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The Effect of Food Thickeners on the Bitterness and Dissolution of Amlodipine Besilate Powder When Co-Administered with Thickeners to Patients with Dysphagia

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Abstract

Purpose: The present research was performed to evaluate the effect of food thickeners on the bitterness and dissolution of bitter drugs when co-administered to patients with dysphagia. **Methods:** Amlodipine besilate (AMPB) powder was used as a model drug. Starch- and xanthan gum-based food thickeners were examined, with swallowing-aid jelly as a reference. The line-spread test (LST), texture prolife analysis (TPA) were done firstly. In related to AMPB powder mixed with food thickeners solution, a conventional dissolution test simulating the oral cavity was performed, the amlodipine (AMP) concentration and taste sensor output for dissolved medium versus time profiles were developed. The dissolution test at pH 1.2 and 4.5, representing typical gastric conditions for younger or elderly people, was performed in two kinds of thickener solution and swallowing-aid jelly those were mixed with AMPB powder. **Results:** LST demonstrated that xanthan gum-based food thickeners fulfilled the requirements for patients with dysphagia but that starch-based food thickeners did not. In TPA, hardness and adhesiveness decreased proportionally as the concentration increased for both kinds of food thickener. Conventional dissolution test simulating oral cavity demonstrated the following bitterness ranking: xanthan gum-based food thickener < starch-based food thickener < swallowing-aid jelly. In dissolution test at pH 1.2 and 4.5, starch-based thickener and swallowing-aid jelly mixed with AMPB powder showed complete AMP dissolution. However, xanthan gum-based food thickeners mixed with AMPB powder showed about only 60% AMP dissolution after 120 minutes. **Conclusion:** Although xanthan gum-based food thickeners were successful in masking the bitterness of AMP, they may reduce its bioavailability in humans. The 7.1 and 4.7 (w/v) % starch-based thickener show bitterness inhibition under simulated oral cavity conditions and complete dissolution of AMP under simulated gastric conditions.

Keywords

Food Thickener, Xanthan Gum-Based Food Thickener, Starch-Based Food Thickener, Taste Sensor, Bitterness, Amlodipine Besilate Powder

1. Introduction

Food thickeners are used to increase the viscosity or the adhesiveness of foodstuffs [1]. They may be used to improve the texture of foods or drinks or to aid swallowability [2] [3], especially important for the elderly or patients with dysphagia. Food thickeners have been used with various pharmaceuticals [4] to improve the texture of an oral dosage formulation and/or reduce its bitterness in the oral cavity.

Xanthan gum-based food thickeners have been reported to affect drug dissolution in the gastrointestinal tract [5]. In an earlier study, orally taken magnesium oxide tablets co-administered with food thickeners were found to be excreted intact [6], while, in another study, magnesium oxide tablets soaked in xanthan gum- or gua gum-based food thickener for 10 or 30 minutes did not completely disintegrate in a 120-minute dissolution test under acidic conditions [7]. Thus, co-administration of food thickeners with medicines may reduce their bioavailability [8].

Another important issue involving food thickeners is bitterness. In our previous paper [9] we showed that, when basic macrolide medicines were mixed with acidic swallowing-aid jelly, the dissolution of the macrolide medicine was dramatically enhanced, resulting in severe bitterness. When macrolide medicines were mixed with a swallowing-aid jelly at neutral pH, no increase in bitterness was found, owing to the low solubility of macrolides in neutral pH jelly. Thus, the choice of an appropriate swallowing-aid jelly as typical additive for swallowing aid could successfully inhibit the bitterness of embedded macrolide medicines.

If food thickeners can successfully mask the bitterness of a medicine, they will obviously aid good adherence to the medicine, but if they cannot effectively mask or even enhance the bitterness of the medicine, this will reduce adherence or, in the worst case, result in rejection of the medicine. Alternatively, the association of bitterness with the food thickener may lead to rejection of the food thickener containing the medicine. Therefore, one aim of this study was to evaluate quantitatively the bitterness of a model medicine mixed with commercial food thickeners.

The most desirable result is complete bitterness inhibition of a mixture of the medicine with the food thickener, accompanied by complete drug dissolution under the conditions found in the stomach.

The texture of kind or concentration of thickener seem also important for acceptance by individual patients. In the present study, therefore, we have tried to clarify three issues as follows:

Firstly, we evaluated the thickness and texture of commercially available starch- and xanthan gum-based food thickeners using the line spread test (LST) and texture profile analysis (TPA), respectively.

