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Preparation and Characterization of Orally Fast-Disintegrating Mini-Tablets Containing Diphenhydramine Hydrochloride and Aspartic or Glutamic Acid as an Umami Amino Acid

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Abstract

The aim of this study was to prepare diphenhydramine hydrochloride (DPH)-loaded orally fast-disintegrating mini-tablets (OFDMTs) containing either L-aspartic acid (Asp) or L-glutamic acid (Glu) as bitterness-suppressant, to characterize the prepared tablets and to evaluate their bitterness under conditions mimicking those of the oral cavity. The preparation of five formulation batches of the OFDMTs involved mixing DPH, with or without two different concentrations of Asp or Glu, and a premix containing a disintegrating agent. When all ingredients were well mixed, the mixture was directly compacted to form small (4 mm diameter) DPH-loaded OFDMTs. There were only small differences between the tablets with respect to mass, diameter, width and hardness. The disintegration times of the five formulation batches of DPH-loaded OFDMTs were measured using the OD-mate, a disintegration test apparatus in which conditions resemble those of the oral cavity. The disintegration times were all within 10 s of exposure to a medium representing the inside of the oral cavity. Rapid release profiles were observed for DPH, Asp and Glu in these dissolution tests. The taste sensor outputs of samples taken at different times (5 - 30 s) from the dissolution test solutions of the four DPH-loaded OFDMTs containing Asp or Glu were significantly inhibited compared with those of control DPH-loaded OFDMT. These results suggest that the inclusion of Asp or Glu in DPH-loaded OFDMTs is sufficient to mask bitterness in the oral cavity for the first 30 s after the tablet is placed in the mouth. It is anticipated that swallowing will have taken place within 30 s.

Keywords

Orally Fast Disintegrating Mini-Tablets, Diphenhydramine, Aspartic Acid,

Glutamic Acid, OD-Mate

1. Introduction

The palatability of oral formulations is critical for good adherence, especially in pediatric and geriatric patients. Therefore, many commercially available orally disintegrating tablets (ODTs) containing bitterness suppressants have been developed for patients with dysphagia or poor swallowing ability [1]. In a recent article, pediatric healthcare professionals have argued that ODTs should be made more available for use in children [2], while in Europe, mini-tablets have been shown to be attractive in allowing dose adjustments for individual pediatric patients [3] [4], their small size improving swallowing ability. Thus, the concept of orally fast-disintegrating mini-tablets (OFDMTs) containing bitterness suppressants is extremely attractive in the drive to improve adherence in patients, especially pediatric ones.

In the present study, OFDMTs were prepared which would be capable of disintegrating in the conditions of the oral cavity. Diphenhydramine hydrochloride (DPH) was chosen as a model drug as it is already widely used in pediatric and geriatric patients. This drug is known to have a bitter taste [5] so the addition of a bitterness suppressant is essential when the OFDMTs containing DPH are expected to disintegrate rapidly in the oral cavity, resulting in high concentrations of DPH being exposed to bitterness receptors on the tongue. Such a level of bitterness would greatly decrease adherence. Therefore, a safe and efficient bitterness suppressant must be incorporated in the DPH-loaded OFDMTs.

In the present study, Asp and Glu were selected as bitterness suppressants; both amino acids are non-toxic and quite stable with bitterness-suppressing effects shown to be almost equivalent to those of L-aspartyl-L-aspartic acid and/or L-glutamyl-L-glutamic acid in our previous study [5].

The aim of the present study was therefore to prepare DPH-loaded OFDMTs (4 mm diameter), containing Asp or Glu as bitterness suppressants, to characterize the prepared tablets and to evaluate their bitterness under conditions mimicking those of the oral cavity.

