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An advanced technique using an electronic taste-sensing system to evaluate the bitterness of orally disintegrating films and the evaluation of model films

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ABSTRACT

Taste detection systems using electronic sensors are needed in the field of pharmaceutical design. The aim of this study was to propose an advanced technique using a taste-sensing system to evaluate the bitterness of an orally disintegrating film (ODF) samples. In this system, a solid film sample is kept in the test medium with stirring, and the sensor output is recorded. Model films were prepared using a solution-casting method with a water-soluble polymer such as pullulan, HPMC, HPC or PVP as film formers, and donepezil hydrochloride and quinine hydrochloride as model bitter-tasting active pharmaceutical ingredients (APIs). The results showed that this advanced techniques could detect the emergence of bitterness along the time course. Increasing the amount of donepezil hydrochloride increased the sensor output. The sensor output was suppressed at the very early stage of the test, and then increased. Both the film thickness and the use of additives markedly affected the delay of the sensor output. The profile of the sensor output was accurately related to the release of APIs. It was concluded that this advanced technique could detect the onset of bitterness during the initial stage of ODF administration.

1. Introduction

One of the most important issues for orally disintegrating pharmaceuticals is their palatability in the oral cavity. Orally disintegrating pharmaceuticals must disintegrate rapidly when placed in the mouth, without drinking or chewing (Ghosh and Pfister, 2005). Owing to their thinness and flexibility, orally disintegrating films (ODFs) are expected to have better palatability in the oral cavity than orally disintegrating tablets (ODTs). ODF forms of pharmaceuticals are being developed for geriatric, pediatric and dysphagic patients who find it difficult to swallow the usual solid dosage forms such as tablets or capsules (Dixit and Puthli, 2009).

It has been pointed out that the bitterness of ODTs is locally much greater than with conventional tablets, because ODTs disintegrate in the mouth (Tokuyama et al., 2009; Hashimoto et al., 2007). For the same reason, ODFs must be scrutinized more closely for palatability. Several researchers (Mahesh et al., 2010; Cilurzo et al., 2011) have performed tests to evaluate the bitterness and taste-masking efficiencies of ODFs. However, these tests were performed, in vivo, using responses in healthy human volunteers.

Electronic taste-sensing systems have already been utilized in pharmaceutical research and development (Miyanaga et al., 2002a; Woertz et al., 2011), and are important in designing pharmaceutical formulations (Uchida et al., 2000, 2003). Using a taste-sensing system (electronic tongue), evaluation of ODTs can be performed without human volunteers and with greater simplicity, safety and rapidity (Lorenz et al., 2009). In the case of ODTs, the bitterness should be traced from the beginning of administration along the whole time-course of disintegration in the oral cavity. However, the conventional method using electronic taste-sensing systems that the eluates of ODTs first be collected from a beaker and then filtrated (Hashimoto et al., 2007; Yoshida et al., 2015; Uchida et al., 2014; Haraguchi et al., 2013). Cilurzo et al. used an electronic taste sensor to select the most suitable taste-masking agents for ODFs. They tested the solutions constituted by APIs and the taste masking agents, and then analyzed the solutions

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obtained by dissolving film formulations (Cilurzo et al., 2011). The usefulness and applicability of an electronic taste-sensing system for taste evaluation of ODFs using a flow-through cell was already demonstrated in the previous study (Takeuchi et al., 2017). A flow-through cell could be utilized to collect eluates of ODFs along the time course. The eluates were then filtrated for application to the sensor. This taste-sensing system could successfully trace the sensor output for ODFs along the time course. On the other hand, it could not elucidate the sensor output at the initial stage of administration, i.e. within the first 30 s in the oral cavity.

The aims of the present study were to develop an advanced technique using an electronic taste-sensing system for evaluation of the emergence of bitterness in ODFs at the initial stage of administration. Model films with the simple formulations were prepared and evaluated. In this evaluation, a BT0 sensor was used rather than a multi-sensing system. Our technique focused on detecting the emergence of bitterness output from the ODFs at the initial stage of administration, given the importance of this stage for the patient's experience.

Model films were prepared using the solution/solvent casting method. A water-soluble polymer such as pullulan, hydroxypropyl methylcellulose, hydroxyl methylcellulose, or polyvinyl pyrrolidone was used as the film former together with chosen additives. Pullulan is one of the most suitable polymers for ODFs, due to its water solubility and palatability (El-Malah and Nazzal, 2013). This polymer has been used as a base material of film for commercial ODFs such as Benadryl® Allergy Quick Dissolve Strips (Johnson & Johnson) and Sudafed PE Quick-Dissolve Orally Disintegrating Strips (Wolters Kluwer Health). Hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC) constitute the base materials of other commercial ODFs such as Triaminic Thin Strips®, Theraflu Thin Strips® (Novartis Consumer Health) and Chloraseptic® sore throat relief strips (Prestige Brands International). Polyvinylpyrrolidone (PVP) is widely used in pharmaceutical industries as a coating material.

