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The Effect of Food Thickeners on the Bitterness and Dissolution of Amlodipine Besilate Loaded Oral Disintegration Tablets: Assessment of Potential Suitability for Patients with Dysphagia

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Abstract

The purpose of this research was to evaluate the effect of starch- and xanthan gum-based food thickeners on the bitterness and dissolution of amlodipine besilate (AMPB) loaded orally disintegrating tablets (ODT) for potential use with patients with dysphagia. A conventional dissolution test simulating the oral cavity was performed and the taste sensor output of the dissolved sample was evaluated over a 60-seconds period. When four types of AMPB loaded ODTs were tested alone, at 60 seconds, branded product (A) was the least bitter, followed by generic product (B)/generic product (C) which were equal, and finally generic product (D) which was the most bitter. Inhibition of bitterness of AMPB loaded ODTs mixed thickeners, 1.0 (w/v) % xanthan gum-based food thickener solution was significantly strong. The 7.1 (w/v) % and 4.7 (w/v) % starch-based food thickeners solution also effective in bitterness inhibition compared to the 2.4 (w/v) % starch-based food thickener solution. The dissolution test under pH 1.2 in related to 7.1 (w/v) % and 4.7 (w/v) % starch-based thickener contained each of AMPB loaded ODTs were associated with an almost complete amlodipine (AMP) dissolution (almost 90% at 10 minutes), whereas the 1.0, 2.0, 3.0 (w/v) % xanthan gum-based food thickener solution containing AMPB loaded ODTs did not show complete AMP dissolution and there were large variations in the initial dissolution stage. This suggests that a mixture of xanthan gum-based thickener and AMPB loaded ODT poses a risk of reduction of bioavailability. In conclusion, a mixture of 4.7 (w/v) % or 7.1 (w/v) % starch-based thickener with ODTs provides complete release of AMP and superior bitterness inhibition, so is the best choice for administration to patients with dysphagia.

Keywords

Orally Disintegrating Tablet, Food Thickener, Xanthan Gum-Based Food Thickener, Starch-Based Food Thickener, Taste Sensor, Bitterness, Amlodipine

1. Introduction

Dysphagia is a medical condition that affects normal swallowing and elderly people are at particularly high risk [1] [2]. To prevent the risk of aspiration or choking in dysphasia patients, thickened fluids and texture-modified foods that are designed to slow down the flow of liquids and foods have been used [3]. Various types of thickeners have been developed and evaluated [4] [5] [6] [7] including modified starch thickeners and gum thickeners, both with and without flavoring [8].

Recently, research has been undertaken to determine the most effective viscosity when mixing food thickener with pharmacological medicines [9]. The tolerability and product properties of a gum-containing thickener in patients with dysphagia were also examined in a previous study [10]. Food thickeners are readily available for the purpose of increasing the viscosity or the adhesiveness of food stuffs [11]. They may be used to improve the texture of foods or drinks or to aid swallow ability [12], and this is especially important for the elderly or patients with dysphagia. Many elderly people with dysphagia take several kinds of medicines every day [13] [14]. Food thickeners have been used with medicines such as antihypertensives because elderly people with hypertension present with delayed swallowing time, *i.e.*, transit time from the oral cavity to bolus [15].

We focused on two aspects related to a trade-off associated with the use of thickeners with medicines. On the one hand, when a medicine is wrapped inside a thickener, the bitterness intensity might be reduced or masked, and this might be advantageous. The use of food thickeners has been used with various pharmaceuticals [16] to improve the texture of oral dosage formulations and/or reduce the bitterness in the oral cavity. On the other hand, excessive suppression of drug release in the oral cavity as a result of mixing with thickeners might result in a less than effective dosage. In our previous article [17], xanthan 1.0, 2.0, 3.0 (w/v) % gum-based food thickeners containing 6.93 mg amlodipine besilate (AMPB)) powder were very successful in inhibiting the bitterness of AMP in a conventional dissolution test with a simulated oral cavity; however, almost 40% of the drug remained undissolved at 120 mins in a dissolution test using 900 mL buffer under a pH of 1.2, and 4.5 in a simulated gastrointestinal tract.

Orally disintegrating tablets (ODTs) were first developed in Japan, and nowadays, many such products are available worldwide. ODTs are beneficial for patients with low swallow ability or dysphasia who need to take medications seem attractive judging from universal design [18].

