

Preparation and Evaluation of Physicochemical Properties of Isosorbide Gel Composed of Xanthan Gum, Locust Bean Gum and Agar for Improving the Patient's Adherence

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Abstract

Isosorbide (ISB) has been widely used as a treatment for improving the endolymphatic hydrops of Meniere's disease. In general, ISB is used as a 70%(w/w) solution in medical treatments; however, ISB has a bitter taste, which reduces patient compliance. In recent years, jelly or gel formulations have been developed as "patient-friendly" and/or "patient-convenient" formulation. In this study, we attempted to develop various gel formulations of ISB to improve patient's adherence. We used xanthan gum (XG), locust bean gum (LBG), and agar as gelling agents. The hardness of the gels was greatest with an XG:LBG mixture ratio of 1:1. When ISB was added to the gels, their strength decreased but still showed suitable values. We also investigated methods to mask the bitterness of ISB. Gel formulations reduced the bitterness of ISB, and the addition of stevia, to the ISB gels improved bitterness. Collectively, these findings indicate that these ISB gels may be useful formulations for improving the patient's adherence.

Keywords: agar; gel formulation; isosorbide; locust bean gum; masking of bitterness; xanthan gum

1. Introduction

Meniere's disease (MD) is an intractable disorder of the inner ear that presents recurring and/or co-occurring symptoms such as rotational vertigo, hearing loss, tinnitus (ringing in the ear), and a feeling of fullness in the ear (Minor, 1999; Hone et al., 2000;

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Diamond et al., 2003; Carey, 2004; Merchant et al., 2005). The prevalence of MD appears to be approximately 35 per 100,000 people in Japan (Mizukoshi et al., 1997). The age of onset of MD is between the late 30s to early 40s (Mizukoshi et al., 1997). As medical treatments for MD, sodium bicarbonate, prednisolone, dexamethasone, betamethasone, isosorbide, acetazolamide, and adenosine triphosphate disodium hydrate have been used in Japan.

In particular, isosorbide (ISB) has been widely used to improve the endolymphatic hydrops (Kitahara et al., 1982; Stahle, 1984; Kakigi et al., 1995; Lee et al., 2016). Since ISB is poorly metabolized, the mega dose of concentrated ISB makes water move from the tissue and into the blood. ISB acts on the stria vascularis in the ear, or on the endolymphatic sac and duct, and decreases endolymphatic pressure. In actual medical treatments, ISB is usually prescribed as a 70% (w/w) solution. However, ISB has a peculiar odor and bitter taste, and improving drug adherence is therefore of primary importance. In recent years, formulations aimed at improving drug adherence such as oral disintegrating tablets and oral gel formulations have been developed. In particular, the oral gel formulations have become widespread as a new form of oral dosage because of their ease of handling and swallowing without water. In addition, the oral gel formulations have a lower risk of accidental ingestion and optimal masking of drug taste (Dairaku et al., 2003). These gel formulations have been prepared with various materials, including sodium caseinate and glycerogelatin (Watanabe et al., 1994a; Watanabe et al., 1994b).

In this study, we evaluated xanthan gum (XG) and locust bean gum (LBG) as gelling agents in the preparations of ISB. XG is a water-soluble exo-polysaccharide produced industrially from carbon sources by fermentation using the gram-negative bacterium *Xanthomonas campestris*. XG is a hetero-polysaccharide with a very high molecular weight (between one and several million). It is a macromolecule consisting of repeating glucose, alpha-D-mannose with an acetyl group, beta-D-glucuronic acid, and beta-D-mannose linked to pyruvate. Its main chain is made up of glucose units linked (1 to 4) to form a backbone similar to cellulose, with added side-chains of trisaccharide (three sugars in a chain). While XG is primarily used as a thickener, it is also the most efficient stabilizer for suspensions, emulsions, foams, and solid particles in water-based formulations. The characteristics of XG make it the most stable among natural gum substances, and it shows resistance to acid, salt, and heat. These characteristics are due to its large number of side chains, which are extremely high compared to other natural polymers, and these side chains protect the main chain of XG. It is well known that XG has a synergistic effect with combinations of galactomannan gum, and causes a significant increase in viscosity or gelling. Galactomannan gum is a macromolecular polysaccharide with mannose as the main chain and galactose as side chains. The interaction between XG and galactomannan is believed to be due to the "clockwork" portion of XG and the smooth part of galactomannan with no side chains. The extent of the interaction is enhanced with a combination of guar gum, which has many side chains consisting of mannose:galactose (2:1), or locust bean gum, which has many smooth parts consisting of mannose:galactose (3.5:1), respectively.

