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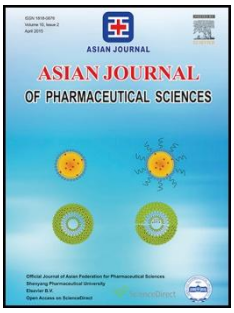

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Author: Tamami Haraguchi, Miyako Yoshida, Honami Kojima, Takahiro Uchida

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<Review>

Usefulness and limitations of taste sensors in the evaluation of palatability and taste-masking in oral dosage forms

Tamami Haraguchi, Miyako Yoshida, Honami Kojima, and Takahiro Uchida

School of Pharmaceutical Science, Mukogawa Women's University

11-68 Koshien 9-bancho, Nishinomiya, 663-8179, Japan.

Abstract

The purpose of this review is to discuss the advantages and limitations of taste sensors in the evaluation of the taste of palatability of different oral dosage forms. Firstly, we consider some ways in which the palatability of various pharmaceutical formulations including orally disintegrating tablets (ODTs), are tested using two different taste sensors. Secondly, we focus on the evaluation of palatability of ODTs. We compare the usefulness of three pieces of apparatus for estimating the disintegration time of ODTs. Finally, we compare the characteristics of the two taste sensors in the evaluation of palatability of various kinds of drug formulations.

Keywords: palatability, taste sensor, orally disintegrating tablet (ODT), disintegration time, drug formulation

Introduction

Of the various types of formulation on the pharmaceutical market, solid oral forms (e.g. tablets, capsules) are the most common. These formulations have many advantages, such as dose accuracy and relatively high stability, and also offer possibilities for modifying the drug release

profile in order to delay or sustain a therapeutic effect. Their palatability, however, especially if they have a bitter taste, is also important in maintaining patient adherence and thereby allowing effective pharmacotherapy to be attained [1, 2].

Even plain tablets may be associated with problems such as difficulty in swallowing, not only in pediatric or geriatric populations but also for handicapped or bedridden patients. This may be due to large tablets sticking to the throat mucosa, causing irritation of the pharyngeal region, coughing or choking. One way to eliminate such problems is the use of the orally disintegrating tablet (ODT) [3-7]. The most important advantages of the ODT are quick disintegration after contact with saliva in the mouth, facilitating swallowing, and ease of delivery, with no need for water to wash down the drug, thus increasing patient adherence.

As leading formulation of ODT, Zydis® [8], or WOWTAB (without water tablet) were developed and commercialized. Nowadays, many ODTs are available [9-13], owing to various manufacturing technologies developed by many researchers [14-21]. The developers of pediatric medicines particularly focus on issues of palatability, for compliance reason [22, 23]. Mini-sized ODTs have now been developed [24, 25] and their usefulness recently evaluated.

ODTs are not only of particular benefit to patients with poor swallowing ability, but also to populations with busy lives, as they can be taken at any time and in any place. In some cases, however, palatability issues such as the bitterness or astringency of the active ingredient may decrease adherence, since the acute drug concentration reached in the oral cavity can be extremely high due to the immediate disintegration of the tablet in saliva. Therefore taste-masking technology must be involved in the design of ODT formulations if the active ingredient is very bitter or astringent. The oral disintegration time of an ODT is a critical factor determining its palatability, rapid disintegration in the oral cavity being an essential feature of ODTs.

The quantitative evaluation of palatability is now an important component in the process of formulation development for various types of oral formulation, including liquids. Human sensation test is major method to evaluate palatability of oral formulations [26-30]. However the use of human volunteers for taste-testing requires the volunteers to be accurate and precise, while ethical issues may prevent human taste-testing of some active drugs, e.g. anti-neoplastics. The use of an artificial taste sensor removes these difficulties. We have used the taste sensor to evaluate the bitterness of many kinds of medicines (both basic and acidic drugs) and have demonstrated its ability to predict accurately the bitterness intensity experienced by human senses [31-52]. The sensor is now available worldwide.

