with CAR alone. These results show that, although it was affected by saccharides, water absorption that was affected too much by CAR could destroy the element of SUC-GEL. We identified SUC-GEL alone as the best matrix for our granules.

Thus, we focused on PEG, which is used as a plasticizer or a solubilizing agent, and evaluated the effect of adding PEG to SUC-GEL to improve the granules. Granules with PEG added at various mixing ratios were compared with granules with XYL added, and granules that included XYL had better elasticity than granules that included low amounts of PEG. By increasing the amount of PEG, the elasticity approached that of granules with XYL. The difference seemed to be in the water retention properties for the amount of PEG that was added. On the other hand, granules that included PEG had better water absorption behavior than granules that included XYL regardless of the amount of PEG that was added, and the rate of apparent water absorption was approximately triple that of granules that included XYL. These results seem to be because of differences in cross-linking and osmotic pressure, which are factors in gelling and swelling. Dissolution behavior of AA was the same as that of granules that included XYL, independent of the amount added.

Strength and water absorption behavior results showed that adding PEG was useful for improving water absorption. However, a large amount was PEG needed to obtain elasticity. We then evaluated the addition of PEG to the granules along with XYL, which resulted in a better preparation for the granules. Consequently, SUC-GEL/PEG (1) that contained a small amount of PEG had improved elasticity and maintained its rapid water absorption behavior. It had no effect for dissolution behavior. These results suggest that it was useful in preparing the target granules by adding PEG and XYL to SUC-GEL.

We evaluated polymers as a matrix and additives for a preparation of targeted oral agents that have elasticity and that are normally smooth, they also had to absorb water quickly and have swelling properties to make swallowing easier. We found that SUC-GEL was suitable for a matrix and that XYL, MAL and SOR were useful for improving elasticity. PEG was best for rapid water absorption, which was an important element in gelation. Additionally, we prepared the best target granules by selecting SUC-GEL as the matrix and then adding a small amount of PEG and XYL in same amount as for SUC-GEL.

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