In particular, hydrogels containing XG and LBG show extremely high gel strength (Watanabe et al., 1994b), elasticity, and water retentiveness. Watanabe et al. prepared a hydrogel consisting of XG and LBG, and confirmed its applicability to external preparations (Watanabe et al., 1992; Watanabe et al., 1993; Watanabe et al., 1996).

In this study, in order to improve patient adherence for medications containing ISB, gel formulations consisting of XG, LBG, and agar (AG) were prepared and investigated their physicochemical properties.

2. Materials and Methods

2.1 Materials

ISB was purchased from Jinan Yuteng Pharma.co., Ltd. (Shandong, China). AG was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). XG and LBG were generously supplied by San-ei gen F.F.I., Inc. (Osaka, Japan). Various sweeteners were chosen to mask the bitterness of ISB. Thaumatin (THADA) was generously supplied by San-ei gen F.F.I., Inc. (Osaka, Japan). Stevia (STV) was generously supplied by Morita Kagaku Kogyo Co., Ltd., (Higashiosaka, Japan). D(+)-galactose (GAL) and xylitol (XYL) were purchased from Nacalai Tesque Co. Ltd. (Kyoto, Japan). β -D-lactose (LAC), sucrose (SUC), D(+)-glucose (GLU), and meso-erythritol (ERY) were purchased from Kanto Chemical Co., Inc. (Tokyo, Japan). D(-)-mannitol (MAN) and aspartame (ASP) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Trehalose (TRE) was generously supplied by Hayashibara Co., Ltd., (Okayama, Japan). All other chemicals were of analytical reagent grade.

2.2 Preparation of gels

A fixed amount of AG (0.3g) and various amounts of XG (0.02-0.08g) and LBG (0.02-0.08g) were physically mixed using a mortar and dissolved in 100mL of distilled water at 80°C. In the mixture, the total amount of XG and LBG did not exceed 1.0g. After dissolving the mixture completely, it was poured into petri dishes and stored at 25°C for 24 hours to gelate. The composition of the gel is shown in Table 1 and 2. First, the mixture ratio of XG and LBG was changed with the constant amount of AG (Table 1). Second, the mixture ratio of XG and LBG was kept constant, and the amount of AG was changed (Table 2).

Table 1. The composition of gels without ISB

| Sample | AG (g) | XG (g) | LBG (g) | Purified water (mL) |
|--------|--------|--------|---------|---------------------|
| 8:2 | 0.3 | 0.08 | 0.02 | 100 |
| 7:3 | | 0.07 | 0.03 | |
| 6:4 | | 0.06 | 0.04 | |
| 5:5 | | 0.05 | 0.05 | |
| 4:6 | | 0.04 | 0.06 | |
| 3:7 | | 0.03 | 0.07 | |
| 2:8 | | 0.02 | 0.08 | |

Table 2. The composition of gels

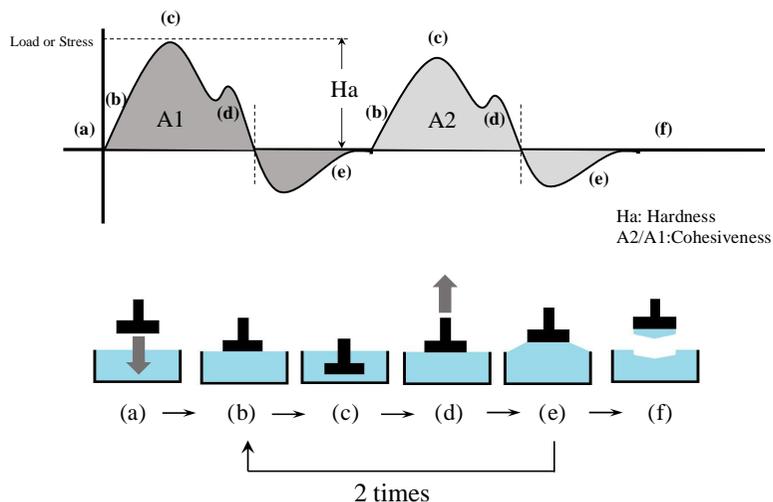
| Sample No. | AG (g) | XG (g) | LBG (g) | 70% w/v ISB solution (mL) or Purified water (mL) |
|------------|--------|--------|---------|--|
| AG 0.25 | 0.25 | 0.05 | 0.05 | 100 |
| AG 0.30 | 0.30 | | | |
| AG 0.35 | 0.35 | | | |
| AG 0.40 | 0.40 | | | |
| ag 0.25 | 0.25 | 0.03 | 0.03 | |
| ag 0.30 | 0.30 | | | |
| ag 0.35 | 0.35 | | | |
| ag 0.40 | 0.40 | | | |

2.3. Evaluation of gel properties

2.3.1 Texture profile analysis

The texture profiles and the elasticity modulus of the gels were carried out using a creep meter (Rheoner II; Yamaden Co., Ltd. Tokyo, Japan) with a load cell of 20 N in full scale at room temperature. A fixed volume of the gel was placed in a container of stainless steel with a diameter and depth of 45 mm and 25 mm, respectively in the texture profiles. In this assessment, a Teflon® plunger (diameter: 20mm) was used for pushing on the surface of the gel (Fig. 1). The top of the plunger was dipped to a depth of 5 mm, and the plunger was pulled up at a speed of 10 mm/s. The hardness was measured when the plunger compressed the gel, and the adhesiveness was measured when the plunger was completely separated from the surface of the gel. Finally, the cohesiveness was calculated by dividing the A2 value by the A1 value.