1. Evaluation of taste including bitterness or astringency of medicines

1-1. Insent taste-sensing system

The first taste sensor, composed of lipid/polymer membrane was developed by Toko [53], and is now marketed as the Insent taste-sensing system (Intelligent Sensor Technology Inc., Atsugi, Japan) [54-56] (Fig. 1). The taste sensor output exhibits different patterns for chemical substances that have different taste qualities, i.e. bitterness, sourness, saltiness, umami and sweetness. We have previously evaluated the bitterness of various medicines and amino acids using this system and suggested that the sensor may be useful to predict quantitatively the bitterness of medicines [31-33]. Antibiotics including clarithromycin dry syrup, have been evaluated using this system and a good correlation was obtained between the results of human gustatory sensation testing and the predicted bitterness intensity calculated from the taste sensor output [34]. Aminoleban EN, an elemental diet containing a large quantity of branched chain amino acids (BCAAs) which have a bitter taste, was also successfully evaluated using this system [35, 36]. Kataoka et al. [39, 40] evaluated bottled nutritive drinks using this system and

founded that the bitterness or sourness predicted by taste sensor output correlated well with the results obtained human sensation testing. Not only the taste of medicines but also the suppression of unpleasant tastes could be predicted by this this system. Tsuji et al. [41], and Ishizaka et al. [42] reported on the bitterness-suppressing effect of the jellies using this system, while Tokuyama et al. [43] used it to demonstrated that $_{L}$-Ornithine suppresses the bitterness of BCAA solutions. Hashimoto et al. [44] demonstrated a method for predicting the bitterness-suppressing effect of sweeteners on a famotidine formulation using the sweetness responsive sensor.

1-2. α-ASTREE electronic tongue

A quantitative taste sensor, the α-ASTREE electronic tongue (Alpha MOS, Toulouse, France) is able to evaluate the overall taste of product by using the output value from different electrodes [50-52, 57-62] (Fig. 2). This taste sensor consists of an array of seven liquid cross-sensitive electrodes or sensors based on the ChemFET technology (Chemical modified field effect transistor), an auto-sampler, and associated interface electronic module. In the presence of dissolved compounds, a potentiometric difference is measured between each of the seven sensors and the Ag/AgCl reference electrode. Each sensor has a specific organic membrane, which interacts with ionic, neutral and chemical compounds present in the sample solution. Any interaction at the membrane interface is detected by the sensor and converted into an electronic signal. The taste sensor output is used to calculate the Euclidian distance, a variable used to quantify the taste of the sample medium [57]. Tokuyama E et al [50] predicted the bitterness intensity of famotidine ODTs using this electronic tongue and demonstrated a good correlation between the taste predicted by principal component analysis and the Euclidean distance obtained, and bitterness intensities obtained in the human sensation test. Ito et al. [51] predicted

the bitterness of H_1-antihistamines and the masking effects of sweeteners using this electronic tongue. Maniruzzaman et al. [58-60], Wei et al. [61] and Nakamura et al. [62] also used this electronic tongue as an in vitro taste assessment tool.

2 Evaluation of ODTs

2-1. Disintegration time

In Japanese pharmacopoeia (JP), ODTs are described as tablets that rapidly dissolve or disintegrate in the mouth. However, no definition of the disintegration time is given and no method is specified for measurement.

Three different pieces of apparatus for estimating disintegration time are marketed in Japan, (1) ODT-101 (Toyama Sangyo Co., Ltd., Osaka), (2) TRI-CORPTESTER (Okada Seiko Co., Ltd., Tokyo) and (3) OD-mate (Higuchi Inc., Tokyo).

(1) ODT-101

The disintegration testing apparatus ODT-101 was developed by Narazaki and Harada et al. [45, 63-65]. An ODT sample is placed on a stainless plate. Weight is provided to the shaft which is capable of moving in the vertical direction and rotating, The liquid surface of the test medium (450 mL purified water) is automatically adjusted by a pump so that the water level is slightly below the lower face of the porous plate. The liquid temperature is set to 37℃. The ODT is sandwiched between the rotating weight and the stainless plate such that the load and shear force can be applied to the ODT. Simultaneously, the block is immersed in the test medium and the water level of the test medium increases. The ODT then absorbs the test medium by capillary suction, resulting in disintegration. The effects of load, shear, and wetting, reproduce the conditions in the oral cavity in which an ODT becomes wet with saliva and is lightly ground

between the tongue and upper jaw.

