Regular Article

Examination of Gelling Agents to Produce Acetaminophen Jelly

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The current study used 3 types of carrageenan (denoted here as Car)—*κ*, *ι*, and *λ*—to prepare a jelly vehicle for acetaminophen (AAP), and then compared their usefulness as jelly vehicles. The rheological characteristics of each preparation were assessed and then drug elution from the preparation was assessed using dissolution testing. The behavior of each preparation when immersed in water was also examined using magnetic resonance imaging (MRI) in order to better understand the drug elution behaviour of each preparation. Viscoelasticity measurements revealed that 0.75 w/v%-*ι*-Car and 1.25 w/v%-*λ*-Car had viscoelasticity values equivalent to that of 0.5 w/v%-*κ*-Car. Dissolution testing of these 3 preparations indicated that 100% drug elution took 45 min with 0.5 w/v%-*κ*-Car while it took only 5 min with 0.75 w/v%-*ι*-Car and 1.25 w/v%-*λ*-Car. When deuterium oxide was added to *κ*-Car 0.5%, the MRI images darkened overall starting immediately after addition. The images revealed that the sample and deuterium oxide quickly mixed. In contrast, images revealed that deuterium oxide gradually penetrated *κ*-Car 1.0%. MRI images had uniform contrast, and deuterium oxide took 6 h or longer to penetrate the samples overall. These findings suggest that water is less apt to penetrate a jelly with an increased car concentration and a denser 3-dimensional network structure. Differences in the structure of car are said to result in better gelling, with *κ* having the best gelling characteristics, followed by *ι* and then *λ*. Thus, this paper discusses the role that vehicle gelling strength plays in the elution of acetaminophen.

Key words carrageenan; magnetic resonance imaging (MRI); viscoelasticity; jelly

In addition to gastrointestinal symptoms like diarrhea as a complication of liquid feeding,[1] patients who have difficulty chewing and swallowing often develop metabolic complications such as dehydration and abnormal blood sugar levels. Semi-solid nutrients cause fewer complications than liquid nutrients, and food in jelly form is used to prevent complications such as regurgitation. Jellies and jelly vehicles for oral ingestion by patients with dysphagia are being developed and assessed.[2] However, pharmaceutical gelling agents for use in feeding tubes and appropriate formulations of those agents have not been studied.

Acetaminophen (*N*-acetyl-*p*-aminophenol; AAP) is a drug that is widely used as an antipyretic analgesic in clinical practice. AAP is commonly used as an antipyretic analgesic in children.[3] On the World Health Organization's 3-step ladder for cancer pain relief, the first step is the use of nonopioid analgesics such as AAP or nonsteroidal anti-inflammatory drugs.[4,5] AAP's usefulness has been recognized in various settings, but the only AAP preparations available are powders, liquids, tablets, or suppositories. Thus, a preparation must be modified so that a drug can be administered by feeding tube to patients following a gastric resection or patients who have difficulty swallowing.

Cyclodextrin (CD) forms inclusion complexes with various drugs, so it is often used to improve drug solubility.[6,7] One CD, *β*CD is reported to form inclusion complexes with AAP and *β*CD is reported to improve the water solubility of AAP.[8] We have verified that use of inclusion complexes results in improved solubility of AAP.[9] Similarly, the current study prepared inclusion compounds in order to improve the solubility of AAP when preparing a drug in gel form.

In the current study, carrageenan was used as a gelling agent. There are 3 types of carrageenan that are of commercial importance: *κ*-carrageenan, *ι*-carrageenan, and *λ*-carrageenan. These types differ in the amount of 3,6-anhydro-galactose they contain and the number and position of sulfate groups. The carrageenans had a molecular weight of around 100000–150000 Da. The carrageenans were white or pale yellow powder that was tasteless and odorless. The presence of more sulfate groups weakens gelling ability, inhibiting gelling. *κ*-Carrageenan has the strongest gelling strength ability, followed by *ι*-carrageenan and then *λ*-carrageenan. *κ*-Carrageenan forms rigid, brittle gels while *ι*-carrageenan forms pliable, adhesive gels and is used as a gelling agent primarily in jellies and milk pudding. *λ*-Carrageenan has weak gelling ability and produces viscous aqueous solutions, so it is used as a thickener in foods such dressings, sauces, and soups. *κ*-Carrageenan is also used as a pharmaceutical additive. Oral jellies containing donepezil hydrochloride or amlodipine also contain carrageenan as an additive in order to mask bitterness or produce a preparation that is easier to swallow.