Figure 1. Schematic view of the texture profile.



Sample gel (diameter, 0.5 cm, length, 5.5 cm) was compressed with the “square with rounded two corners” shaped Teflon® plunger at definite speed (1 mm/sec), and the elastic modulus were measured (Figure 2a,b). Figure 2c shows the typical waveform of elastic modulus obtained in this study. In Figure 2c, the slope of tangent at the initial gradient (line 1) was defined as the “initial elastic modulus”, and a slope of tangent 2 was defined as the “apparent elastic modulus”. The slope of line 1 corresponds to “hardness”, and that of line 2 corresponds to “firmness”, respectively.

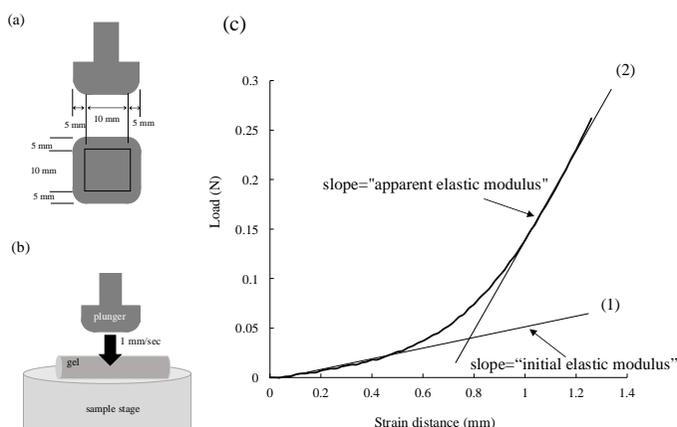


Figure 2. Schematic view of elastic modulus of gels.

(a) Schematic view of the using plunger, (b) Schematic view of the measurement, (c) The calculation of the elastic modulus

2.3.2 Evaluation of gel syneresis

Spherical gels (diameter of 25mm) were prepared in ice tray. The gels were placed in a nylon bag, and stored in a desiccator containing silica gel. The diameter of the gel was measured with a vernier caliper for seven days every 24 hours (from day 0 to day 7). The syneresis rate of the gel was calculated by the volume change of the gel using the following equation:

$$\text{The syneresis rate of the gel (\%)} = (1 - V_x/V_0) \times 100 \quad (1)$$

V_0 : The volume of gel at day 0, V_x : The volume of gel at day X

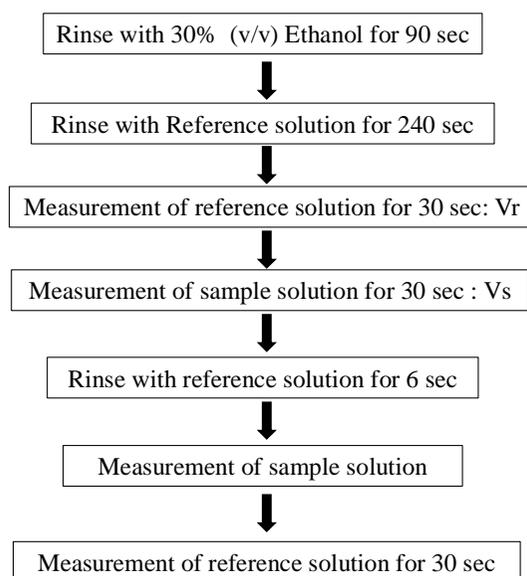
2.3.3 Evaluation of the stability of the ISB gels

ISB gels were prepared and stored in an airtight container at 23°C. The concentration of ISB in the gels was measured using an optical rotation method every 24 hours (from day 0 to day 7) using a polarimeter (P-1030; JASCO Corporation, Tokyo, Japan) at a wavelength of 589 nm in a cuvette of 100 mm length at 20°C (Kricheldorf and Probst, 1995).

2.4 Evaluation of the bitterness of ISB preparations

ISB was dissolved to 70%(w/v) solution with 10mM KCl. For sweetening, THADA was added at 0.05%(w/v), STV and ASP were added at 0.5%(w/v), and others were added at 5%(w/v) in 70%(w/v) ISB solution or ISB gel, respectively. When gels were measured with a taste-sensing system, they were crushed using a mill (TK-AM5, Tokken, Inc. Kashiwa, Japan).