The preparation of the OFDMTs involved mixing DPH, Asp or Glu with a premix [6] containing a disintegrating agent, stearic magnesium (St-Mg) and talc. These components were mixed well and compacted to form DPH-loaded OFDMTs. The DPH-loaded OFDMTs were then characterized (hardness, tablet size, drug content uniformity) and their disintegration times evaluated using the OD-mate under conditions mimicking those of the oral cavity. A brief dissolution test was performed using the OD-mate, and high-performance liquid chromatography (HPLC) was used to determine the concentrations of DPH, Asp and Glu in the eluate. The eluate was also evaluated using the taste sensor and the bitterness-suppressing effects of Asp and Glu on DPH were determined.

2. Material and Methods

2.1. Materials

Diphenhydramine hydrochloride, L-aspartic acid and L-glutamic acid were purchased from FUJIFILM Wako Pure Chemical Corp., Japan. The structural formulae of diphenhydramine hydrochloride, L-aspartic acid and L-glutamic acid are shown in Figure 1. ODIFUL®, a granulated mixture of mannitol, crystalline cellulose, low-substituted hydroxypropyl cellulose and POVACOAT Type MP (polyvinyl alcohol/acrylic acid/methyl methacrylate copolymer), was used as a premix. St-Mg and talc were donated by Pharmpolytech. Inc. (Osaka, Japan).

Five different formulations containing varying quantities of DPH, Asp or Glu, premix, St-Mg and talc were mixed well (see Table 1). Formulation (A), without Asp or Glu, was used as control. In formulations (B), (C), (D) and (E) the DPH: Asp/Glu ratio was either 1:1 or 1:2. Direct compaction was performed using a Rotary Tablet Press (Kikusui Seisakusho Ltd., Kyoto, Japan) with a 4-mm pestle. Turntable speed was set to 20 revolutions per minute.

The individual mini-tablet weights were adjusted to be 32 mg per mini-tablet, as shown in Table 2.

2.2. Measurement of Mass, Diameter/Width, and Hardness of Prepared DPH-Containing OFDMTs

Ten tablets were randomly chosen from each prepared batch, and individually

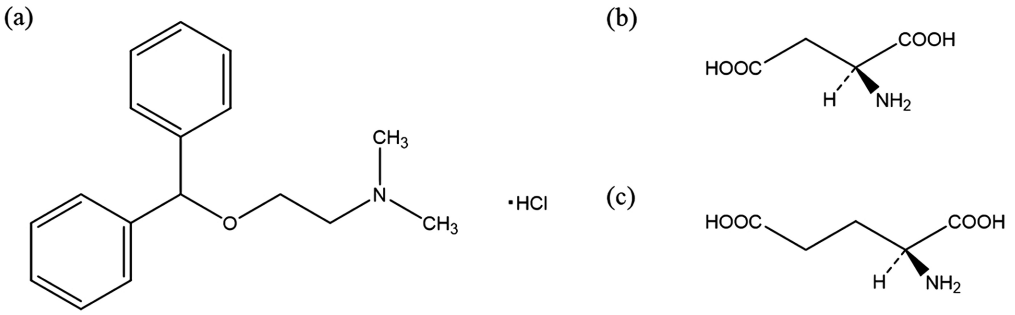

Figure 1. The structural formula of diphenhydramine hydrochloride, L-aspartic acid and L-glutamic acid: (a) diphenhydramine hydrochloride, (b) L-aspartic acid, (c) L-glutamic acid.

Table 1. Five formulations of DPH-loaded OFDMTs (diameter 4 mm).

	DPH	Asp	Glu	ODIFUL®*	St-Mg
OFDMT (A)	3 mg	-	-	28.68 mg	0.32 mg
OFDMT (B)	3 mg	1.37 mg	-	27.31 mg	0.32 mg
OFDMT (C)	3 mg	2.74 mg	-	25.94 mg	0.32 mg
OFDMT (D)	3 mg	-	1.51 mg	27.17 mg	0.32 mg
OFDMT (E)	3 mg	-	3.02 mg	25.65 mg	0.32 mg

*ODIFUL®: granulated mixture of mannitol, crystalline cellulose, low-substituted hydroxypropyl cellulose, POVACOAT Type MP (polyvinyl alcohol/acrylic acid/methyl methacrylate copolymer).