The current authors previously prepared a jelly by kneading AAP and *β*CD at a molar ratio of 1 : 1 (AAP : *β*CD) and they examined appropriate types and concentrations of gelling agents based on dissolution testing and rheological measurements. Results led to a discussion of whether a formulation with 0.5% *κ*-carrageenan (w/v) would be useful or not. The current study prepared 3 types of carrageenan, *κ*, *ι*, and *λ*, as a jelly vehicle for AAP. This study compared their usefulness as a gelling agent and it assessed the rheological properties of jellies. A dissolution test was also performed and drug elution from jellies was assessed. Penetration of jellies by water was

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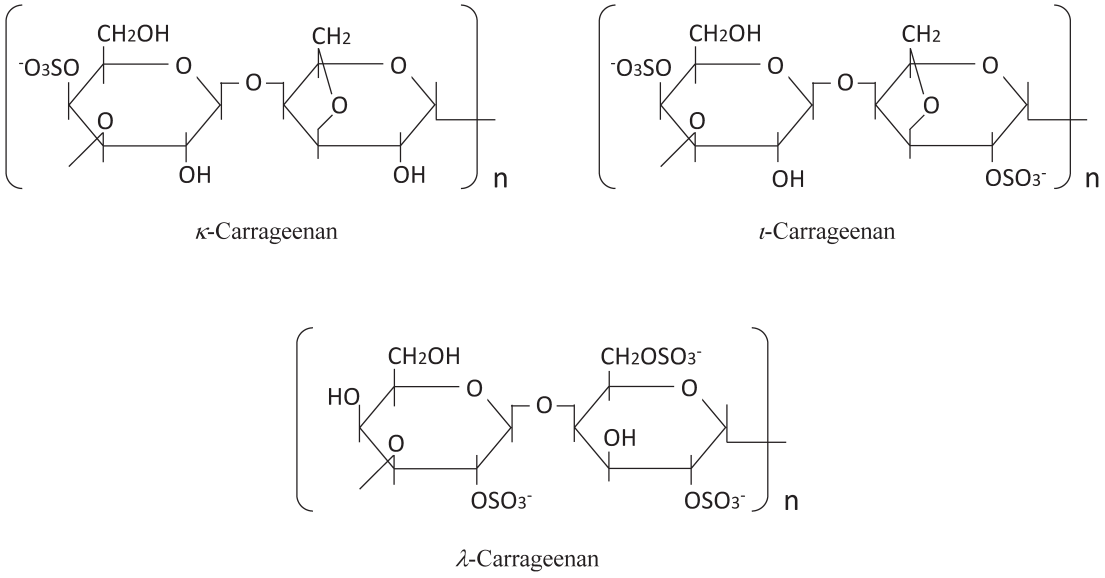

Fig. 1. Basic Chemical Structures of Carrageenans

Table 1. κ-Car, ι-Car, and λ-Car Concentrations in Each of the Jellies Preparation

Formulation	Percentage of gel (w/v%)				
	0.5	0.75	1.0	1.25	1.5
κ-Carrageenan	κ-Car-0.5	κ-Car-0.75	κ-Car-1.0	κ-Car-1.25	κ-Car-1.5
ι-Carrageenan	ι-Car-0.5	ι-Car-0.75	ι-Car-1.0	ι-Car-1.25	ι-Car-1.5
λ-Carrageenan	λ-Car-0.5	λ-Car-0.75	λ-Car-1.0	λ-Car-1.25	λ-Car-1.5

Each formulation contained the AAP 100 mg.

also examined with magnetic resonance imaging (MRI) to better understand their drug elution behavior.