The disintegration times of propiverine hydrochloride ODTs [45], ambroxol tablets [66] were measured using the ODT-101 and the results showed good agreement with the results of human sensation tests.

(2) TRI-CORPTESTER

Hoashi et al. [67] developed a simple test apparatus to evaluate the disintegration time of rapidly disintegrating tablets (RDTs). This apparatus consists of a simple device, which provides a similar environment to that of the oral cavity, and has been commercialized by Okada Seiko Co., Ltd. (Tokyo, Japan) as TRI-CORPTESTER. The device is composed of two meshes; a lower mesh, on which the ODT is placed, and an upper mesh, attached to holders, which is in contact with the ODT and on which artificial saliva is dripped from above. The disintegration time is measured as the time elapsed until the tablet completely disintegrates and the two meshes touch each other. Yoshita et al. [68] reported that the in vitro disintegration time of ODTs measured using TRI-CORPTESTER is a good reflection of the disintegration time in the oral cavity. Matsui et al. [69] also used this method to confirm the disintegration time was within 30s, as recommended by the FDA.

(3) OD-mate

Kakutani et al. [70] developed a disintegration method for ODTs which was more similar to the human sensory test than the JP disintegration test. The method was commercialized by Higuchi Inc. (Tokyo, Japan) as the OD-mate. ODT is placed on a stainless mesh in a flat-bottomed test tube corresponding to the tongue and compressed by two weights (30 g inner weight and 100 g outer weight) corresponding to the upper palate. Test media (10 mL or 20 mL) replicates the inside of the mouth. Using this apparatus, disintegration time of amlodipine ODTs [71], ebastine

ODTs [52], famotidine ODTs [49] have been evaluated by Uchida et al. In all cases, a good correlation was obtained between predicted disintegration time and that measured by human testing. This apparatus was also used for donepezil ODTs to evaluate disintegration time by Hazekawa et al [72, 73].

2-2 Combined taste sensor and apparatus to estimate disintegration time of ODTs

While human gustatory sensation testing is the major method for the in-vivo evaluation of palatability, this method is associated with difficulties and limitations, as mentioned above. A well-established statistical method is required to overcome errors and variability between volunteers within the limits of threshold taste perceptions. Pediatric formulations cannot be tested by pediatric volunteers for ethical reasons. Taste sensor systems which can predict human taste accurately are required as alternative methods for the evaluation of palatability.

Taste masking is almost always necessary for ODTs because most active pharmaceutical ingredients produce an unpleasant taste sensation, such as bitterness, when they dissolve in the oral cavity. Therefore, ODT formulations are required which disintegrate quickly but without expressing bitterness. The combination of taste-sensing system and an apparatus to estimate disintegration time to predict the palatability of ODTs has been reported in several papers. The combination of the Insent taste-sensing system and OD-mate was reported by Uchida et al. [71] and Yoshida et al. [49], while Haraguchi et al. [52] reported a combination of the α-ASTREE electronic tongue and the OD-mate. Table 1 shows the list of evaluated ODTs using systems for estimating disintegration time and taste.

3. Conclusion

Woerts et al. [74] have conducted a comparative study of the Insent taste-sensing system and α-ASTREE electronic tongue for pharmaceutical formulations. Those authors reported that both

systems have their merits and limitations. The Insent taste-sensing system, in which each taste sensor membrane responds to a particular taste, is highly skilled in the quantitative evaluation of taste, such as bitterness intensity. However, some substances are not detected by this system. On the other hand, α-ASTREE electronic tongue is particularly good at evaluating overall taste. It is also capable of qualitative evaluation by comparing Euclidean distances, representing the similarity of tastes. From our previous studies, solifenacine succinate has been evaluated by both Insent taste-sensing system and α-ASTREE electronic tongue [47]. However the taste sensor output produced by ebastine was too low for the bitterness of the formulations to be evaluated [52].

Thus, although the combination of a taste-sensing system and an apparatus to estimate disintegration time would be useful for predicting the palatability of ODTs, we have to select the appropriate devices for combination based on the characteristics of the formulation and its ingredients.