Table 2. Mass, diameter, width and hardness (shear strength and destruction strength) of five formulations of DPH-loaded OFDMTs. Data are expressed as means ± SD (n = 10).

	Mass (mg)	Diameter (mm)	Width (mm)	Hardness	
				Shear strength (kgf)	Destruction strength (kgf)
OFDMT (A)	31.4 ± 0.87	4.07 ± 0.01	2.48 ± 0.02	1.71 ± 0.48	4.31 ± 0.36
OFDMT (B)	32.3 ± 1.18	4.07 ± 0.02	2.52 ± 0.03	1.34 ± 0.47	3.92 ± 0.47
OFDMT (C)	34.5 ± 1.60	4.08 ± 0.02	2.57 ± 0.04	2.28 ± 0.37	5.10 ± 0.71
OFDMT (D)	33.2 ± 0.85	4.07 ± 0.01	2.53 ± 0.03	1.85 ± 0.41	5.39 ± 1.04
OFDMT (E)	35.6 ± 0.87	4.07 ± 0.01	2.58 ± 0.06	1.96 ± 0.37	4.95 ± 0.53

weighed. The diameter and width were measured using digital calipers (Mitutoyo Corp., Kanagawa, Japan). The Monsanto hardness tester (Fujirika Kogyo Co., Ltd., Osaka, Japan) was used for measurement of shear strength and destruction strength.

2.3. Test of Content Uniformity

The test of content uniformity was performed for the five OFDMT formulations according to the method described in the Japanese Pharmacopoeia (JPXVII) as follows:

Ten individual OFDMTs were picked at random from each batch, crushed in an agitated mortar and suspended in purified water in a volumetric flask. After centrifugation (2383 g, 10 min, room temperature), the supernatant was filtered and the DPH concentration determined by HPLC, as described in a previous article [7]. The acceptance value was then calculated.

2.4. Measurement of Disintegration Time

The *in vitro* oral disintegration time was measured using the OD-mate (Model IMC-14D1; Higuchi Inc., Tokyo, Japan). The OD-mate is a unique disintegration testing device intended to simulate the disintegration of an ODT in the human oral cavity [8]. An OFDMT is placed on a trapezoidal mesh, corresponding to the tongue, in a flat-bottomed test tube and compressed by two weights (30 g inner weight and 100 g outer weight) corresponding to the upper palate. The test medium was 20 mL of purified water at 37˚C. The measurement starts immediately the test tube comes into contact with the water, as shown in **Figure 2(a)**, and the time was taken for each tablet to completely disintegrate (for the inner weight to reach the bottom of the test tube) as shown in **Figure 2(b)** is recorded.

The experiment was repeated six times and the mean value was taken as the *in vitro* oral disintegration time of the OFDMT.

2.5. Determination of DPH and Asp/Glu Concentrations in the Dissolution Medium

Aliquots of the dissolution medium (20 mL) from the disintegration test (see 2.4

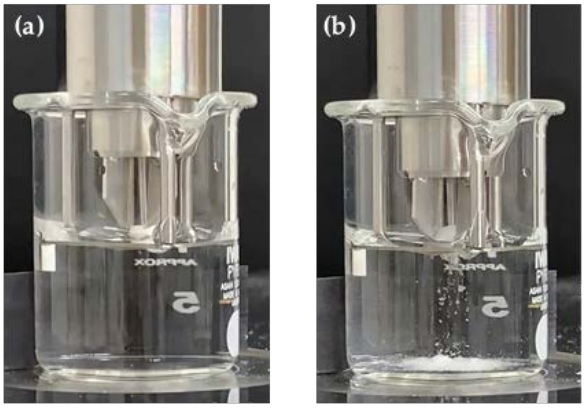

Figure 2. The photographs show the disintegration of an OFDMT at the start (a) and near the end (b) of the dissolution test.

above) were withdrawn 4, 5, 10, 20 and 30 s after the test tube contacted the water and filtered immediately using a 0.45-μm filter. The concentrations of DPH and Asp or Glu in each sample were determined using HPLC as described in previous articles [7] [9].