The taste-sensing system (TS-5000Z, Intelligent Sensor Technology Co. Ltd, Atsugi, Japan), was used to measure the electric potential of ISB and various sweeteners. AC0, which is the bitterness sensor of aftertaste for medicines, was used as the lipid/polymer membrane. The measurement procedure in this study is shown in Fig. 3. KCl solution (30 mM) containing 0.3 mM tartaric acid was used as the reference solution, and to rinse the electrodes after every measurement. First, the electrode was dipped into the reference solution and the electric potential (mV) obtained was defined as V_r . Then, the electrode was dipped into the sample solution and the electric potential (mV) obtained was defined as V_s . In this study, the effect of masking was evaluated using the difference of V_s and V_r , which represents an evaluation of first taste.



*Relative value (R) = $V_s - V_r$

Figure 3. The measurement procedure of taste-sensing system.

2.5 Dissolution behavior of ISB from gels (dissolution test)

The dissolution of ISB from gels with a weight of 30 g was evaluated in 500 mL of distilled water (pH 5.5). Dissolution was measured using the "paddle method" from the Japanese Pharmacopoeia 16th edition. Then, 200 or 800 polystyrene beads (size of one quarter inches, diameter of 6.35 mm) were added in a vessel using the "paddle-beads method" described by Hanawa et al. (Hanawa et al., 1995; Hanawa et al., 1996). The paddle speed was 100 rpm, and the temperature of the test solution was 37°C. The gel was placed into the cube container with mesh (the mesh size was 3.5 × 3.5 mm), and was then pushed out into a vessel. The ISB concentration was then measured by a polarimeter. Measurements were carried out in triplicate and the mean and standard deviation were calculated.

3. Results and Discussion

3.1 Evaluation of gel properties

The hardness of gels is an important factor for the evaluation of their texture and whether it can be swallowed. Fig. 4 shows the hardness, adhesiveness and cohesiveness of the gels prepared in various mixing ratios of XG and LBG. Between XG:LBG=8:2-5:5, the hardness fluctuates between 15,000 and 18,000 N/m². When the mixing ratio of LBG was 50% or more, the hardness decreased with an increase of LBG ratio. Watanabe et al. described that the mixing ratio of XG and LBG which exerts the maximum synergistic effect was 1:1 (Watanabe et al., 1992). Varying ratios of LBG have been shown to influence gel structure, in that gel strength suddenly decreased at certain ratios (Watanabe et al., 1992; Watanabe et al., 1993; Watanabe et al., 1996; Copetti et al., 1997; Hishikawa et al., 2016). It is believed that the structure of the straight chain of LBG and the non-straight chain of XG associate at a ratio of 1:1 (Copetti et al., 1997). In the case of this study, AG has been added to the mixture of XG and LBG (Table 1), the reason for not showing the highest hardness at XG:LBG=1:1 is considered to be due to the fact that the coexistence of AG might impair the synergistic effect. The patients felt ill with MD have to take 20-30 mL each time. In response to this, the amount of gel which must be taken would also increase. In the gel formulation, it is supposed that almost all patients would crush the gel in their mouth when they take. When taken into consideration of practical use, we looked on cohesiveness as the most important factor to prepare the gel which has properties widely acceptable among people of all age groups. Cohesiveness is one of the characteristics typified by an example of chewing gum, and it imparts energy for chewing solid food until it can be swallowed. The lower cohesiveness is, the easier to chew and swallow are. When focusing on cohesiveness, it was considered that the mixing ratio at XG:LBG=1:1 is appropriate for the ISB gel, the following study was carried out by the gel of this ratio. Also in this study, the addition of ISB to gel attenuates the gel strength, it seemed that the existence of ISB impaired the interaction between molecular chains forming the gel network. Fig. 5 shows the texture profile of gels when the amount of XG and LBG changed and added ISB into these gels. When the amount of added AG increased, the hardness of the gels increased, regardless of the amount of XG and LBG (0.05g or 0.03g) (Fig. 5a). However, the hardness of gels decreased at 0.03g AG when the amount of XG and LBG was 0.03g and 0.05g (Fig. 5a). It has been reported that when XG and LBG are mixed, gel strength increases. Furthermore, when the mixture ratio is 1:1 (the weight ratio), gel strength is at the maximum.