Experimental

Materials The AAP used was special reagent grade (Wako Pure Chemical Industries, Ltd., Osaka, Japan). The βCD used was from MicroBiopharm Japan. The κ-carrageenan (κ-Car) used was from Wako Pure Chemical Industries, Ltd., and the ι-carrageenan (ι-Car) and λ-carrageenan (λ-Car) used were from Tokyo Chemical Industry (Fig. 1). The powder and tablets used were Calonal® powder 20% and Calonal® tablets 200 (Showa Yakuhin Kako Co., Ltd., Japan). This study was conducted fairly and impartially and ethical considerations were taken into account.

Preparation of Gelling Agents AAP–βCD inclusion complexes were dissolved in 50 mL of distilled water and the mixture was heated to 80°C in a water bath. Each gelling agent was mixed with this solution and the mixture was mixed with a stirrer for 3 min at 260 rpm until uniform, producing a sol. Samples of this sol were left to stand for 30 min at room temperature and then stored at 4°C. The concentration of gelling agent in each jelly was 0.5% (w/v), 0.75% (w/v), 1.0% (w/v), 1.25% (w/v), and 1.5% (w/v) (Table 1).

Rheological Measurements Rheology was measured using a HAAKE Mars rheometer from Thermo Scientific. Conditions were a measuring temperature of 25°C, a cone rotor (cone angle: 1°, cone diameter: 35 mm), a gap of 0.051 mm, and a shear rate from 0–500 s^{-1} (90 s)→500–0 s^{-1} (90 s). The viscosity (Eta (mPa·s)) and shear stress (Tau (Pa)) were measured each second for each of the samples. Rheology of 0.75% ι-Car (w/v), 1.0% ι-Car (w/v), 1.5% ι-Car (w/v), 1.25% λ-Car (w/v), 1.5% λ-Car (w/v), and 2.0% λ-Car (w/v) was measured, and rheological properties were compared to those of 0.5% κ-Car (w/v) and PGWater™.

Dissolution Test Dissolution testing was done with a dissolution tester from Toyama Sangyo. The test solution was 900 mL of purified water as specified in the Japanese Pharmacopeia. Dissolution testing (the paddle method) was performed in accordance with the 16th edition of the Japanese Pharmacopeia, with conditions of a temperature of 37±0.5°C and 50 rpm. Ten milliliters of the dissolved solution was collected after 0, 5, 10, 15, 30, 45, and 60 min, and the sample was filtered through a membrane filter (non-sterile mixed cellulose ester membrane filter) with a pore size of 0.45 μm. Two milliliters of the sample was accurately weighed and diluted with a mixed solution of water and methanol (23 : 25) to yield exactly 50 mL. This solution served as the sample solution. An assay was done with a HPLC from Shimadzu (SPD-20A). Conditions were a column of Inertsil ODS-3 (4.6 mm×150 mm, ϕ5 μm), a column temperature of 40°C, a mobile phase of 0.05 mol/L of a mixed solution of potassium dihydrogen phosphate and methanol (4 : 1, pH of 4.7), and a detection wavelength of 245 nm. Conditions were adjusted so that the AAP retention time would be about 5 min.

Measurement of MRI For sample preparation, 500 μL of jellies were prepared in microcentrifuge tubes (1.5-mL) according to the method mentioned above. Afterwards, 800 μL of deuterium oxide were overlaid gently on the jellies. T_1-