Previous studies have not examined the use of commercial thickeners in terms of both the reduction of the bitterness in the oral cavity and the complete release from commercial ODTs mixed with commercial thickeners solution. Therefore, in the present study, using conventional dissolution tests that simulated the oral cavity, and dissolution tests, we aimed to investigate both the bitterness and the dissolution of amlodipine (AMP) from four different types of AMPB loaded ODT mixed with commercial thickeners with a view to assessing the suitability of various thickeners for use with patients with dysphagia.

First, in a conventional dissolution test simulating the oral cavity, taste sensor output of four kinds of ODT as alone were evaluated over the course of 1 minute.

Second, the bitterness inhibitory effect of food thickeners mixed with each of the four types of ODT was analyzed. The 1.0 (w/v) % of xanthan gum-based thickener solution, and the 2.4, 4.7, and 7.1 (w/v) % starch-based food thickener solutions were evaluated using a brief dissolution test and the taste sensor output was measured for each dissolved medium and bitterness was evaluated.

Third, a dissolution test at pH 1.2 was performed using the 1.0, 2.0, 3.0 (w/v) % xanthan gum-based thickener solutions the 4.7, 7.1 (w/v) % starch-based thickeners solutions, those mixed with each ODT and results were examined up to 60 minutes. The AMP dissolution % was determined using a high-performance liquid chromatographic (HPLC) method. The dissolution rate constants for each dissolution profile were calculated and the effect of thickeners on the dissolution of AMP from four different types of AMPB loaded ODT was analyzed.

2. Materials and Methods

2.1. Materials

The AMPB loaded ODT included one branded product A from Viatris Pharmaceutical Co. Ltd. Japan. Three generic AMPB loaded ODTs products manufactured by Nichi-Iko Pharmaceutical Co. Ltd. Japan, Takata Seiyaku Co. Ltd. Japan, and Towa Pharmaceutical Co. Ltd. Japan, respectively. Three genetic AMPB loaded ODTs were randomly named as B, C, and D. Two food thickeners were used in this study: starch-based food thickener granules (Toromerin; purchased from NUTRI Co. Ltd. Japan) and xantham-based food thickener (Tsururinko Quickly; Clinico Co. Ltd. Japan).

2.2. Initial Evaluation of the Orally Disintegrating Tablets Alone

In a conventional dissolution test simulating the oral cavity, taste sensor outputs of the four types of ODT alone were measured over the course of 1 minute.

2.3. Preparation of Food Thickener Solutions

Starch-based food thickener granules were mixed well with purified water and allowed to stand for 2 minutes. They were then prepared to 2.4, 4.7, and 7.1 (w/v) % solutions according to the method described in the package insert. Each of the four types of AMP loaded ODT were mixed in each prepared food thickener solution for 30 seconds. The 1.0, 2.0, and 3.0 (w/v) % xanthan gum-based food thickener solutions were simultaneously prepared according to the method described in the package insert, and each of four types of AMPB loaded ODT were wrapped in each prepared food thickener solution for 30 seconds.

2.4. *In Vitro* Assessment of Bitterness Using Taste Sensor Measurements

Each AMPB loaded ODT was mixed in the starch-based food thickener solutions (2.4, 4.7, 7.1 (w/v) %) and xanthan gum-based food thickener solutions (1.0 (w/v) %) weighing 5.0 g for 30 seconds. A 1.0 (w/v) % xanthan gum-based thickener was used in this study because xanthan gum-based thickeners at 1.0, 2.0, and 3.0 (w/v) % completely suppressed bitterness in our previous study [18]. Portions weighing 5.0 g of each of the above 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 [19] water contained in a 20 mL glass beaker. A small bar magnet (4 × 10 mm) which rotated at 150 rev/min, was placed in the bottom of the beaker. The water temperature was maintained at 37˚C. Samples (20 mL) were dissolved from the mixture in the beaker after 5, 15, 30, and 60 seconds. As a reference, each of the four types of ODT was assessed alone, and experiments were performed simultaneously for 60 seconds.

Taste sensor measurements of the eluted solutions were performed as described in previous articles [20] [21] [22] [23] as follows. The bitterness of the eluted solutions was measured by the change in the membrane electric potential caused by adsorption (CPA) using a 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 the bitterness of basic substances.