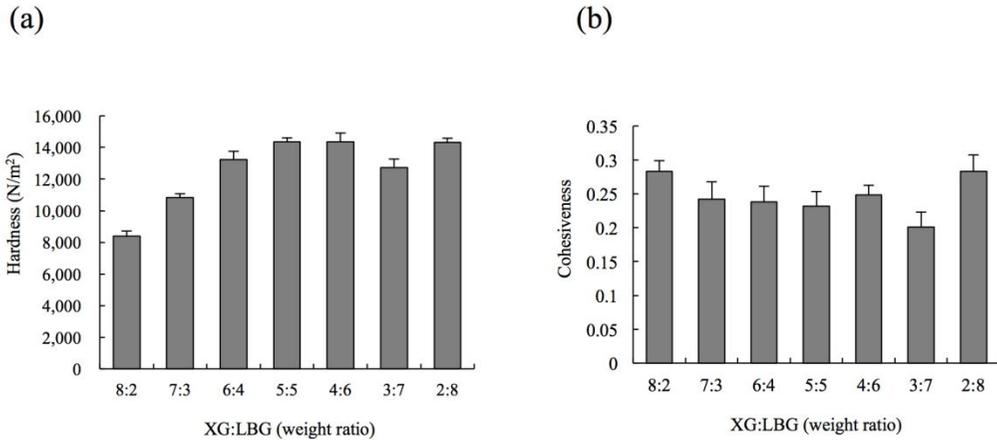


Figure 4. The texture profile of gels.
 (a) Hardness of gels, (b) Cohesion of gels

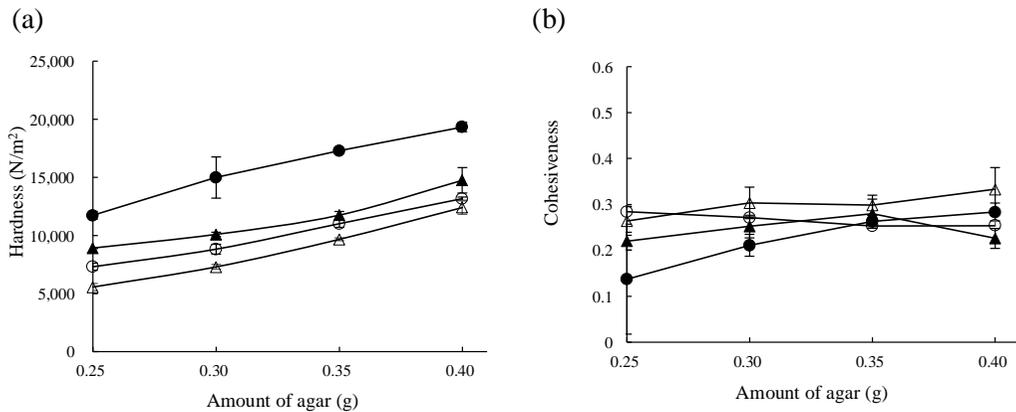


Figure 5. The texture profile of gels in the amount of addition of various AG.
 (a) Hardness of gels, (b) Cohesion of gels, ●: AG, ▲: ag, ○: AG-ISB, △: ag-ISB

The adhesiveness had the tendency to increase with AG. However, the addition of ISB did not have a great influence. In this study, the cohesiveness of the gels increased with increasing amounts of XG, LBG, and AG (Fig. 5b). Adhesion energy increased when ISB was added to the gels; however, it only slightly changed when the content of AG increased. Since the easiness for chewing and/or swallowing of food has to do a lot with the physicochemical properties of foods, the “elastic modulus” is the important indicator which indicates the firmness of foods (Fujii et al., 2001; Yoshimura et al., 2002; Onodera et al., 2011).

Therefore, the elasticity was considered to affect the easiness to swallow, and the elastic modulus of each gel was measured (Fig. 6). Fig. 6 depicts the “initial elastic modulus” and the “apparent elastic modulus” of AG0.03 and AG0.05. In every gel, the “initial elastic modulus” increased with adding of ISB. On the other hand, the “apparent elastic modulus” decreased with adding of ISB. Especially, as for AG0.03, the decrease of the “apparent elastic modulus” was significant. That is, while the elasticity might increase by adding ISB, the gel formation of inner part seemed to be incomplete. Furthermore, between XG:LBG=0.03:0.03 and 0.05:0.05, there were no significant differences in the “initial elastic modulus”. On the other hand, with the addition of ISB to XG:LBG=0.03:0.03, the “apparent elastic modulus” significantly decreased. Though the reason for this significant decrease could not be clarified, existence of the excess amount of ISB might impair to form comparatively rigid gel. That is, once gel was deformed by the compression, the restoration to original shape might be impaired by ISB.