Donepezil hydrochloride (DH) or quinine hydrochloride (QH) was loaded into ODF samples as the model drug. DH is a very useful active ingredient for Alzheimer's disease, but it is extremely bitter (Yan et al., 2010; Liew et al., 2012). It has been prescribed in commercial ODTs and ODFs, at dose of 3 mg, 5 mg and 10 mg: for example, Aricept® (Eisai) and Donepezil Hydrochloride OD film (Elmed Eisai). In the present study, we used 3 mg or 5 mg of DH per film strip based on these commercial formulations. Tween80 (0.3% based on the total weight except solvents) is also required in a pullulan film formulation as a surfactant to achieve a smooth, flat casting. Selected additives were also added to the film formulation with the goal of delaying the release of the API and thereby suppressing the bitterness. Apart from DH, QH is a standard active ingredient known to have a strongly bitter taste (Uchida et al., 2000; Miyanaga et al., 2002b; Ogawa et al., 2005).

The viability of our advanced technique using an electronic taste-sensing system with the BT0 sensor was confirmed with its application to model ODFs prepared for the study, along with ten ODTs and one ODF currently on the commercial market.

2. Materials and methods

2.1. Materials

Pullulan was purchased from Tokyo Chemical Industry (Tokyo, Japan). Hydroxypropyl methylcellulose (HPMC) (Hypromellose TC-5R, Shin-Etsu Chemical, Tokyo, Japan), hydroxypropyl cellulose (HPC) (Nisso HPC-SSL, Nippon Soda, Tokyo, Japan) and polyvinylpyrrolidone (PVP) (Kollidon 90F; BASF Japan, Tokyo, Japan) were kindly provided by Shin-Etsu Chemical, Nippon Soda and BASF Japan, respectively. Donepezil hydrochloride (DH9 (lot. No. DNPJN0K001) was supplied as a gift sample. Quinine hydrochloride (QH) was purchased from Kishida Chemical (Osaka, Japan). Phosphatidic acid (Benecoat BMI-40; Kao Chemicals, Tokyo, Japan), as a commercial bitterness-suppression agent, and pectin (Unipectine AYD 5110SB, HM pectin, UNITEC Foods, Osaka, Japan) were received as gift samples. Tween80 and sodium alginate were purchased from Kishida Chemical and Nacalai Tesque (Kyoto, Japan), respectively. All the solvents were of analytical grade.

Various marketed ODTs and an ODF loaded with donepezil hydrochloride (Eisai, Tokyo, Japan; Elmed Eisai, Tokyo, Japan; Meiji Seika Pharma, Tokyo, Japan; Mochida Pharmaceutical, Tokyo, Japan; Nichi-Iko Pharmaceutical, Toyama, Japan; Nipro Pharm Corporation, Osaka, Japan; Ohara Pharmaceutical, Tokyo, Japan; Sawai Pharmaceutical, Osaka, Japan; Sumitomo Dainippon Pharm, Osaka, Japan; Taiyo Pharmaceutical Industry, Nagoya, Japan; TEVA-KOWA Pharma, Tokyo, Japan) were purchased.

2.2. Preparation of oral disintegrating films

The water-soluble polymers pullulan, HPMC, HPC and PVP, were used as the film formers. Donepezil hydrochloride (DH) and quinine hydrochloride (QH) were used as the model drugs. DH is well known for its high bitterness and its utility in treating Alzheimer's disease (Yan et al., 2010; Liew et al., 2012). QH is the substance most commonly used as a bitterness standard (Nakamura et al., 2002; Ogawa et al., 2005). The amount of DH loaded onto the film strips (3 mg and 5 mg per strip) was based on the formulations of commercial DH tablets and film. The formulations of our casting films are shown in Table 1.

The preparation of casting solutions depended on the film-forming polymers used. Pullulan solutions were prepared with distilled water, along with Tween80 as a surfactant, to enable smooth, even spreading on the flat base during the casting process. HPMC powder was dispersed gradually in distilled water maintained over 70 °C, and then cooled down in a chilled water bath with stirring until HPMC dissolved completely. HPC solutions were prepared with a 1:1 distilled water: ethanol solvent. PVP solutions were prepared with distilled water, together with Tween80. DH was dissolved into water and added into the polymer solutions. Additives were also added into the dispersions/solutions, if formulated. Polymer solutions were sucked using a vacuum pump to remove the trapped air bubbles before casting onto a base film (polypropylene) using a YBA-type Baker Applicator (Yoshimitsu

Table 1
Formulations of orally disintegrating films

Polymer	Pullulan				HPMC			HPC	PVP
APIs content (mg/strip)	3	3	3	5	3	3	5	3	3
Weight of a film strip (mg)	30	30	60	30	30	60	30	30	30
Polymer	89.7	69.7	94.7	83.0	90.0	95.0	83.3	90.0	89.7
Tween 80	0.3	0.3	0.3	0.3	–	–	–	–	0.3
APIs	10.0	10.0	5.0	16.7	10.0	5.0	16.7	10.0	10.0
Additives	–	20.0	–	–	–	–	–	–	–
Total (%)	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0