2.5. *In Vitro* Dissolution Test of AMPB Loaded Orally Disintegrating Tablets

In vitro dissolution tests of AMP from the AMPB loaded ODTs mixed with two types of thickener were carried out using a conventional dissolution tester (PJ-62N, Riken's; Miyamoto Riken Ind. Co. Ltd. Osaka, Japan) according to the 17th edition of the Japanese Pharmacopoeia. The test was performed using the paddle method at 37˚C and 50 rev/min using 900 mL of both the first fluid (pH 1.2). At 10, 20, 30, 45 and 60 minutes, 1.5-mL aliquots were withdrawn. We used 1.0, 2.0, and 3.0 (w/v) % xanthan gum-based thickeners. Also we used 4.7, 7.1 (w/v) % starch-based thickeners because starch-based thickeners at 2.4, 4.7, and 7.1 (w/v) % solution were completely dissolved from AMPB powder mixed with the thickener in our previous study [17].

Analysis of the four kinds of AMPB loaded ODT were performed as follows. The dissolution test was performed under the same conditions as mentioned above, and 1.5-mL samples were taken at 10, 20, 30, 45, 60 and 300 seconds. The samples were filtered through a membrane filter with a pore size of 0.20 μm, and the concentrations of dissolved AMP in the filtrate were determined by high performance liquid chromatographic (HPLC) as described as below.

The HPLC method was based on the Japanese Pharmacopoeia and a previous report [24]. 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 maintained 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. The run time was 14 minutes. The ultraviolet detection wavelength was set at 237 nm.

First-order dissolution rate constants from each food thickeners solutions were calculated from undissolved AMP %.

2.6. Statistical Analysis

Results are expressed as mean ± standard deviation (S.D.). Multiple comparisons were evaluated by the Tukey/Dunnett test after one way analysis of variance. $P < 0.05$ was considered to indicate statistical significance.

3. Results and Discussion

3.1. *In Vitro* Assessment of Bitterness Using Taste Sensor Measurements

Among the four ODTs assessed alone for 60 seconds, the branded product (A) was the least bitter, followed by generic product (B)/generic product (C) which were equal, and then generic product (D) which was the most bitter, as shown in Figure 1. In terms of inhibition of bitterness of all four kinds of AMPB loaded ODTs mixed with thickeners of various concentrations, the 1.0 (w/v) % xanthan gum-based food thickeners and the 7.1, 4.7 (w/v) % starch-based food thickeners were significantly more effective than the 2.4 (w/v) % starch-based food thickener. Among all food thickeners, 1.0 (w/v) % xanthan gum-based food thickener was the strongest inhibitor of bitterness. The bitterness inhibitory effect of 7.1 (w/v) %, 4.7 (w/v) % starch-based food thickeners solution not seem differ. Starch-based food thickeners blend easily with water [25]. As such, a low concentration (2.4 (w/v) %) starch-based thickener might not be as useful since its inhibition of diffusion of AMP through the starch-based polymer network might not be as strong as other thickeners. Among the four ODTs mixed with 2.4 (w/v) % starch-based food thickener solution, the bitterness was lowest in branded product (A), followed by generic product (B) and generic product (C) which were equal, and generic product (D) which was the most bitter. This rank order was the same as that found for case of the ODTs alone. For the 2.4 (w/v) % starch-based food thickener solution, at 30 and 60 seconds in the conventional dissolution test, the sensor output results with the generic (D) ODT were near to or slightly greater than the $\tau 1$ value of 7.33 mV which is the cut-off value for bitterness control. This suggested that the bitterness suppression was not adequate in this case.