Secondly, small-scale conventional dissolution tests, under simulated oral cavity conditions, were performed with powdered AMPB mixed with the two types of food thickener. The bitterness of the dissolved solutions was measured using an artificial taste sensor and by HPLC. Commercial swallowing-aid jelly was used as a reference compound.

Thirdly, dissolution tests at pH 1.2 and 4.5 were performed with mixtures of AMPB powder and the two types of food thickener, with swallowing-aid jelly as reference. Bioavailability was evaluated under these conditions, which were assumed to represent the gastric conditions of elderly and younger people, respectively. First-order dissolution rate constant of AMP were calculated, based on conventional dissolution test results under conditions simulating the oral cavity and under gastric pH conditions; bitterness suppression and drug dissolution were confirmed quantitatively.

2. Materials and Methods

2.1. Materials

AMPB powder was purchased from Tokyo Chemical Industry Co., Ltd, Japan, Starch-based food thickener granules was Toromerin, purchased from NUTRI Co., Ltd, Japan, xantham-based food thickener was Tsururinko Quickly, Clinico Co., Ltd, Japan, swallowing-aid jelly was Ryukakusan Co., Ltd, Japan.

2.2. Preparation of Thickener Solution

Starch-based food thickener granules (Toromerin, purchased from NUTRI Co., Ltd, Japan) were mixed well with purified water and allowed to stand for 2 minutes before preparing 2.4, 4.7 and 7.1 (w/v) % solutions according to the method described in the package insert. AMPB (6.93 mg) was mixed into each of these solutions. Xantham-based food thickener (Tsururinko Quickly, Clinico Co., Ltd, Japan) was mixed well with purified water and allowed to stand for 2 minutes before preparing 1.0, 2.0 and 3.0 (w/v) % solutions according to the method described in the package insert. AMPB (6.93 mg) was mixed into each of these solutions. As reference, 6.93 mg of AMPB was mixed with (wrapped in) 5 g swallowing-aid jelly (Ryukakusan Co., Ltd, Japan).

2.3. Line Spread Test (LST) of Two Types of Food Thickener Solution and Swallowing-Aid Jelly

The thickness of the two kinds of food thickener was performed according to

The Japanese Society of Dysphagia Rehabilitation recommendations [10]. The samples tested were: starch-based food thickener solutions (2.4, 4.7 and 7.1 (w/v) %), xanthan-based food thickener solutions (1.0, 2.0 and 3.0 (w/v) %) and 5 g swallowing-aid jelly. The test was performed as follows: an empty cylindrical ring (30 mm diameter) was placed in the centre of concentric circles drawn on a horizontal sheet. A sample of food thickener or swallowing-aid jelly (20 mL) was poured into the inside of the ring and held there for 30 seconds. The ring was then lifted vertically and the spread of the sample on the sheet with the concentric circles was evaluated after 30 seconds on a 6-point scale. The distance (mm) was determined as a mean value ± S.D. (n = 3). The standard criteria for high, medium and low concentrations were 32 - 30, 36 - 32 and 43 - 36 mm, respectively.

2.4. Texture Profile Analysis (TPA) of Two Types of Food Thickener Solution and Swallowing-Aid Jelly

TPA was carried out to evaluate the physical properties of the food thickener solutions using TA. XT plusC texture analyzer (Stable Micro Systems, Surrey, UK) [11]. The samples tested were: starch-based food thickener solutions (2.4, 4.7 and 7.1 (w/v) %), xanthan-based food thickener solutions (1.0, 2.0 and 3.0 (w/v) %) and 5 g swallowing-aid jelly. The TPA was performed according to the method used to determine the acceptability criteria for persons with difficulty swallowing, as published by the Japanese Consumers Affairs Agency [12]. The texture parameters were hardness, adhesiveness and cohesiveness. Textural properties were analyzed in two sequential "two-bite" compression tests with a cylindrical-shaped probe, diameter 20 mm, height 100 mm. All samples were compressed to 70% of their original length. The test speed was set to 10 mm/s. The values of hardness, adhesiveness and cohesiveness were calculated from the obtained profiles using software provided by Stable Micro Systems. The stress-strain curves for the two types of thickener and the swallowing-aid jelly were drawn using the data from the TA. XT plusC texture analyzer.