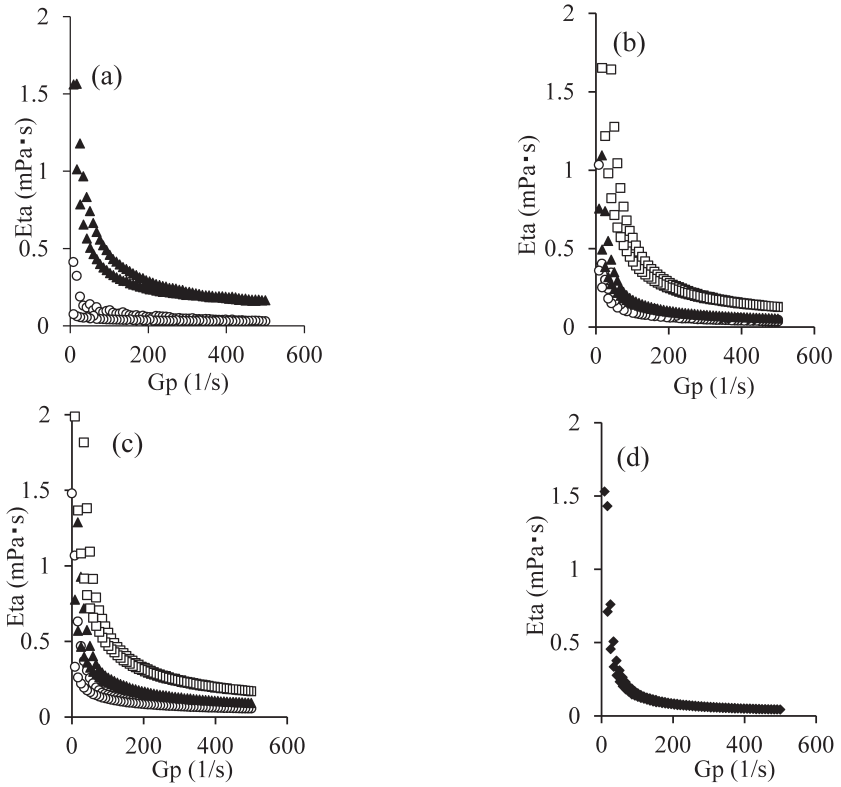

Fig. 2. Coefficient of Viscosity *versus* Shear Speed Curves of AAP Gel at 25°C

Results were expressed as mean±S.D. (n=3). (a) ○: κ-Car-0.5, ▲: κ-Car-1.0; (b) ○: ι-Car-0.75, ▲: ι-Car-1.0, □: ι-Car-1.5; (c) ○: λ-Car-1.25, ▲: λ-Car-1.5, □: λ-Car-2.0; (d) ◆: PGWater.

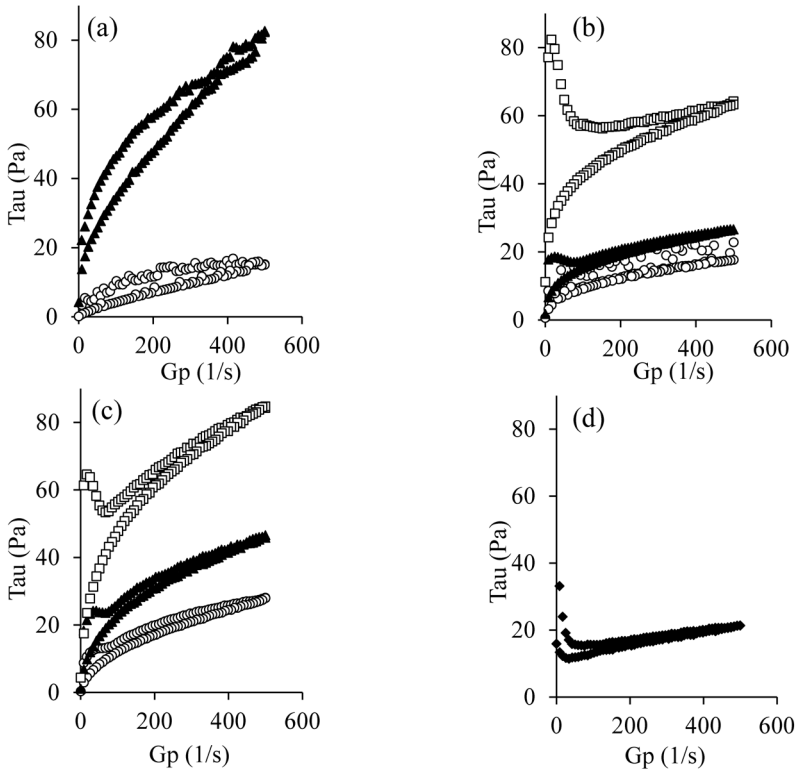

Fig. 3. Coefficient of Shear Stress *versus* Shear Speed Curves of AAP Gel at 25°C