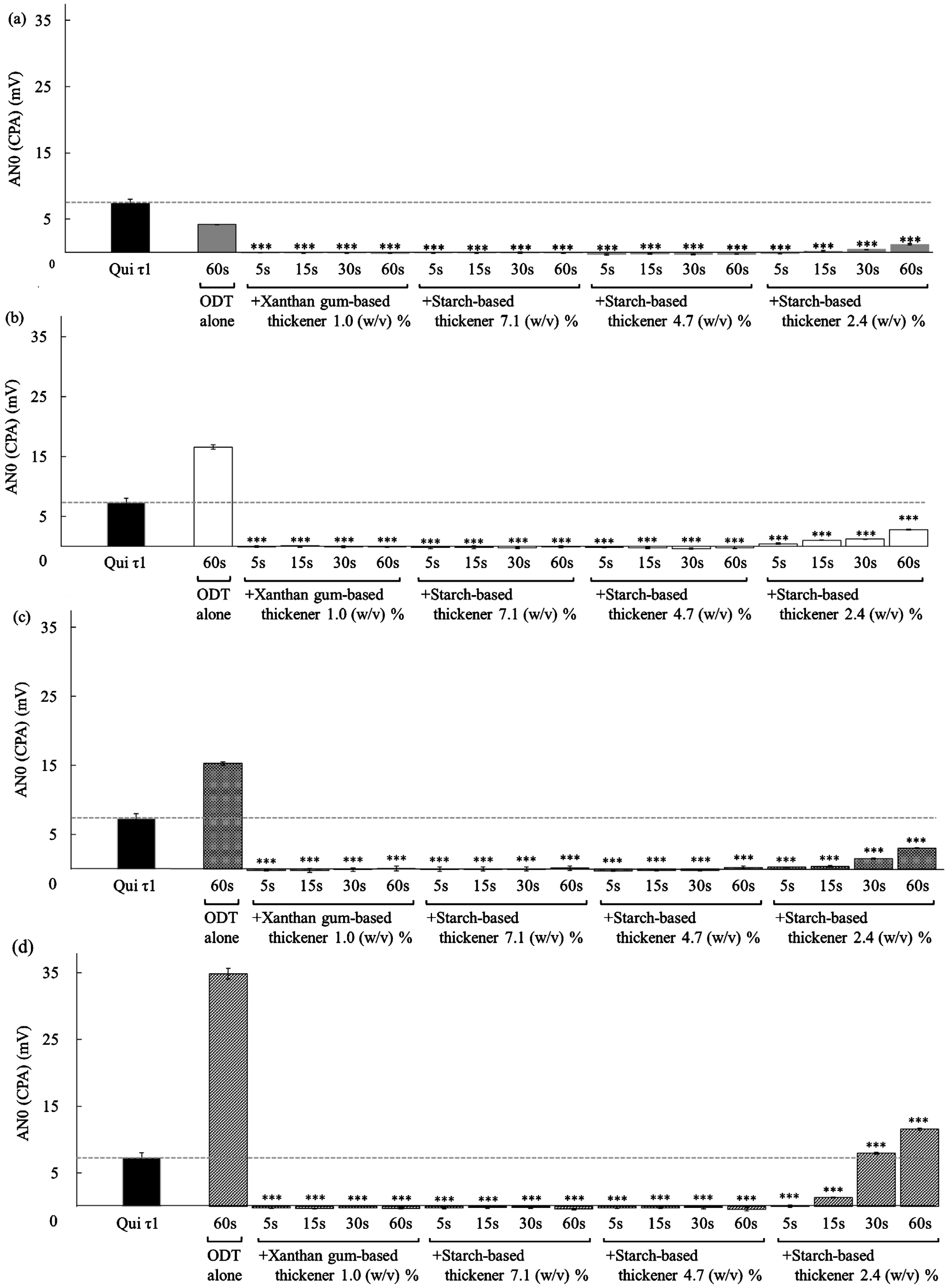

Figure 1. Taste sensor outputs [AN0 (CPA)] of dissolved medium in conventional dissolution test. Each AMTB loaded ODT alone and Each AMTB loaded wrapped with Xanthan gam-based thickener 1.0 (w/v) %, Starch-based thickener 7.1 (w/v) %, Starch-based thickener 4.7 (w/v) %, Starch-based thickener 2.4 (w/v) %, respectively. n = 3, mean ± S.D., *P < 0.05, **P < 0.01, ***P < 0.001 vs. ODT alone at 60 s (Dunnett's test).

3.2. *In Vitro* Dissolution Test of AMPB Loaded Orally Disintegrating Tablets Mixed with or Without Thickeners

As shown in **Figure 2(a)**, testing of the four kinds of AMPB loaded ODTs alone for up to 60 seconds showed that branded product (A) had the lowest AMP dissolution % ranking, followed by generic product (B) and generic product (C) which were equal, and then generic product (D) with the highest dissolution %. However, at 300 seconds, the AMP dissolution % did not differ significantly between among ODTs; in other words, all four types of AMPB loaded ODT were easily degraded and almost all of the AMP was dissolved in the short period of 5 minutes.

Figure 2(b) and **Figure 2(c)** show the dissolution of AMP from the four types of AMPB loaded ODTs mixed with 4.7 (w/v) % or 7.1 (w/v) % starch-based thickener solution. In all samples, the dissolution % reached 90% in just 10 min and AMP dissolved % did not differ among the samples.

Figures 2(d)-(f) show the dissolved AMP %-time profile of mixtures with 1.0, 2.0, 3.0 (w/v) % of xanthan gum-based thickener and each of the four types of AMPB loaded ODTs. As the xanthan gum-based thickener concentration increased from 1.0, 2.0, 3.0 (w/v) %, the dissolution % of AMP decreased, and only 60% - 80% was dissolved at 60 minutes, especially in the case of 3.0 (w/v) % xanthan gum-based thickener solution mixed with each of the four types of AMPB loaded ODTs, and almost 20% - 30% of the AMP remained undissolved at 60 minutes.