2.6. Taste Sensor Measurement of Dissolution Samples

Taste sensor SA402B (Intelligent Sensor Technology Inc., Kanagawa, Japan) was used to measure the electric potential of the sample solutions collected after 5, 10, 20 and 30 s in the disintegration test (see 2.4 above). Sensors have been developed specifically to detect various tastes. Sensor AN0 which detects the bitterness of basic substances [8] [10] [11] [12] [13] [14] was selected for this study. Taste sensor measurements were performed as described in previous articles [8] [10]-[17]. In brief, the electrode set is attached to a mechanically controlled robot arm. The detecting sensor part of the equipment consists of a reference electrode and a working electrode composed of lipid/polymer membranes. The electrodes have an internal cavity filled with 3.3 M KCl solution. The difference between the electric potentials of the working electrode and the reference electrode is measured using a high-input impedance amplifier connected to a computer. Fresh 30 mM KCl solution containing 0.3 mM tartaric acid (corresponding to saliva) is used as the reference solution and also to rinse the electrode after every measurement.

The measurement procedure is as follows: the electrodes are dipped first into the reference solution and the electric potential obtained (mV) is defined as Vr_0. Then a sample solution is measured and the electric potential obtained defined as Vs. The electrodes are then rinsed with a fresh reference solution for 6 s. When the electrodes are dipped into the reference solution again, the new potential of the reference solution is defined as Vr_1. The difference between the potentials of the reference solution before and after sample measurement (Vr_1-Vr_0) is defined as the "change in the membrane potential caused by adsorption" (CPA), and corresponds to the so-called "aftertaste". CPA is a specific expression of bitterness.

2.7. Statistical Analysis

BellCurve for Excel® (Social Survey Research Information Co., Ltd., Tokyo, Japan) was used for statistical analysis. Tukey's test was used for multiple comparisons in taste sensor outputs of OFDMT sample solutions collected 5, 10, 20 and 30 s after the test tube contacted the water. The 5% level of probability was considered significant.

3. Results and Discussion

3.1. Characterization of DPH-Containing OFDMTs with Asp or Glu

As shown in Table 2, there were no significant differences between the five formulations with respect to mass, diameter, width or hardness.

In the content uniformity examination, the actual DPH content (average value ± standard deviation) of each tablet was as follows: (A) 91.48% ± 2.87%, (B) 104.40% ± 3.76%, (C) 100.58% ± 4.23%, (D) 101.32% ± 2.12%, and (E) 98.81% ± 3.67%. The acceptance values of the five formulations were evaluated according to the criterion equation for content uniformity described in JPXVII, and were as follows; (A) 4.6 ± 0.75 s, (B) 6.9 ± 0.92 s, (C) 7.0 ± 1.33 s, (D) 7.3 ± 1.33 s, (E) 7.2 ± 0.87 s. All OFDMT formulations had completely disintegrated within 10 s and are therefore considered likely to be rapidly dissolved in the oral cavity.

3.2. Evaluation of the Release Profiles of DPH-Containing OFDMTs with Asp or Glu under Conditions Resembling Those of the Oral Cavity

The release profiles of DPH, Asp or Glu in the five formulations of OFDMT are shown in Figures 3(a)-(e).

For the control OFDMT (A), immediate release of DPH was confirmed, with almost 80% of DPH being released within 10 s. For OFDMTs (B) and (C), similar DPH release profiles were observed after about 5 s, as shown in Figure 3(b) and Figure 3(c), respectively. In both these batches, simultaneously immediate Asp release was observed, although the release rate of Asp was lower than the corresponding DPH release. For OFDMTs (D) and (E), similar rapid release patterns were observed for DPH and Glu, as shown in Figure 3(d) and Figure 3(e), respectively.