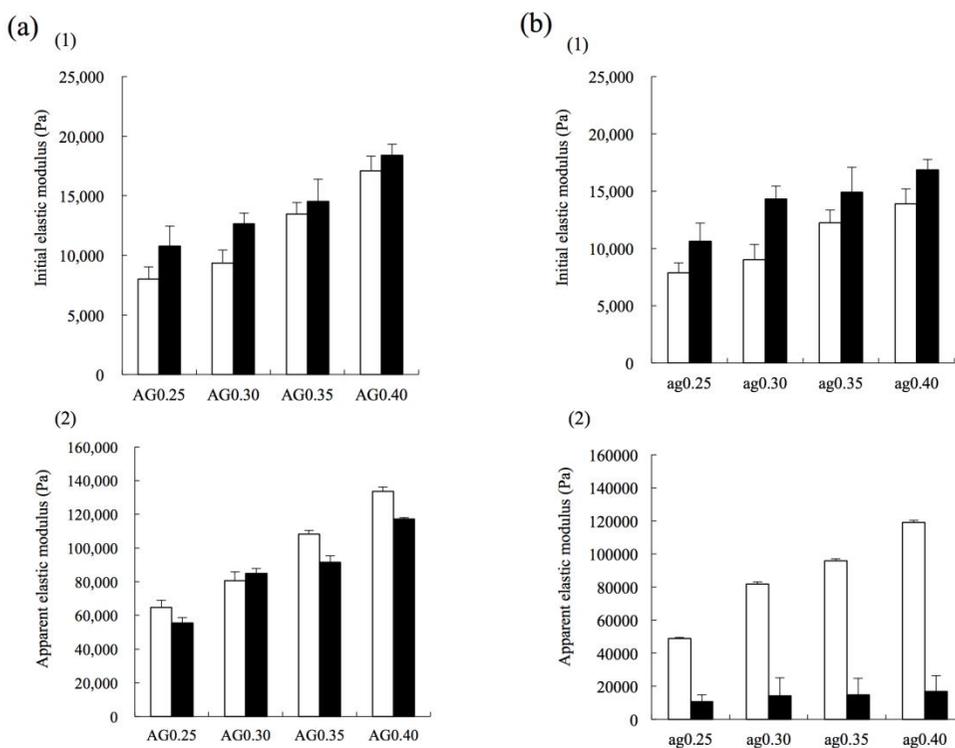


Figure 6. The elasticity modulus of gels.

(a) XG:LBG=0.05:0.05, (b) XG:LBG=0.03:0.03,

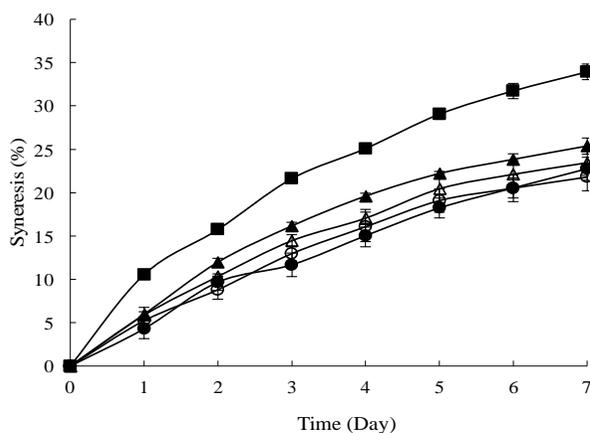
(1)Initial elastic modulus, (2) Apparent elastic modulus, □: without ISB, ■: containing ISB

3.2 Evaluation of syneresis and stability of ISB gels

With the composition of AG0.25, ag0.25 and ag0.30, the preparation of spherical gels were difficult, and not able to determine their diameter.

The syneresis rate of the AG0.30 gel was the highest (approximately 34%). In other words, gels containing small amount of AG seemed to tend to release water and occur the syneresis (Fig. 7). Meanwhile, increases in the amount of added XG and LBG did not influence the syneresis of the gels, it seemed that the water in the gels was remained by the gelling agents. Furthermore, although XG and LBG were involved in retaining water in the gels, changes in their amounts did not change the water retention of the gels.

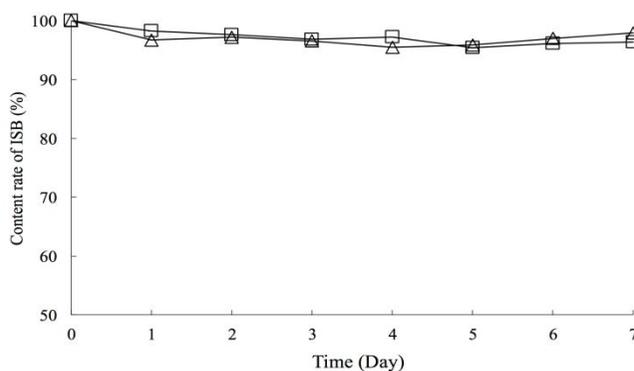
Figure 7. The syneresis behavior of ISB gels at various storage conditions.