In addition, there was much variance in the dissolution % of AMP with the use of xanthan gum-based thickener, as shown in **Figure 2(d)** and **Figure 2(e)**. Generic (B) and (D) showed larger variances. For generic D type mixed with 1.0 (w/v) % xanthan gum-based thickener, in the initial dissolution stage, a thinner film formation was observed, and after this film start disappear at 10 minutes, thereafter a dramatic increase in the AMP dissolution was observed (data not shown). On the other hand, generic C mixed with 1.0 (w/v) % xanthan gum-based thickener showed a more gradual dissolution of AMP. It is thought that this may be due to the influence of additives to that formulation, such as mannitol. Further studies will be needed to clarify the detail mechanism even though many factors such as additive component different among commercial products.

The first-order dissolution rate constants were calculated and are summarized in **Table 1**. The first-order dissolution rate constants were the highest for starch-based food thickener (4.7 (w/v) %), followed by starch-based food thickener (7.1 (w/v) %), and finally, lowest for xanthan gum-based food thickeners in all AMPB loaded ODT judging from their dissolution rate constants.

Among the 1.0, 2.0, and 3.0 (w/v) % xanthan gum-based food thickeners, the first-order dissolution rate constant was highest in 1% xanthan gum, followed by 2.0 (w/v) % xanthan gum, and the lowest in 3.0 (w/v) % xanthan gum, although there were small variances in generic (B) and (D).