2.5. *In Vitro* Conventional Dissolution Test of AMPB Powder Mixed with Two Types of Thickener Solution and Swallowing-Aid Jelly and Their Bitterness Evaluation of Dissolved Medium by the Taste Sensor and HPLC

Aliquots of 6.93 mg powdered AMPB were precisely weighed and mixed with the starch-based food thickener solutions (2.4, 4.7 and 7.1 (w/v) %), xanthan gum-based food thickener solutions (1.0, 2.0 and 3.0 (w/v) %), and 5 g swallowing -aid jelly for 30 seconds. Portions weighing 5.0 g of each of the above mixtures, were wrapped in nylon mesh (N-No.255HD; material: nylon66, nylon fiber width 43 μm, mesh opening size 57 μm) and dipped in 20 mL water contained in a 50 mL glass beaker. A small bar magnet (4 × 10 mm) which rotated at 150 rev/min, was put in the bottom of the beaker. The water temperature was kept at 37˚C. Samples (20 mL) were taken from the mixture in the beaker after 5, 15, 30 and 60 seconds and the concentration of AMP in the dissolved medium was determined by HPLC (LC-2010C, Shimadzu Corp., Japan). The HPLC method was based on the Japanese Pharmacopoeia and a previous report [13]. An integrator (LC solution; Shimadzu Corp., Japan) and reverse-phase column (CAPCELL PAK C18 UG120 S5: 150 × 4.6 mm i.d.; OSAKA SODA Co., Ltd, Japan) were used for HPLC. The column temperature was kept at 25˚C. The mobile phase composition was methanol: potassium dihydrogen phosphate (41 → 10,000) (13:7, v/v) and the flow rate was 1.0 mL/min. Run time was 10 minutes. The ultraviolet detection wavelength was set at 237 nm. First-order dissolution rate constants for the food thickeners and swallowing-aid jelly were calculated from the dissolved AMP concentrations.

Taste sensor measurements of the dissolved solutions were performed as follows. The bitterness of the dissolved solutions was measured by the change in the membrane electric potential caused by adsorption (CPA) using taste sensor SA501 (Intelligent Sensor Technology Inc., Atsugi, Japan). In this study, the CPA of membrane AN0 was used, which is suitable for the evaluation of bitterness of basic substances. The taste sensor measurements were performed as described in previous articles [13] [14] [15] [16] [17].

2.6. Dissolution Test of AMP from Two Types of Thickener Solution and Swallowing-Aid Jelly, Those Containing AMPB Powder

In vitro dissolution tests of AMP from two types of thickener and swallowing-aid jelly were carried out using a conventional dissolution tester (PJ-62N, Riken's, Miyamoto Riken Ind., Co., Ltd., Osaka, Japan) according to the Japanese Pharmacopoeia, 17th edn. The test was done using the paddle method at 37˚C and 50 rev/min using 900 mL of both the first fluid (pH 1.2) and/or diluted Mcllvaine buffer (pH 4.5) [18]. At various time intervals, 2 mL aliquots were withdrawn and replaced by the same volume of fresh medium. The concentration of AMP was determined by HPLC as described above. First-order dissolution rates from the food thickeners and swallowing-aid jelly were calculated from the dissolved AMP concentrations.

3. Results and Discussion

3.1. Results

3.1.1. LST Evaluation of Two Kinds of Food Thickener Solution and Swallowing-Aid Jelly

Table 1 shows the results of the LST performed using 20 mL of starch-based food thickener solutions (2.4, 4.7 and 7.1 (w/v) %) and xanthan gum-based thickener solutions (1.0, 2.0 and 3.0 (w/v) %), with 20 mL of swallowing-aid jelly as reference compound. The xanthan gum-based thickener solutions (1.0, 2.0 and 3.0 (w/v) %) were all within the standard criteria for persons with difficulty swallowing, as published by The Japanese Society of Dysphagia Rehabilitation. However, only the 4.7% solution of starch-based food thickener fell within these criteria.

Table 1. Line Spread Test result

Sample	Mean value (mm)	Acceptability
Swallowing-aid jelly	30.89 ± 1.66	fit as high concentration thickener
Starch-based 7.1 (w/v) %	20.72 ± 0.70	not fit as high concentration thickener
Starch-based 4.7 (w/v) %	31.72 ± 0.80***	fit as medium concentration thickener
Starch-based 2.4 (w/v) %	43.89 ± 1.00***	not fit as low concentration thickener
Xanthan gum-based 3.0 (w/v) %	31.44 ± 0.39	fit as high concentration thickener
Xanthan gum-based 2.0 (w/v) %	34.72 ± 0.87	fit as medium concentration thickener
Xanthan gum-based 1.0 (w/v) %	40.33 ± 0.83***	fit as medium concentration thickener

The acceptability criteria for high, medium and low concentrations of thickener were 32 - 30, 36 - 32 and 43 - 36 mm, respectively. Data are presented as mean (n = 3) ± S.D. ***$p < 0.001$ vs. Starch-based thickener 7.1 (w/v) % (Tukey's test) or vs. Xanthan gum-based thickener 3.0 (w/v) % (Tukey's test).