■: AG0.30, ▲: AG0.35, ●: AG0.40, △: ag0.35, ○: ag0.40

Further analysis indicated that the water retentiveness depended on the amount of added AG. Water evaporation to the air appeared to be related to the syneresis rate, as syneresis was observed. Further evaluation of the syneresis of gels over long term periods is necessary. The content of ISB in the gels were more than 95% after preparations at room temperature for 7 days (Fig. 8). The ISB gels remained stable for 7 days after preparation. The stability of the ISB gels over long periods should be further evaluated in the future.

Figure 8. Stability of ISB containing various amount of agar.



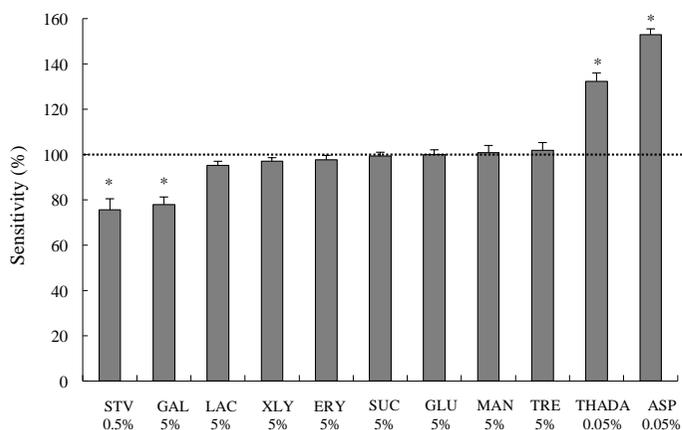
□: ag0.30, △: ag0.35

3.3 Evaluation of the bitterness of ISB

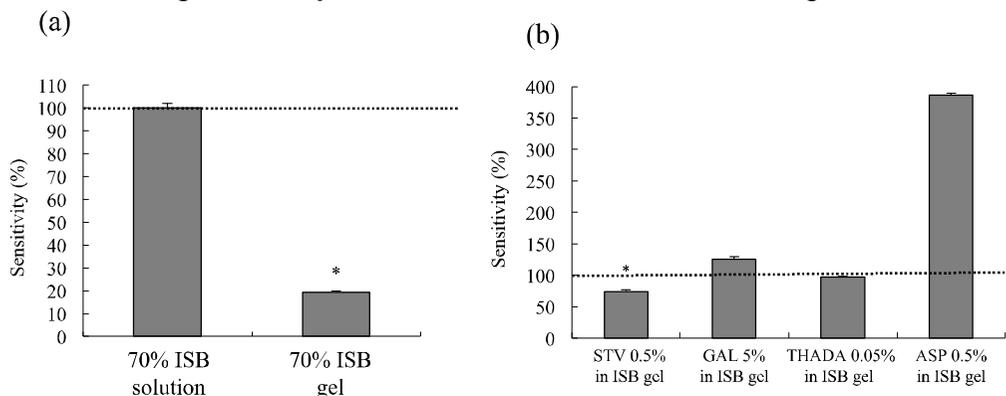
Fig. 9 shows the percentage of the bitterness sensitivity of various sugars. It was assumed that the bitterness sensitivity of the 70%(w/v) ISB water solution was 100%. The bitterness sensitivity of 70%(w/v) ISB water solutions significantly decreased with the addition of 0.5%(w/v)STV, and 5.0%(w/v)GAL. However, for ASP and THADA, the bitterness sensitivity increased. ASP is approximately 200 times sweeter than SUC. Generally, the sweetness of the artificial sweetener appears slowly. In this study, the first taste was evaluated. Therefore, we considered that the relative value of ASP did not decrease. On the other hand, THADA is approximately 2,000–3,000 times sweeter than SUC and has a slow onset of sweetness that builds up to a maximum intensity, followed by a long, lingering sweet licorice-like aftertaste (Vishwanath and Tammi, 1991). In this study, we evaluated the sensation of first taste using the relative values. The relative values of THADA did not decrease, and ASP and THADA did not decrease the bitterness of ISB.

In this study, we discovered that the bitterness of ISB could be significantly controlled by certain preparations of the gels (Fig. 10a). The contact area of the sensor membrane decreased due to the preparation of the gels, and when the ISB gel with added STV [0.5%(w/v)] was compared with the ISB gel with no added sweeteners, the sensitivity of the bitterness decreased by 25%(w/v) (Fig. 10b). The hardness, adhesiveness, and cohesiveness of the ISB gels did not change with the addition of 0.5%(w/v)STV (date not shown). Thus, STV appears to be a useful addition to the gels in order to mask the bitterness of ISB without affecting the physical properties of the gels.

Figure 9. The sensitivity of various sugars added in the gel basis solution.