4. Conclusions

The purpose of this research was to evaluate the effect of starch- and xanthan

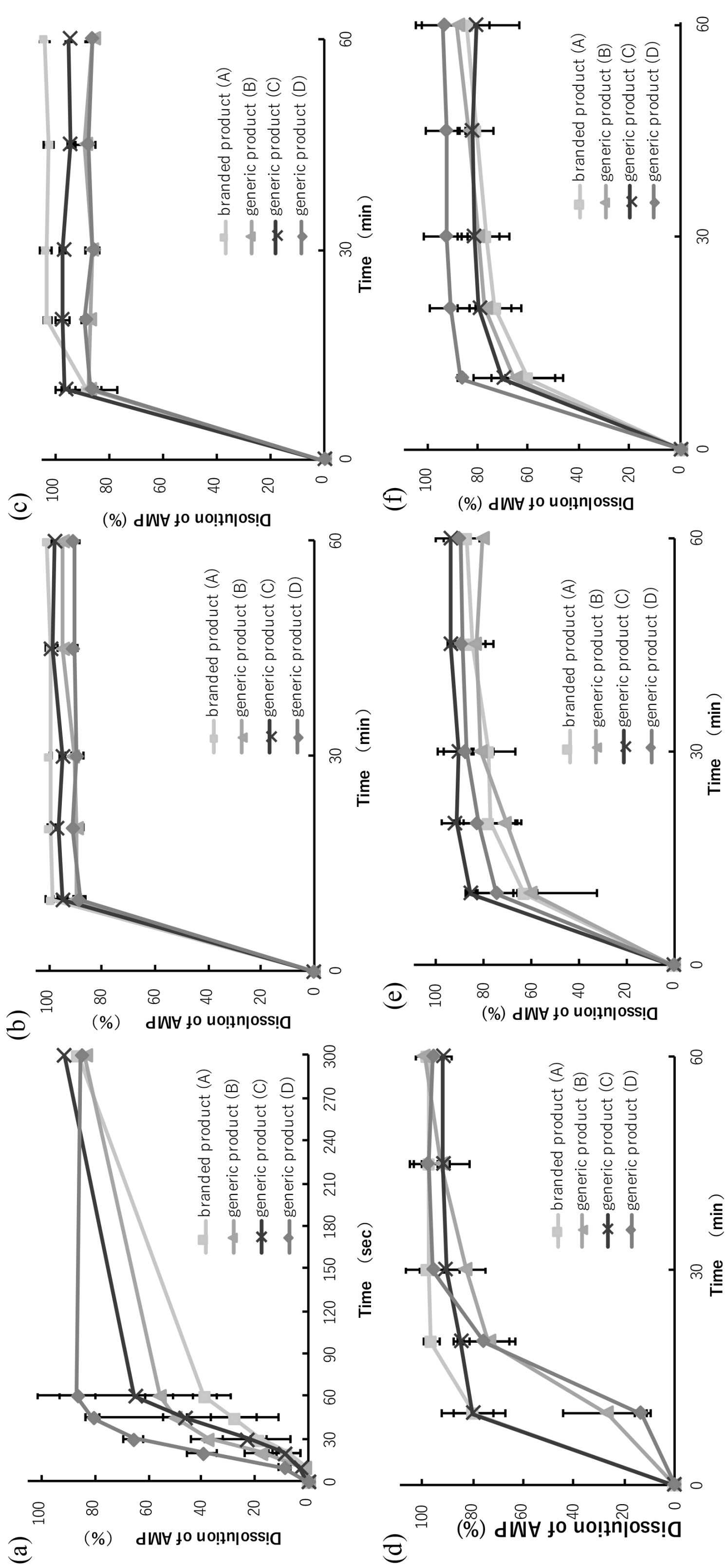

Figure 2. The dissolution profiles of AMP (pH1.2) for various formulations with or without thickeners. (a) ODT alone; (b) from Starch-based thickener (4.7 (w/v) %); (c) from Starch-based thickener (7.1 (w/v) %); (d) from Xanthan gum-based thickener (1.0 (w/v) %); (e) from Xanthan gum-based thickener solution (2.0 (w/v) %); (f) from Xanthan gum-based thickener (3.0 (w/v) %) n = 3, mean ± S.D.

Table 1. The first-order dissolution rate constants for AMP dissolution % versus time profile for two types of thickeners mixed with each of four kinds of generic products. Data are presented as mean (n = 3) ± standard deviation. *p < 0.05, **p < 0.01, ***p < 0.001 vs. product A (Tukey's test).

	The first-order dissolution rate constant (Mean ± S.D. (min^{-1}))			
	branded product	generic product		
	A	B	C	D
Starch based 7.1 (w/v) %	0.205 ± 0.080	0.182 ± 0.029***	0.253 ± 0.02*	0.176 ± 0.012*
Starch-based 4.7 (w/v) %	0.430 ± 0.089	0.230 ± 0.029	0.305 ± 0.09	0.222 ± 0.023
Xanthan gum-based 3.0 (w/v) %	0.093 ± 0.040	0.095 ± 0.024*	0.120 ± 0.002	0.201 ± 0.011**
Xanthan gum-based 2.0 (w/v) %	0.094 ± 0.005	0.108 ± 0.073	0.191 ± 0.014	0.118 ± 0.019
Xanthan gum-based 1.0 (w/v) %	0.152 ± 0.036	0.036 ± 0.031	0.169 ± 0.061	0.016 ± 0.001*

gum-based food thickeners on the bitterness and dissolution of amlodipine (AMP) from AMPB loaded ODTs mixed with commercial thickener solution.

First, in the conventional dissolution tests simulating the oral cavity, taste sensor output of dissolution medium from each AMPB loaded ODT sample mixed with commercial thickeners solutions was evaluated for bitterness of dissolved medium for up to 1 minute. Of the food thickeners mixed with AMPB loaded ODTs and tested in this study, 1.0 (w/v) % xanthan gum-based, and 7.1 (w/v) % and 4.7 (w/v) % starch-based food thickeners were significantly more effective in inhibiting bitterness. Of the four AMPB loaded ODTs wrapped with 2.4 (w/v) % starch-based food thickener, the sensor output indicated that the bitterness was the lowest with branded product (A), followed by generic product (B)/generic product (C), and finally generic product (D) which was the most bitter. This order was the same as the order found for ODT alone.

In the dissolution test with a pH of 1.2, the 7.1, 4.7 (w/v) % starch-based thickeners showed complete dissolution of AMP at 10 minutes, whereas this was not the case with 1.0, 2.0, 3.0 (w/v) % xanthan gum-based food thickeners and there were large variations. This suggests that the use of 1.0, 2.0, 3.0 (w/v) % xanthan gum-based thickener solution with AMP loaded ODTs poses a risk of reduction of bioavailability.

In conclusion, 4.7 (w/v) % and 7.1 (w/v) % starch-based thickener solution mixed with each ODT showed complete dissolution of AMP and inhibition of bitterness. For the 2.4 (w/v) % starch-based food thickener solution, at 30 and 60 seconds in the conventional dissolution test, the sensor output results with the generic (D) ODT were near to or slightly greater than the $\tau 1$ value of 7.33 mV which is the cut-off value for bitterness control.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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