These results confirmed that the five formulations of DPH-containing OFDMTs with Asp or Glu started disintegrating after around 5 s, and had completely disintegrated within 10 s, coinciding with the rapid release of DPH and Asp or Glu into the medium. The rapid release of Asp or Glu is critical for bitterness suppression of OFDMTs that dissolve in the oral cavity.

3.3. Evaluation of Bitterness of DPH-Containing OFDMTs with Asp or Glu Using the Taste Sensor

Figure 4 shows the taste sensor outputs of AN0 (CPA) for sample solutions of the five formulations of OFDMT derived from the OD-mate dissolution test.

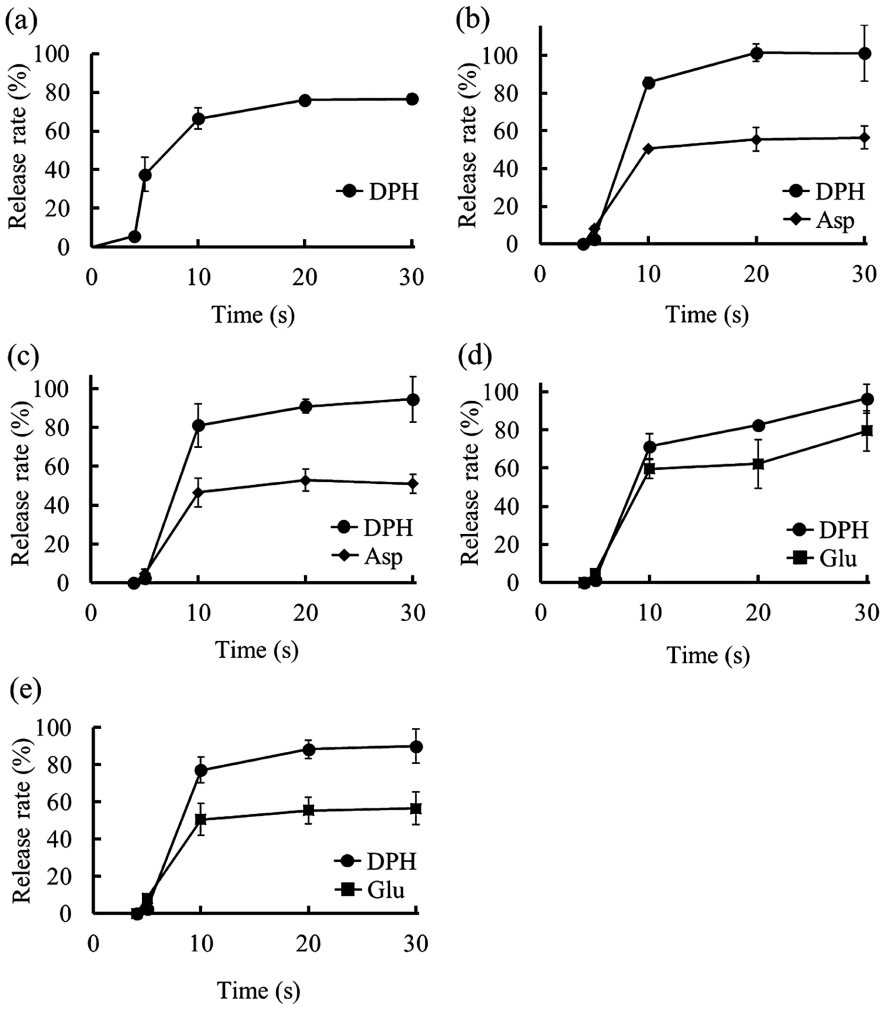

Figure 3. DPH and Asp/Glu release as % in dissolution medium over time as measured by the OD-mate; (a)-(e) refer to OFDMTs (A)-(E), respectively. Data are expressed as means ± SD ($n = 3$).