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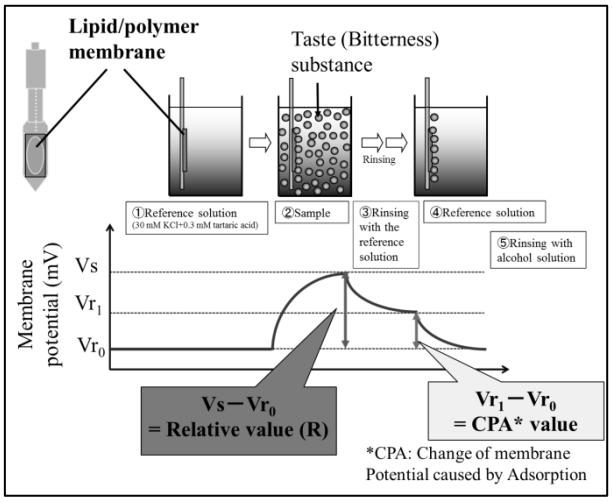

Fig. 1 Measurement procedure of Insent taste-sensing system

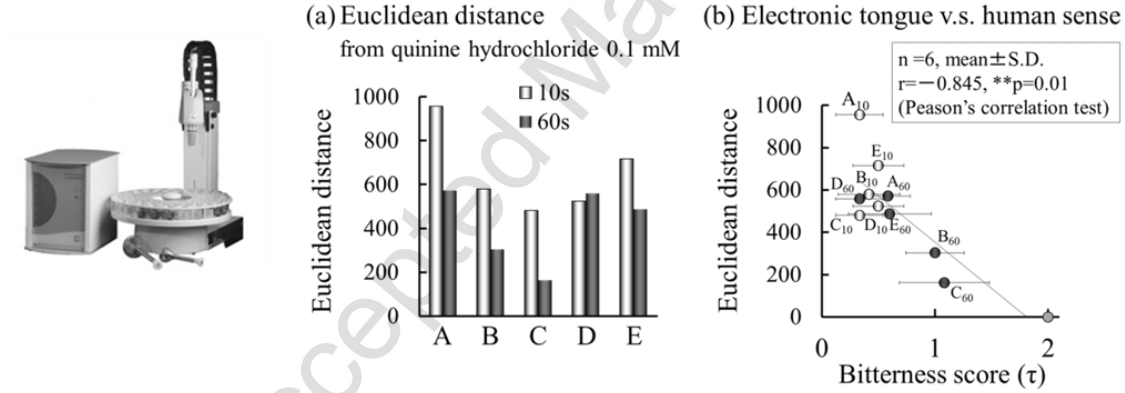

Fig. 2 Evaluation of ebastine orally disintegrating tablets using α-ASTREE electronic tongue [Ref. 52]

Table 1 List of evaluated ODTs using systems for estimating disintegration time and taste