Results were expressed as mean±S.D. (n=3). (a) ○: κ-Car-0.5, ▲: κ-Car-1.0; (b) ○: ι-Car-0.75, ▲: ι-Car-1.0, □: ι-Car-1.5; (c) ○: λ-Car-1.25, ▲: λ-Car-1.5, □: λ-Car-2.0; (d) ◆: PGWater.

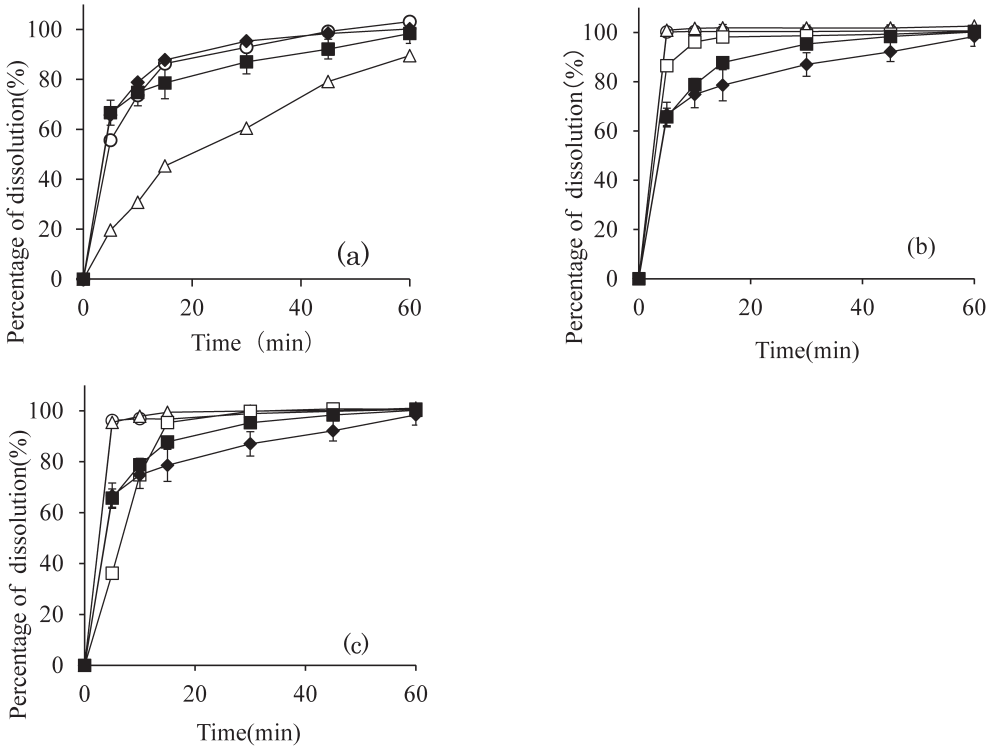

Fig. 4. Dissolution Profiles of AAP Gel

Results were expressed as mean±S.D. (n=3). (a) ○: κ-Car-0.5, △: κ-Car-1.0, ◆: Powder, ■: Tablet; (b) ○: ι-Car-0.75, △: ι-Car-1.0, □: ι-Car-1.5, ◆: Powder, ■: Tablet; (c) ○: λ-Car-1.25, △: λ-Car-1.5, □: λ-Car-2.0, ◆: Powder, ■: Tablet.