3.1.2. TPA of Two Kinds of Food Thickener Solution and Swallowing-Aid Jelly

The values of hardness, adhesiveness and cohesiveness of the seven samples (three concentrations each of starch- and xanthan-based thickener solutions with swallowing-aid jelly as reference) are summarized in Table 2. The values of hardness and adhesiveness both increased with the concentration of food thickener. Of all the starch-based and xanthan-based thickener solutions, the 7.1 (w/v) % starch-based food thickener solution had the highest values for hardness, adhesiveness and cohesiveness of the seven samples.

3.1.3. *In Vitro* Conventional AMP Dissolution Test of AMPB Powder Mixed with Two Kinds of Thickener Solution and Swallowing-Aid Jelly and Bitterness Evaluation of the Dissolved Medium by HPLC and Taste Sensor Measurement

Figures 1(a)-(c) shows the dissolved AMP (%) versus time profiles for up to 60 seconds using swallowing-aid jelly (a) as a reference and three concentrations each of starch-based thickener (b) and xanthan-based thickener (c) solutions, all containing 6.93 mg AMPB. The dissolution amount (%) of the solutions was ranked as follows: swallowing-aid jelly = 2.4 (w/v) % starch-based thickener > 4.7 (w/v) % starch-based thickener > 7.1 (w/v) % starch-based thickener > 1.0 (w/v) % xanthan gum-based thickener > 2.0 (w/v) % xanthan gum-based thickener > 3.0 (w/v) % xanthan gum-based thickener. The first-order dissolution rate constants were calculated using the dissolution profiles as shown in Figure 1; these are summarized in Table 3. The ranking of the first-order dissolution rate constants were as follows: xanthan gum-based food thickener < starch-based food thickener < swallowing-aid jelly. The dissolution rate constants were ranked in inverse relation to the dissolved AMP amount (%) ranking, as shown in Figure 1.

The AMP dissolution % from AMPB powder mixed with the starch-based thickener solutions were significantly greater than those of xanthan gum-based thickeners, and their dissolution rate constants decreased as the concentration of

Table 2. Texture evaluation test result

Sample	Hardness (N/m²)	Adhesiveness (J/m³)	Cohesiveness
Swallowing aid jelly	865.17 ± 37.52	260.42 ± 104.94	0.51 ± 0.05
Starch-based 7.1 (w/v) %	3245.75 ± 189.46	2871.84 ± 304.87	0.80 ± 0.02
Starch-based 4.7 (w/v) %	1016.45 ± 46.12***	1197.11 ± 70.78***	0.72 ± 0.03
Starch-based 2.4 (w/v) %	342.36 ± 55.55***	10.07 ± 11.33***	0.79 ± 0.13
Xanthan gum-based 3.0 (w/v) %	777.58 ± 32.74	107.36 ± 18.75	0.72 ± 0.03
Xanthan gum-based 2.0 (w/v) %	403.40 ± 15.01**	21.75 ± 6.77	0.71 ± 0.02
Xanthan gum-based 1.0 (w/v) %	318.47 ± 6.50***	17.00 ± 12.02	0.78 ± 0.07

Data are presented as mean (n = 3) ± S.D. **$p < 0.01$, ***$p < 0.001$ vs. Starch-based thickener 7.1 (w/v) % (Tukey's test) or vs. Xanthan gum-based thickener 3.0 (w/v) % (Tukey's test).

Table 3. The first-order dissolution rate constants for AMP dissolution % versus time profile for swallowing-aid jelly and two kinds of thickeners in a dissolution test under conditions simulating the oral cavity

Sample	Dissolution rate constants (mean ± S.D. (min^{-1}))
Swallowing aid jelly	0.0175 ± 0.0061
Starch-based 7.1 (w/v) %	0.0003 ± 0.0004***
Starch-based 4.7 (w/v) %	0.0039 ± 0.0017**
Starch-based 2.4 (w/v) %	0.0179 ± 0.0043
Xanthan gum-based 3.0 (w/v) %	0.0000057 ± 0.0000032
Xanthan gum-based 2.0 (w/v) %	0.0000022 ± 0.0000003
Xanthan gum-based 1.0 (w/v) %	0.0000062 ± 0.0000027

Data are presented as mean (n = 3) ± S.D. **$p < 0.01$, ***$p < 0.001$ vs. Starch-based thickener 2.4 (w/v) % (Tukey's test).

starch-based thickener increased. When an AMP solution was used as sample, it was completely dissolved into the water (medium) within 30 seconds through the nylon mesh (data not shown). The fast dissolution and higher dissolution % were obtained for swallowing-aid jelly.