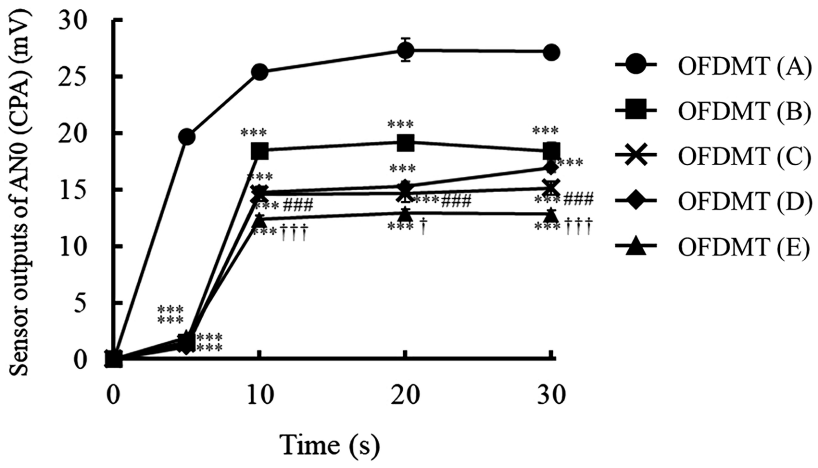

Figure 4. The taste sensor outputs of AN0 (CPA)-time profiles for five formulations of OFDMT obtained in the OD-mate dissolution test; data are expressed as means ± SD ($n = 3$). $^{***}p < 0.001$ vs. A, $^{###}p < 0.001$ vs. B, $^{\dagger}p < 0.05$, $^{\dagger\dagger\dagger}p < 0.001$ vs. D (Tukey's test).

The start of release for the five OFDMT formulations was found to be around 5 s and release was complete by about 10 s. Compared with the taste sensor output of OFDMT (A) as control, the taste sensor outputs for OFDMTs (B)-(E) were significantly reduced after between 10 and 30 s, this being the assumed typical holding time in the human oral cavity. The bitterness of the released DPH was therefore reduced by the simultaneous release of Asp or Glu in the oral cavity.

The taste sensor profiles of DPH and Asp or Glu in the dissolution test solutions, shown in **Figure 4**, resemble the corresponding release profiles shown in **Figure 2**. This finding supports the bitterness-suppressing effects of Asp or Glu on DPH.

Bitter commercial pharmaceuticals, such as solid and liquid oral formulations of morphine often contain monosodium glutamate as bitterness suppressant.

Cyclodextrin also plays an important role in suppressing bitterness and is often included to improving a formulation's properties. For example, cyclodextrin has been incorporated in prostaglandin E1 injections, itraconazole oral solutions and cetirizine hydrochloride OD tablets [18] [19] [20]. Usually, an excess of cyclodextrin relative to the amount of drug is considered necessary to suppress bitterness. Cyclodextrin has, however, been reported to cause gastrointestinal disorders as a side-effect [18]. Using an umami-flavored amino acid as bitterness suppressant offers several advantages in terms of stability, lack of toxicity and general applicability [21].

4. Conclusions

In the present study, five batches of DPH-loaded OFDMTs (4 mm diameter), containing a disintegrating agent and two different concentrations of either Asp or Glu as bitterness suppressant, were prepared and characterized. All five batches disintegrated within 10 s when evaluated in the OD-mate under conditions mimicking those of the oral cavity.

The taste sensor outputs of samples from the dissolution test taken after between 5 and 30 s were significantly reduced in OFDMTs containing Asp or Glu compared with the control OFDMT. This reduction is considered to be due to the bitterness-suppressing effects of the umami amino acids Asp or Glu.

The immediate release profiles of Asp or Glu were similar to that of DPH in dissolution tests carried out under conditions mimicking the oral cavity. These findings suggest that these two amino acids may be useful bitterness-suppressing agents for OFDMTs containing bitter active ingredients which disintegrate within 30 s in the oral cavity. By 30 s it is anticipated that the tablet would have been swallowed.

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Conflicts of Interest

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

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