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The prediction of the palatability of orally disintegrating tablets by an electronic gustatory system

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ABSTRACT

In this study, the human gustatory palatability sensation of taste-masked famotidine and amlodipine orally disintegrating tablets (ODTs) was quantitatively predicted by an electronic gustatory system (α-Astree e-Tongue). Furthermore, its use in formulation design was evaluated. The famotidine- and amlodipine-containing ODTs, which were bitter- and highly bitter-tasting, respectively, were prepared using a physical (granules spray-coated with ethyl cellulose) or organoleptic (the addition of a sweetener and a flavor) masking method and combinations thereof. The taste-masking effects of different masking methods on the ODTs were investigated in a human gustatory sensation test. In the test, volunteers scored the overall palatability using a 100 mm visual analog scale (VAS). The electronic gustatory system was evaluated using the Euclidean distance (the distance between each drug-containing ODT and its corresponding placebo) and partial least squares (PLS) regression analysis of the sensor response values. A good linear relationship was observed between each ODT's Euclidean distance analysis, PLS regression analysis, and clinical VAS scores. Cross-validation verification of each analysis confirmed the model's predictive power. This study suggests that the α-Astree can quantitatively evaluate physical and organoleptic taste masking and that the palatability of unknown formulations can be predicted by Euclidean distance and PLS regression data analysis.

1. Introduction

Many elderly and bedridden patients and children have difficulty swallowing the currently available oral medication forms such as tablets and capsules. To overcome this problem, a fast-disintegrating tablet (ODT) formulation has been developed (Chang et al., 2000; Sandri et al., 2006). ODT formulations that can rapidly and easily disintegrate in the mouth without the need for water are also applicable to active working people who do not have ready access to water. For many patients, the medication compliance and therapeutic effect could be improved by taking ODTs (FDA, 2008; William and Tapash, 2005). Recently, based on the requests from patients to enhance their quality of life (QOL), several pharmaceutical companies have developed various (new) types of ODTs. For example, RACTAB® technology is one of the new technologies for the preparation of ODTs, consisting of rapid disintegration granules (RDGs) spray-coated with a suspension of wicking agents using a fluidized-bed granulator. ODTs prepared using the RACTAB® technology, which is a simple preparation method, have superior properties, including a comparatively high tablet hardness, high physical stability, high resistance against humidity, fast oral disintegration rate, and improved mouth feel (Okuda et al., 2009, 2012, 2014).

Bitterness of the active pharmaceutical ingredient is one of the major challenges faced by pharmaceutical scientists formulating oral dosage forms. Drugs with an unpleasant, bitter taste are generally difficult to swallow for patients, resulting in poor adherence to treatment regimens and, consequently, reduced drug efficacy. Therefore, taste masking is used to mask the unpleasant taste of drugs and plays an important role in formulating ODTs. Taste-masking methods are mainly based on the organoleptic method, adding flavors and sweeteners, and the physical method, avoiding the unpleasant bitter taste of drugs coming into direct contact with the patient's gustatory buds by coating or granulation (Gao et al., 2006; Lieberman et al., 1989; Shishu and Singh, 2007; Suzuki et al., 2003).

Abbreviations: ODT, orally disintegrating tablet; VAS, visual analog scale; PLS, partial least squares; QOL, quality of life; RDGs, rapid disintegration granules; ChemFET, chemical field effect transistor; ICH, International Conference on Harmonization; SD, standard deviation; PCA, principal component analysis; MPE, mean prediction error; MAE, mean absolute error; RMSE, root mean square error.

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Since the palatability of drug products is becoming increasingly important, taste masking has become an essential component of pharmaceutical development, particularly for ODTs, sublingual tablets, or dry syrups containing unpleasant bitter-tasting drugs. In the bitterness-masking formulation development, pharmaceutical scientists need to ensure that the bitterness is acceptably masked in the formulation. The use of the human gustatory sensation test is a commonly applied method for taste assessment of pharmaceutical formulations. Previously, we have shown to be able to quantitatively evaluate palatability of ODTs using the visual analog scale (VAS) (Matsui et al., 2015; Nakano et al., 2013; Sugiura et al., 2012). However, it is difficult to test and evaluate the palatability of candidate ODT formulations using clinical trials, because of the high number of candidate formulations that needs to be investigated during the development process. Other drawbacks of the human gustatory sensation test are ethical and safety concerns due to the potential toxicity of the active pharmaceutical ingredients, especially for new chemical entities. Furthermore, children have difficulties making valid statements of differences in taste perception (Sjovall et al., 1984).