Figure 2 shows taste sensor measurement data for up to 60 seconds for swallowing-aid jelly (left) as reference and three concentrations each of starch-based thickeners (middle) and xanthan-based thickeners (right) solutions, all containing 6.93 mg AMPB. The taste sensor value ranking was as follows: 2.4 (w/v) % starch-based thickener > swallowing-aid jelly > 4.7 (w/v) % starch-based thickener > 7.1 (w/v) % starch-based thickener > 1.0 (w/v) % xanthan gum-based thickener > 2.0 (w/v) % xanthan gum-based thickener > 3.0 (w/v) % xanthan gum-based thickeners. The dotted line (8.62 mV at vertical axis) shows the taste sensor threshold for bitterness, using the bitterness of quinine (0.03 mM) as bitterness standard.

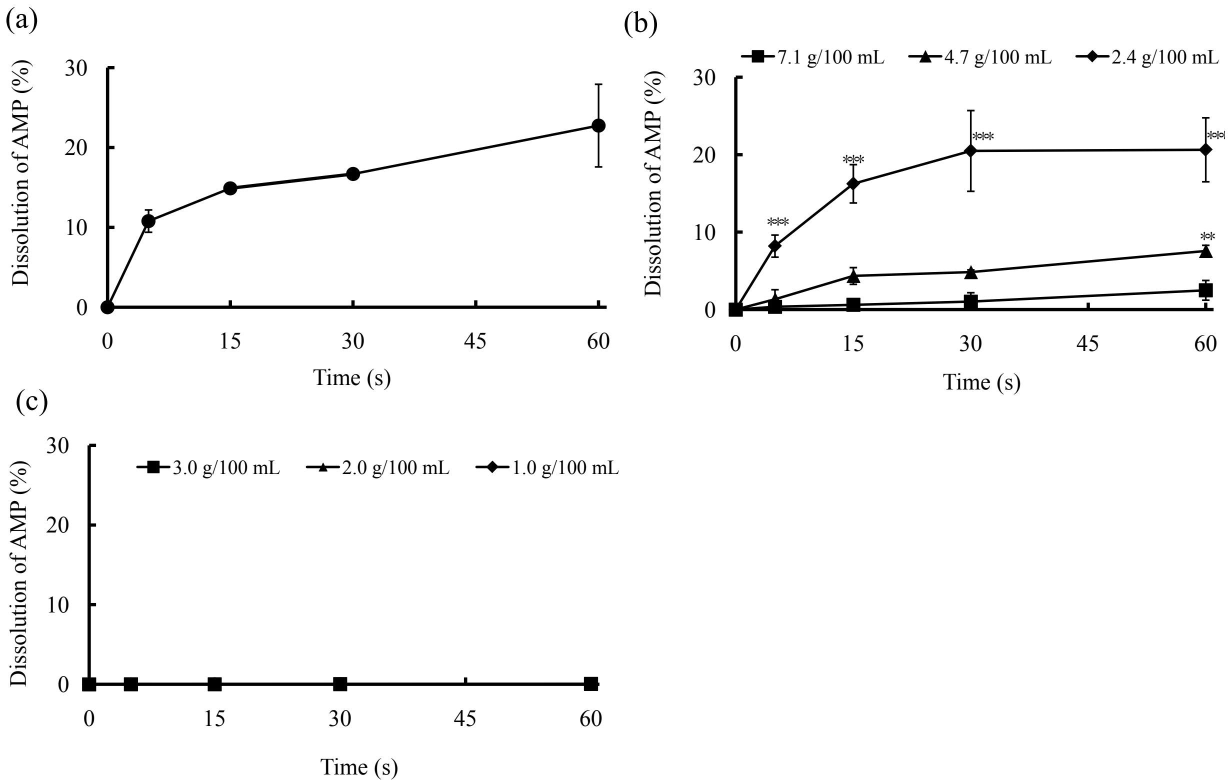

Figure 1. Dissolved AMP (%) versus time profile of AMPB powder mixed with swallowing-aid jelly and two kinds of thickener. (a) Swallowing-aid jelly; (b) Starch-based thickener; (c) Xanthan gum-based thickener. n = 3, mean ± S.D. $^{**}p < 0.01$, $^{***}p < 0.001$ vs. 7.1 (w/v) % substances (Tukey's test).