Weighted images (T_1WIs) of the samples were acquired using a 9.4-T vertical MRI scanner (Varian, Palo Alto, CA, U.S.A.). A gradient echo sequence were used for the acquisition. The acquisition parameters were as follows: repetition time (TR) of 12 ms, echo time (TE) of 6 ms, flip angle of 20°, 256×256 matrix size, field of view (FOV) of 40×35 mm, and slice thickness of 1 mm.

Results and Discussion

Assessment of the Viscoelasticity of Jellies Different gelling agents were used to prepare jellies of AAP–βCD inclusion complexes. Rheology was measured to compare the viscoelastic properties of various jellies at 25°C. In addition, the coefficient of viscosity Eta (mPa·s) and shear stress Tau (Pa) of the commercially available PGWater™ were measured and compared to those of different jellies. Results are shown in Figs. 2 and 3. PGWater™ is commonly used to facilitate water intake in forms such as high-calorie liquid food supplements. Eta and Tau were measured as clinical indices of viscoelasticity. The viscosity of 0.5% κ-Car, 0.75% ι-Car, 1.0% ι-Car, 1.25% λ-Car, and 1.5% λ-Car jellies and PGWater™ behaved similarly (Figs. 2a–d). The 1.0% κ-Car, 1.5% ι-Car and 2.0% λ-Car jellies were found to have a higher viscosity than that of PGWater™ and 0.5% κ-Car (Figs. 2a–d). The elasticity of the 0.5% κ-Car, 0.75% ι-Car, 1.0% ι-Car, and 1.25% λ-Car jellies and PGWater™ behaved similarly (Figs. 3a–d). Stress increased with an increase in the shear rate for 1.0% κ-Car, 1.5% ι-Car and 2.0% λ-Car, which had greater elasticity than PGWater™. The 2 jellies were found to have a larger flow curve area than PGWater™ (Figs. 3a–d). Thus, this gel is highly thixotropic. Presumably, greater force is needed to disrupt its structure (Figs. 3a, c, d). In addition, the large slope in the figures suggests that the gel has a robust structure. The κ-Car had greater gelling ability, followed by ι-Car and then λ-Car. The 0.75% ι-Car, 1.0% ι-Car, 1.25% λ-Car, and 1.5% λ-Car jellies had viscoelasticity equivalent to that of 0.5% κ-Car and PGWater™. The concentration of ι-Car and λ-Car as gelling agents must be increased to compensate for their weak gelling strength. An increase in viscosity and elasticity with an increase in the concentration of gelling agent was noted for all of the jellies. This is presumably because the concentration and viscoelasticity of the gelling agent are correlated, resulting in a jelly's dynamic properties.

The viscoelasticity of a jelly is evident in the reduced load when pushing a syringe connected to a feeding tube. A smaller load lessens the burden on the caregiver and makes use easier. In addition, ease of use allows food or nutrients to be infused in a short amount of time. This also reduces the need for patients with pressure sores to change position and it reduces the time they must remain in one position. One-point-five percent ι-Car, 1.5% λ-Car, and 2.0% λ-Car are surmised to be hard, rigid gels that will presumably result in an increased load when pushing a syringe connected to a feeding tube.

In contrast, the elasticity of 0.75% ι-Car, ι-Car, and 1.25% λ-Car behaved almost like that of PGWater™, so the gels have a flexible structure and will allow a syringe to be pushed with a smaller load. This means that they are easier to use.

In addition, the large flow curve area noted with 1.5% ι-Car and 2.0% λ-Car indicates a strong internal structure. This presumably means that their internal structure is less susceptible to disruption even at room temperature and that the gels will maintain their structure. These gelling agents allow gels to remain in a stable form as a jelly.