Ingredient	ODTs	Disintegration time (Sec)	Apparatus	Reference No.
Famotidine 20 mg	BLOSTER®M (Elmet Eisai Co., Ltd.) Famotidine D tablet (Nichi-Iko Pharm. Co., Ltd.) GASTER®D (Astellas Pharma Inc.) GASRICK®D (Sawai Pharm. Co., Ltd.) Famotidine OD tablet [YD] (Yoshindo Inc.) STOMARCON®D (Taisho Pharm. Ind. Ltd.)	15-30 (s)	ODT-101	[64]
Ambroxol 15 mg	Mucosolvan® (Teijin Pharma Ltd.) Ponophen® (Aska Pharmaceutical Co., Ltd.) Coughnol (Nichi-Iko Pharmaceutical Co., Ltd.) Nontas® (Ono Pharmaceutical Co., Ltd.) Pulsmarin®A (Takata Seiyaku Co., Ltd.) Fuzuleban (Tatsumi Ltd.) Grinkool® (Nippon Chemiphar Co., Ltd.) Ambroxol hydrochloride tablets 15 mg [Ze] (Zensei Pharm. Ind. Co., Ltd.) Ambroxol hydrochloride tablets 15 mg [Sawai] (Sawai Pharm. Co., Ltd.) Ambroxol hydrochloride tablets 15 mg [Ch] ((Mylan Seiyaku Ltd.)	20-400 (s)	ODT-101	[66]
Lansoprazole	Takepron® OD (Takeda Pharmaceutical Co., Ltd.)	25 (s)		
Triazoram	Triazolam tab. [EMEC] (Elmet Eizai Co., Ltd.)	10 (s)		
Enalapril	Enalapril M tab. [EMEC] (Elmet Eizai Co., Ltd.)	10 (s)	TRI-CORPTESTER	[67]
Famotidine	Gaster® D (Astellas Pharma Inc.)	10 (s)		
Brotizolam	Lendormin® D (Nippon Boehringer Ingelheim Co., Ltd.)	15 (s)		
Amoldipine besilate	Amlodin® OD tablets 5 mg , 25 mg (Dainippon Sumitomo Pharma Co., Ltd.)	18 (s)		
Donepezil hydrochloride		17 (s)		
Voglibose	AMLODIPINE-OD TABLETS 2.5 mg (Towa Pharmaceutical Co., Ltd.)	20 (s)		
Brotizolam	AMLODIPINE-OD TABLETS 5 mg (Towa Pharmaceutical Co., Ltd.)	15 (s)		
Ebastine	Amlodipine 2.5 mg (Nippon Chemiper Co., Ltd.)	24 (s)	TRI-CORPTESTER	[68]
Famotidine	Amlodipine 5 mg (Nippon Chemiper Co., Ltd.)	5 (s)		
Irsogladine malate	Aricept® D tablets 5 mg (Eisai Co., Ltd./Pfizer Japan Inc.)	29 (s)		
Tamsulosine hydrochloride	BASEN® OD Tablets 0.2 mg (Takeda Pharmaceutical Co., Ltd.)	13 (s)		
Lansoprazole	Lendormin D tablets 0.25 mg (Boehringer Ingelheim Japan Inc.)	13 (s)		

Polaprezinc	BROTIZOLAM (Teva Pharma Japan Inc.)	17 (s)		
Magnesium oxide	EBASTEL® (Dainippon Sumitomo Pharma Co., Ltd.)	19 (s)		
Risperidone	Gaster® D tablets 10 mg (Astellas Pharma Inc.)	27 (s)		
	Gaster® D tablets 20 mg (Astellas Pharma Inc.)	28 (s)		
	Gaslon N® OD tablets 2 mg, 4 mg (Nippon Shinyaku Co., Ltd.)	10 (s)		
	Harnal D tablets 0.1 mg (Astellas Pharma Inc.)	31 (s)		
	Harnal D tablets 0.2 mg (Astellas Pharma Inc.)	17 (s)		
	TAMSLON-OD TABLETS 0.1 mg (Towa Pharmaceutical Co., Ltd.)	24 (s)		
	TAMSLON-OD TABLETS 0.2 mg (Towa Pharmaceutical Co., Ltd.)	24 (s)		
	Takepron® OD tablets 15 mg (Takeda Pharmaceutical Co., Ltd.)	32 (s)		
	Takepron® OD tablets 30 mg (Takeda Pharmaceutical Co., Ltd.)	9 (s)		
	Promac® D tablets 75 (Zeria Pharmaceutical Co., Ltd.)	9 (s)		
	Magmitt Tab 250 mg (Kyowa Chemical Industry Co., Ltd.)	12 (s)		
	Magmitt Tab 330 mg (Kyowa Chemical Industry Co., Ltd.)	24 (s)		
	RISPERDAL® OD Tablets 1 mg (Japan Pharmaceutical Co., Ltd.)	27 (s)		
	RISPERDAL® OD Tablets 2 mg (Japan Pharmaceutical Co., Ltd.)			
Ebastine	Ebastel® OD 10 mg (Dainippon Sumitomo Pharm. Co., Ltd.)	25 (s)	OD-mate,	[52]
Amlodipine besilate	and 4 generic products	20-40 (s)	α-ASTREE	[71]
Famotidine	Amlodine® OD 5 mg (Dainippon Sumitomo Pharm. Co., Ltd.)	10-35 (s)	OD-mate,	[49]
Donepezil hydrochloride	and 9 generic products	10-60 (s)	Insent	[72], [73]
	Gaster®D 10 mg (Astellas Pharma Inc.)		taste-sensing	
	and 9 generic products		system	
	Aricept® D 5 mg (Eisai Co., Ltd.)		OD-mate,	
	and 8 generic products		Insent	
			taste-sensing	
			system	
			OD-mate	