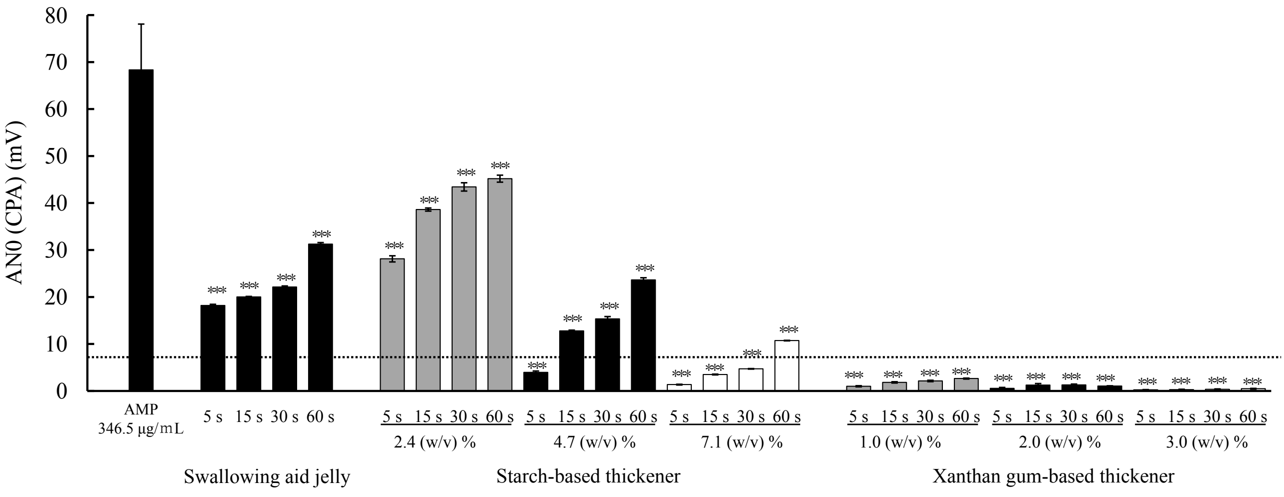

Figure 2. Taste sensor outputs (CPA) in response to AMPB powder mixed with jelly or thickener solution. n = 3, mean ± S.D. $^{***}p < 0.001$ vs. AMP 346.5 μg/mL (Tukey's test).

3.1.4. The Dissolution Test for Two Types of Thickener and Swallowing-Aid Jelly Containing AMPB Powder at pH 1.2 and pH 4.5

The dissolution profiles of AMP from swallowing-aid jelly and two kinds of thickener, all containing 6.93 mg AMPB at pH 1.2 and pH 4.5, are shown in Figures 3(a)-(c). Under both pH conditions, the mixture of AMPB with starch-based