Assessment of Dissolution A dissolution test was per-

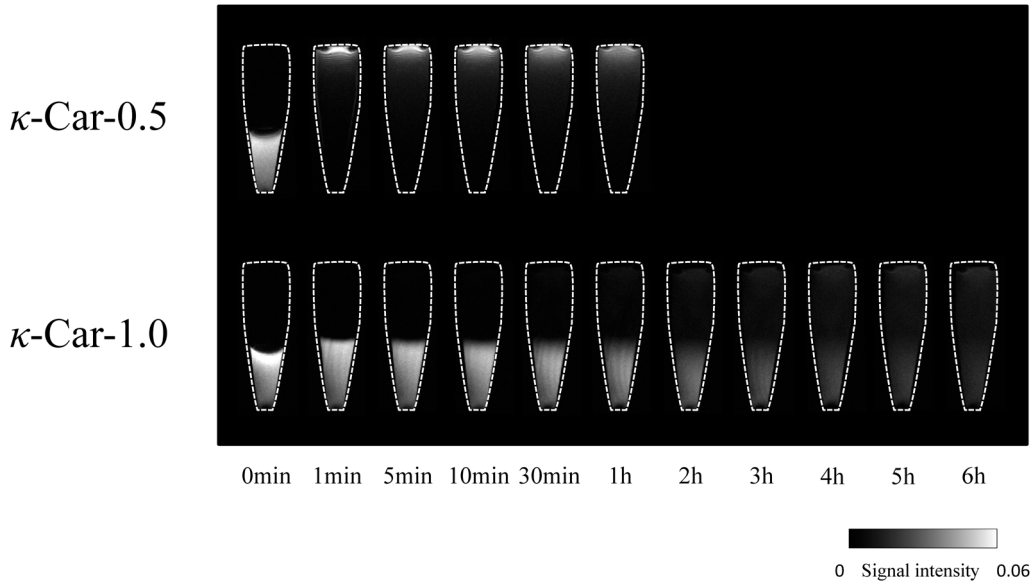

Fig. 5. Diffusion Study of Water in κ-Car

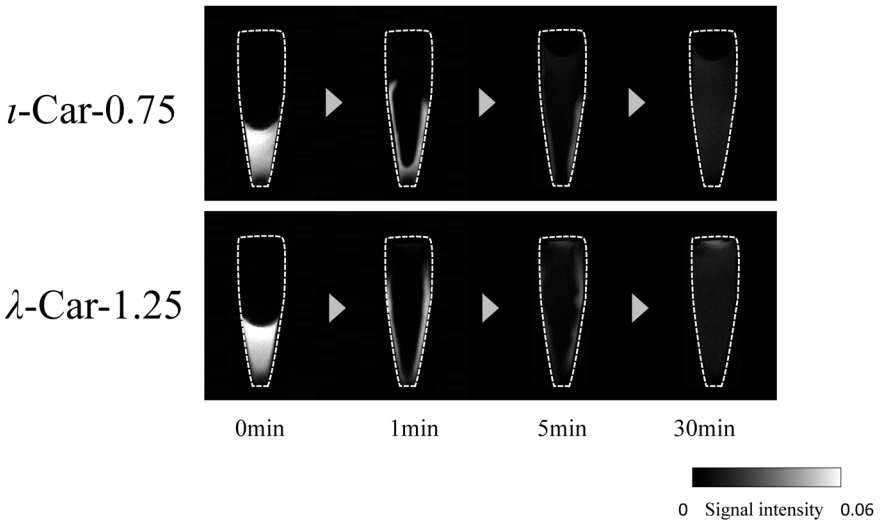

Fig. 6. Diffusion Study of Water in ι-Car and λ-Car

formed with different jellies, and results are shown in Fig. 4. ι-Car at every concentration was found to have a faster rate of AAP elution than a jelly of 0.5% κ-Car and AAP (Fig. 4b). At 5 min, 0.75% ι-Car and 1.0% ι-Car had a rate of AAP elution of 100% while 1.5% ι-Car had a rate of AAP elution of 86.5%. A fast rate of AAP elution was noted with 1.25% λ-Car and 1.5% λ-Car; both had a rate of AAP elution of almost 100% at 5 min (Fig. 4c). At 5 min, 2.0% λ-Car had a rate of AAP dissolution of 36.2% (Fig. 4c).