The sensitivity of the 70%(w/v) ISB solution was defined as 100%. Means \pm S.D. (n=3), statistical analysis was performed by *t*-test. *: $p < 0.05$ vs. 70%(w/v) ISB aqueous solution. All percentage shows w/v.

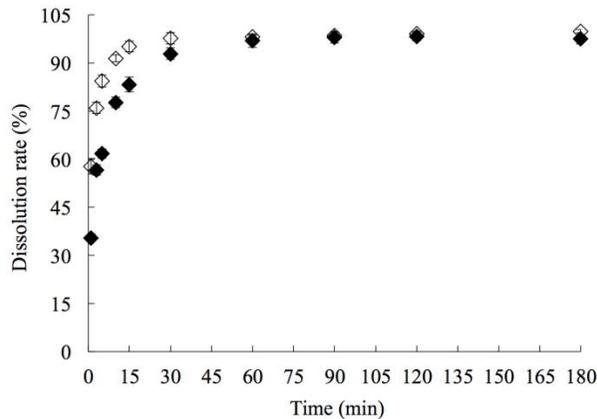
Figure 10. Depression effect of the bitterness of ISB gels.

(a) 70%(w/v)ISB aqueous solution and 70%(w/v)ISB gel, (b) Various sugars added in gels
 (a)The sensitivity of the 70%(w/v) ISB solution was defined as 100%. Means±S.D.(n=3), statistical analysis was performed by *t*-test. *: $p < 0.05$ vs. 70%(w/v) ISB aqueous solution.
 (b) The sensitivity of the 70%(w/v)gel was defined as 100%. Means±S.D. (n=3), statistical analysis was performed by *t*-test. *: $p < 0.05$ vs. 70%(w/v) ISB gels.All percentages show w/v.

3.4 Dissolution behavior of ISB from gels

The dissolution behavior of ISB from the gels was evaluated using the paddle-beads method. In this study, the polystyrene beads were added to a vessel in the dissolution test. The paddle-beads method assumes that the motion of the beads in the *in vitro* apparatus reflects the *in vivo* GI mobility. When 200 beads were used, this was assumed to reflect the conditions prior to a meal. In contrast, when 800 beads were used, this was used to reflect the conditions after a meal. Fig.11 shows main dissolution behavior of gels. In addition, Table 3 shows the average of 90% dissolution time of ISB from various gels. As for the release of ISB from various gels using 800 beads in the vessel was faster than using 200 beads. All the gel dissolved with the release of ISB. When the number of beads increased, the disintegration of the gel was faster because the shearing force of the gel increased. In other words, the state after a meal makes the release of ISB from gels faster. Differences in the composition of the gels or the addition of STV did not influence the dissolution behavior of ISB (Table 3).

Figure 11. Typical dissolution profiles of ISB from AG0.35(with STV) by crushing with various number of polystyrene beads.



Means±S.D. (n=3), The number of beads were ◆: 200 and ◇: 800, respectively.

Table 3. The average of 90% dissolution time of ISB from various gels

| number of beads | 90% dissolution time (min) | | | |
|-----------------|----------------------------|--------|-------------|--------|
| | with STV | | without STV | |
| | AG0.35 | ag0.35 | AG0.35 | ag0.35 |
| 200 | 25.5 | 24.2 | 27.4 | 24.2 |
| 800 | 9.0 | 10.0 | 9.5 | 9.5 |

n=3

4. Conclusion

ISB has a bitter taste and the improvement in drug adherence is of primary importance. In this study, we prepared different compositions of gels in order to mask the bitterness of ISB. In addition, we focused on the synergy of the physical properties of the gels through the combination of XG and LBG in the gels. When the composition of the gels was XG:LBG=1:1 (the weight ratio), the cohesiveness of the gels became the lowest, and syneresis of the gels decreased with increasing amounts of added AG. In ISB gels in results of cohesiveness and syneresis studies, the most suitable prescription was AG:XG:LBG = 35:3:3 (the weight ratio). This preparation reduced the bitterness of ISB in the prepared gels. Furthermore, the bitterness of ISB was reduced with the addition of 0.5%(w/v)STV. In contrast, THADA, which is 2000-8000 times sweeter than SUC, did not reduce the bitterness of ISB. The results of these evaluations used relative values as an evaluation of first taste.

We also considered that the contents of the stomach may affect the dissolution of ISB from gels. Our findings indicate that ISB is quickly dissolved after a meal, the contents of which appear to influence the absorption and the efficacy of ISB. In conclusion, the addition of STV in ISB gels can reduce the bitterness of ISB. Furthermore, the addition of STV did not affect the dissolution of ISB or gel stability, and thus this preparation should be considered as a promising method to increase ISB patient compliance.

Acknowledgments

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