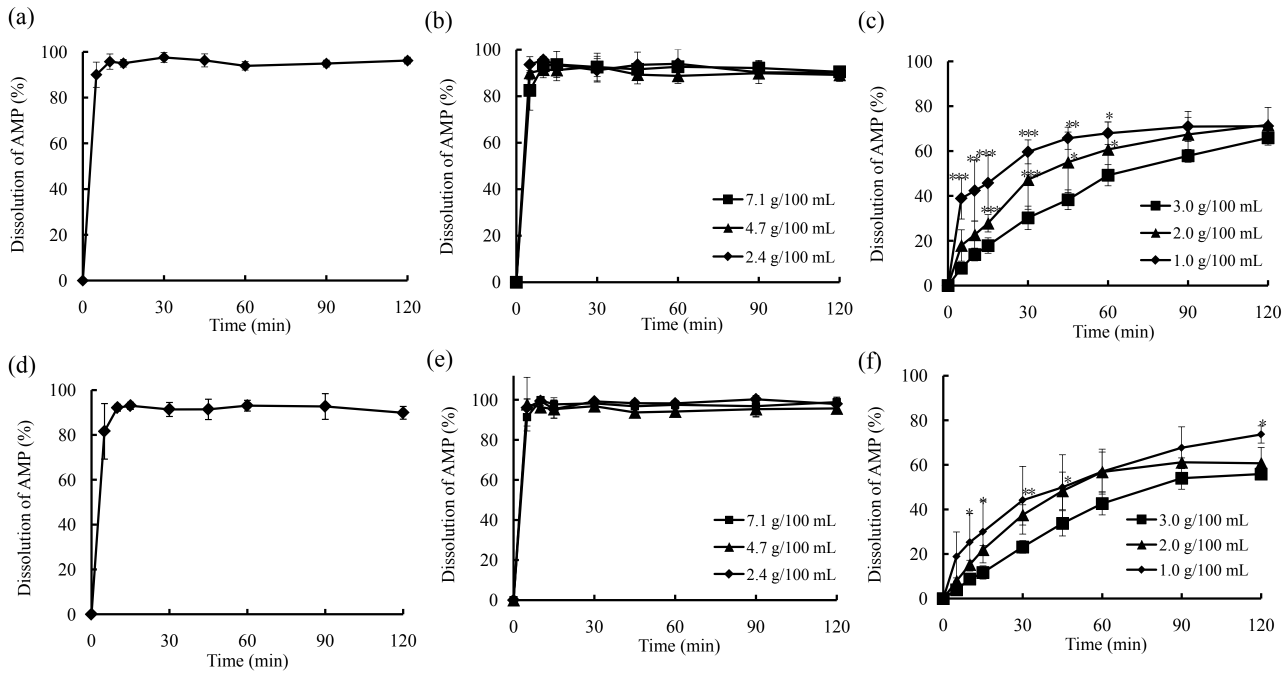

Figure 3. Dissolution profiles of AMP from swallowing-aid jelly and two kinds of thickener solution containing AMPB powder at different pHs. (a) Swallowing-aid jelly (pH1.2); (b) Starch-based thickener (pH1.2); (c) Xanthan gum-based thickener (pH1.2); (d) Swallowing-aid jelly (pH4.5); (e) Starch-based thickener (pH4.5); (f) Xanthan gum-based thickener (pH4.5). n = 3, mean ± S.D. *p < 0.05, **p < 0.01, ***p < 0.001 vs. Xanthan gum-based thickener 3.0 (w/v) % (Tukey's test).

thickener or swallowing-aid jelly showed 100% dissolution. However, in all concentrations of xanthan gum-based thickener mixed with AMPB powder was much smaller than those of AMPB mixed with starch-based thickener or swallowing-aid jelly. At 120 minutes, only about 60% - 70% dissolution was observed, with 30% - 40% remaining undissolved.

The first-order dissolution rate constants were calculated from the dissolution profiles shown in Figure 3, and are summarized in Table 4. The ranking of the first-order dissolution rate constants were as follows: xanthan gum-based food thickener < starch-based food thickener < swallowing-aid jelly. The dissolution rate constants ranked inversely with the dissolution amount % ranking as shown in Figure 2.

The smallest dissolution rate constants were observed for xanthan gum-based thickener, as shown in Table 4.

3.2. Discussion

Regarding to LST evaluation of two kinds of food thickener solution and swallow ing-aid jelly, only 4.7% solution of starch-based food thickener fell within these criteria. This suggests that the LST criteria are determined based on the use of xanthan gum-based thickener solutions [19] [20].

The data of TPA suggest that patients may need considerable powers of chewing and swallowing when 7.1 (w/v) % starch-based food thickeners are used and that more dilute starch-based food thickeners may be more suitable for patients with

Table 4. The first-order dissolution rate constants for AMP dissolution % versus time profile for swallowing-aid jelly and two kinds of thickener solution containing AMPB powder in pH 1.2- and 4.5-buffered dissolution test.

Sample	Dissolution rate constants (mean ± S.D. (min^{-1}))	
	pH 1.2	pH 4.5
Swallowing aid jelly	0.472 ± 0.158	0.378 ± 0.224
Starch-based 7.1 (w/v) %	0.332 ± 0.097	0.522 ± 0.121
Starch-based 4.7 (w/v) %	0.466 ± 0.057	0.720 ± 0.348
Starch-based 2.4 (w/v) %	0.532 ± 0.193	0.709 ± 0.241
Xanthan gum-based 3.0 (w/v) %	0.015 ± 0.003**	0.009 ± 0.001
Xanthan gum-based 2.0 (w/v) %	0.038 ± 0.019*	0.014 ± 0.004
Xanthan gum-based 1.0 (w/v) %	0.100 ± 0.031	0.029 ± 0.019

Data are presented as mean (n = 3) ± S.D. *$p < 0.05$, **$p < 0.01$ vs. Starch-based thickener 2.4 (w/v) % (Tukey's test) or vs. Xanthan gum-based thickener 1.0 (w/v) % (Tukey's test).

low powers of chewing and swallowing. The cohesiveness of swallowing-aid jelly was the lowest of all the thickeners. Swallowing-aid jelly is considered to have physical properties that make it easy to swallow for dysphasia.