Zero-point seventy-five percent ι-Car, 1.0% ι-Car, 1.25% λ-Car, and 1.5% λ-Car were found to have a rate of AAP elution of almost 100% at 5 min and a fast rate of elution despite exhibiting viscosity equivalent to that of 0.5% κ-Car. This may be due to the properties of those gelling agents, *i.e.*, the weak gelling ability of ι-Car and the lack of gelling ability by λ-Car.

Differences in AAP elution due to differences in the concentration of the gelling agent were noted in the jellies. This is presumably because the viscosity and elasticity of Car0 affects AAP elution and may relate to the 3-dimensional network structure of the gel. The network structure of a gel is generally known to change in a concentration-dependent manner, so disparities in elution were noted as a result of an increase in the concentration of Car. Moreover, Car is a water-soluble polysaccharide containing hydrophilic sulfate groups,[10] so more water can be retained by types of Car with more sulfate groups. This fact suggests that the low rate of AAP elution noted with 2.0% λ-Car was due to concentration-dependent changes in the structure of gels and properties of their substituents. A characteristic of ι-Car-0.75 and λ-Car-1.25 was the rapidity with which AAP was eluted. Compared to κ-Car, ι-Car and λ-Car have weaker gelling ability, and this property may have greatly affected the elution of AAP. Behavior in the dissolution test also indicated that gels prepared with ι-Car and λ-Car had a weak structure. Mixing with a paddle appeared to have quickly disrupted that structure. The elution of

AAP from a gel prepared with ι-Car or λ-Car may be affected more by the gel strength resulting from differences in the gel structure than by diffusion of water into the gel. In addition, the type and amount of the ion that a carrageenan includes and the structure of the carrageenan differ, resulting in carrageenans with different properties. These differences may have affected the experimental results.

In the next phase of this study, we assessed the penetration of the outer fluid into the jellies by MRI. The penetration behavior was assumed to be closely related to the drug elusion property of the jellies. We note this study was performed by overlaying deuterium oxide on the jelly made from water. MR image enables to distinguish the distribution of water and deuterium oxide, because their resonance frequencies are different from each other; an intense MR signal is observed from water of the jelly, while no MR signal is detected from deuterium oxide.[11] From the time course of the change in MR images, we investigated the penetration behavior of deuterium oxide into the jelly.

Consecutive MR images after addition of deuterium oxide to the jellies composed of different concentrations of κ-Car are shown in Fig. 5. The jellies were clearly observed from the pre-contrast MR images which was acquired prior to the addition of deuterium oxide. Deuterium oxide penetration into 0.5% κ-Car seemed to be very quick; the bright image turned into dark just after the addition of deuterium oxide. In contrast to the case of 0.5% κ-Car, deuterium oxide gradually penetrated into 1.0% κ-Car; it took over 6 h until the contrast of MR image became uniform. As well as greater gel strength and slower drug elution properties shown in Figs. 2–4, the gradual deuterium oxide penetration was probably attributed to a denser 3-dimensional network structure caused by a higher polymer concentration.

This study also examined the deuterium oxide penetration into 0.75% ι-Car and 1.25% λ-Car, because their rheological properties were equivalent to those of 0.5% κ-Car (Fig. 6). As is the case with 0.5% κ-Car, bright image of the jellies disappeared just after the addition of deuterium oxide, indicating that deuterium oxide penetrated into the entire jellies very quickly. Thus, this study identified jellies that are suited to tube feeding. These jellies may mix with digestive juices soon after administration and elute the drug.

Conclusion

The results of the current study indicate that 0.5% Car is useful and safe as a jelly vehicle for AAP in a hospital preparation. The design of such preparations can help to improve patient quality of life. In addition, MRI results suggested that penetration of a jelly by water is closely related to the characteristics of drug elution by that jelly. A jelly form lessens the burden on the caregiver in terms of ensuring compliance and improves compliance by patients not taking their medication. Given the increase in disease as society ages, jellies should be widely utilized in future clinical practice.

Conflict of Interest The authors declare no conflict of interest.

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