Currently, two electronic gustatory systems are commercially available: the taste sensing system SA402B/TS-5000Z (Insent Inc., Atsugi-chi, Japan) and the α-Astree (Alpha M.O.S, Toulouse, France). Both systems measure changes in the electronic potential while investigating liquid samples; the underlying sensor technologies, however, are different. The taste sensing system SA402B/TS-5000Z is equipped with lipid membrane sensors whereas the α-Astree uses chemical field effect transistor (ChemFET) technology. The results of these analytical tools correlate well with those of the human gustatory sensation test (Eckert et al., 2011; Woertz et al., 2011a,b). Taste assessment using electronic gustatory systems is becoming more established as a novel alternative to the human gustatory sensation test (Ito et al., 2013). In a novel approach, the International Conference on Harmonization (ICH) guideline Q2 was adapted to taste sensing systems (Pein et al., 2013; Woertz et al., 2010). In the pharmaceutical industry, bitterness evaluation using electronic gustatory systems is also attracting increasing attention (Zheng and Keeney, 2006).

However, although a correlation between "bitterness evaluation" of the formulations and drugs using electronic gustatory systems and the human gustatory sensation test has been reported, a correlation between the palatability of ODTs in different taste-masking methods, such as physical and organoleptic taste masking, using the VAS has not been found (Hashimoto et al., 2007; Inoue et al., 2012; Julie et al., 2009; Maniruzzaman and Douroumis, 2014; Rachid et al., 2010; Tokuyama et al., 2009; Woertz et al., 2011a,b). In addition, there are few studies that have investigated what is possible in terms of formulation design using electronic gustatory systems. Thus far, no studies have been published on method validation and still no systematic approach testing the limitations of gustatory systems exists (Woertz et al., 2010).

In the present study, we investigated the possibility of quantitatively evaluating the overall palatability of ODTs prepared using different taste-masking methods, and evaluated the predictability of the human gustatory sensation by an electronic gustatory system. In addition, we examined the possibility of developing ODT formulations based on the results of the electronic gustatory system. Famotidine, a histamine-2 receptor antagonist, and amlodipine besylate, a long-acting calcium antagonist, are the bitter-tasting model drugs widely used to evaluate bitterness-suppressing effects in various taste-masking methods. Therefore, we have used famotidine and amlodipine ODTs that were prepared using the RACTAB® technology as the sample drugs in this study.

2. Materials and methods

2.1. Materials

Famotidine, purchased from Sanyo Chemical Laboratory Co., Ltd. (Osaka, Japan), was used as model of an unpleasant-tasting drug. Amlodipine besylate, purchased from Sagami Chemical Industry Co., Ltd. (Tokyo, Japan), was used as model of a highly unpleasant-tasting drug. RDGs were prepared using a suspension spray-coating method. Aspartame, purchased from Ajinomoto Co., Inc. (Tokyo, Japan), was used as a sweetener. L-Menthol, purchased from Nagaoka & Co., Ltd. (Hyogo, Japan) and commercial peppermint flavor, purchased from Takasago International Corp. (Tokyo, Japan), were used as flavors. D-Mannitol, purchased from Merck KGaA (Darmstadt, Germany), light anhydrous silicic acid, purchased from Freund Corp. (Tokyo, Japan), and magnesium stearate, purchased from Taihei Chemical Industrial Co., Ltd. (Osaka, Japan), were used as excipients for tablet formulation in this study. All raw materials used in the formulations were Japanese Pharmacopoeia- or special commercial-grade chemicals.

2.2. ODT manufacturing method

Famotidine ODTs were manufactured as described previously (Sugiura et al., 2012). Briefly, famotidine and D-mannitol powder (1:1) or amlodipine besylate and D-mannitol powder (1:4) were granulated and spray-coated with ethyl cellulose solution in a fluidized-bed granulator (MP-01, Powrex Corp., Hyogo, Japan) in one 400-g batch. Granules without famotidine or amlodipine were prepared in the same manner using D-mannitol powder only.

ODTs were prepared using a rotary tableting machine (Virg, Kikusui Seisakusho Ltd., Kyoto, Japan) of which the test design is shown in Table 1. For the non-physical taste-masking ODT (C−)

Table 1
ODT formulations used in the human gustatory sensation test and the electronic gustatory test.

Formula	Famotidine or amlodipine (D)	Physical masking	Organoleptic masking	
		Spray coating (C)	Aspartame (A)	Flavor (F)
P	−	−	−	−
F	−	−	−	+
A	−	−	+	−
AF	−	−	+	+
D	+	−	−	−
DC	+	+	−	−
DA	+	−	+	−
DF	+	−	−	+
DAF	+	−	+	+
DCAF	+	+	+	+