In related to *in vitro* conventional dissolution test of AMPB powder mixed with two types of thickener solution and swallowing-aid jelly, xanthan gum-based thickeners show very low dissolution of AMP, approximating zero order dissolution, as shown in **Figure 1(c)** and **Table 3**. This may be caused by the xanthan-based thickener acting as a protective wetting agent for AMPB powder, as reported previously [21]. The AMP dissolution % from AMPB powder mixed with the starch-based thickener solutions and their first-order dissolution rate constants decreased as the concentration of starch-based thickener increased. This suggests that the hydrophilic starch molecular network might work as a barrier to diffusion of AMP into the medium. Whereas the fast dissolution and high dissolved % of AMP were obtained in AMPB powder mixed with swallowing-aid jelly. This is probably due to the low cohesiveness of swallowing-aid jelly, as shown in **Table 2**.

Regarding the taste sensor data shown **Figure 2**. The taste sensor value ranking coincided with the ranking of dissolution concentrations of AMP, as shown in **Figure 1**. This easily expects that much dissolution AMP from each of food thickener or swallow-aid jelly, give rise to enhance the bitterness in oral cavity. None of the three concentrations of xanthan gum-based thickeners (1.0, 2.0 and 3.0 (w/v) % showed any bitterness for the first 60 seconds. The 7.1 (w/v) % starch-based thickener solution did show any bitterness suppression effect for at least 30 seconds, while swallowing-aid jelly and 2.4 and 4.7 (w/v) % starch-based thickener solutions can be expected to show bitterness inhibition in the oral cavity.

In addition, the lack of AMP dissolution from xanthan gum-based thickeners under conditions mimicking the oral cavity may have a risk of less dissolution under gastric conditions, thereby decreasing the bioavailability of the drug.

In related to dissolution test of AMPB powder mixed with food thickeners, as shown in **Figure 3**, the mixture of AMPB with starch-based thickener or swallowing-aid jelly showed 100% dissolution, and therefore seem not limit bioavailability in patients. The smallest dissolution rate constant was observed for xanthan gum-based thickener, as shown in **Table 4**. As mentioned above, this could be due to a protective effect of the xanthan gum-based thickener's act on the AMPB powder. Alternatively, the xanthan gum-based thickener may act as a diffusion barrier limiting AMP dissolution into the medium. It has been reported that xanthan gum adsorbs various drugs [21] [22]. It is postulated that the reason for this is the excellent acid resistance, heat resistance and drought resistance of the gum [23] [24], and the intermolecular associations of xanthan gum wrapping around the drug and preventing it from getting wet, even though xanthan gum-based thickeners are said safety and their effect in modifying bolus rheology in the therapeutic medical for dysphagia [25].

4. Conclusions

In the present study, the effect of two types of food thickener on the bitterness and dissolution of AMPB powder was examined, mimicking conditions in which the drug is co-administered with food thickeners in patients with poor swallowing ability or dysphagia.

In the LST all the xanthan gum-based food thickeners but only the 4.7 (w/v) % starch-based food thickener fell within the acceptance criteria. The TPA results were all within the required criteria for starch- or xanthan gum-based food thickeners.

In the conventional dissolution test (1 minute in water), under conditions mimicking those of the oral cavity, the bitterness intensity of dissolved AMP was examined by HPLC and using the taste sensor. Bitterness suppression was observed with both types of food thickener, with xanthan gum-based food thickener being a more effective bitterness suppressant. Swallowing-aid jelly containing AMPB powder showed complete AMP dissolution and therefore was not at risk of reducing bioavailability in patients. However, all concentrations (1.0 - 3.0 (w/v) %) of xanthan gum-based food thickener reduced the dissolution rate of AMP, far below the levels achieved with starch-based thickener or swallowing-aid jelly. At 120 minutes, only about 60% dissolution was observed from xanthan gum-based food thickener.

The xanthan gum-based food thickener solutions were successful in bitterness masking but may risk reducing the bioavailability of AMP in humans.

Swallowing-aid jelly and 7.1 (w/v) % and 4.7 (w/v) % starch-based thickener solution was expected to show complete bitterness inhibition under oral cavity conditions and complete dissolution of AMP under gastric conditions.

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Conflicts of Interest

The authors declare that they have no conflicts of interest to disclose.

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