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Preparation and evaluation of orally disintegrating tablets containing taste masked microparticles of acetaminophen

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In the present work, taste masked particles of acetaminophen (AAP), a highly soluble bitter tasting drug, were developed and ODT containing the taste masked particles were prepared. Taste masked particles of AAP were prepared using different amounts of tetraglycerol polyricinoleate (TGPR) and Eudragit® E100. Although the drug content ratio and drug recovery decreased with increasing TGPR, drug release from AAP-CR100 particles containing a large amount of TGPR was mostly suppressed for 2 min. Hence, AAP-CR100 was incorporated into ODT as taste masked particles for AAP. Three major disintegrants were used for ODT, and it was confirmed that the tensile strength of all formulations showed applicable hardness for handling. The AAP-CR100-CP(40) formulation containing crospovidone showed the shortest disintegration time and the drug release from AAP-CR100-CP(40) into pH 6.8 test solution was suppressed compared with commercial AAP tablets. Because the drug release from AAP-CR100-CP(40) into the pH 1.2 test solution was rapid, it was suggested that drug release from AAP-CR100-CP(40) is suppressed in the oral cavity, and the drug is released promptly in the stomach. Thus AAP-CR100-CP(40) may be useful as an ODT in which the dissolution of AAP in the oral cavity is suppressed.

1. Introduction

Orally disintegrating tablets (ODT) disintegrate quickly with saliva when administered into the oral cavity and taken without water or chewed. ODT are easy to take for children and the elderly, who may experience difficultly in taking ordinary oral preparations such as tablets, capsules, and powders (Mizumoto et al. 2005; Yoshida et al. 2008; Yıldız et al. 2016). In addition, ODT can be taken regardless of time and place because administration does not require water. ODT often include sweeteners and flavoring agents in order to suppress the bitterness or unpleasant taste caused by the elution of drug substances in the oral cavity (Shiino et al. 2010; Hirata et al. 2016; Drašković et al. 2017; Kande et al. 2017; Kobayashi et al. 2018). Although ODT containing controlled release microparticles of the drug will reduce the unpleasant taste by the suppression of drug release in the oral cavity, ODT still need to disintegrate in the oral cavity, and in general manufacturing ODT with functions such as taste masking or controlled release (sustained release and site-specific release) are very difficult to achieve (Kondo et al. 2011). Although functional (taste-masking or controlled-release) ODT can be prepared by tableting powders containing film-coated drug particles, it was reported that such ODT lack the necessary robustness due to the low compactability of coated particles and the release profile of the coated particles when the coating membrane ruptured during compression (Aulton et al. 1994; Maganti and Çelik 1994; Debunne et al. 2004).

In this study, acetaminophen (AAP) was selected as a highly soluble bitter tasting drug substance (Kalantzi et al. 2006), and in order to suppress the bitterness of AAP in the oral cavity, taste masked particles of AAP were developed. The pH of saliva is usually close to neutral with a pH of 6.49-7.28, and different buffer systems such as proteins, hydrogen phosphate, and hydrogen carbonate are in place to stabilize its pH (Gittings et al. 2015; Hoffmann and Daniels 2018). Hence, Eudragit® E100 (Eudragit), amino alkyl methacrylate copolymer insoluble above pH 5 (Rao et al. 2003; Obeidat et al. 2015; Drašković et al. 2017), was used as a taste masking polymer.

Table 1: Composition of taste masked particles of AAP

Formulation	AA	Eudragit	TGPR
		mg	
AAP-CR50	200	100	50
AAP-CR75	200	100	75
AAP-CR100	200	100	100
AAP-CR100-E75	200	75	100

Because AAP is a water-soluble drug, we attempted to prepare particles using a water in oil (w/o) type emulsifier, tetraglycerol polyricinoleate (TGPR). Although TGPR is commercially available as a food additive and can be used to obtain stable w/o and w/o/w emulsions (Márquez et al. 2010; Pradhan et al. 2014; Wakisaka et al. 2014), there have only been few reports where TGPR was used to prepare taste masked microparticles. Taste masked particles containing AAP were prepared by varying the amount of TGPR, and the drug release properties were evaluated. Furthermore, ODT incorporating the taste masked particles were prepared. Three major disintegrants, low-substituted hydroxypropyl cellulose (HPC), crospovidone (CP), and croscarmellose sodium (CMC) (Desai et al. 2016; Fujimoto et al. 2016), were added to ODT and the formulation properties were evaluated. Using the most suitable disintegrant, ODT containing taste masked particles of AAP was prepared and the drug release properties were evaluated.

2. Investigations, results and discussion

2.1. Characterization of taste masked particles of AAP

The composition of the taste masked particles of AAP is shown in Table 1. The taste masked particles of AAP were prepared using an emulsification method with Eudragit as the taste masking polymer.

Table 2: Drug content ratio and drug recovery in taste masked particles of AAP

	Drug content ratio	Drug recovery
	%	
AAP-CR50	63.6±3.6	84.4±2.7
AAP-CR75	60.1±1.1	62.7±8.1
AAP-CR100	53.4±4.4	45.0±5.4

Each value represents the mean±S.D. (n = 3).

The amount of Eudragit was set as 100 mg or 75 mg, and the particles were prepared using different amounts of TGPR. Although it was confirmed to be a homogeneous emulsified solution when 100 mg of Eudragit was used, precipitates were confirmed using 75 mg of Eudragit. Hence, the amount of Eudragit was set to 100 mg. The drug content ratio and drug recovery in the AAP particles are shown in Table 2. The drug content ratio decreased relatively with increasing TGPR. The drug recovery also decreased with increasing TGPR. The formulation plasticity increased with increasing TGPR loading, and the adhesive properties to the sieve increased on the particles containing a lot of TGPR. Because a portion of the formulation adhered to the sieve, the drug recovery decreased. The drug release profiles from the particles are shown in Fig. 1. Drug release from the taste masked particles of AAP was suppressed after 5 min compared with AAP bulk powder. Because drug release in the oral cavity causes the bitterness, suppression of the initial drug release is needed. The percentages of drug released until 1 min from AAP bulk powder, AAP-CR50, AAP-CR75, and AAP-CR100 were 25.0±8.0 %, 33.3±3.5 %, 25.1±3.1 %, and 18.1±5.4 %, respectively. The percentages of drug released until 2 min from AAP bulk powder, AAP-CR50, AAP-CR75, and AAP-CR100 were 41.3±5.2 %, 47.5±4.4 %, 43.2±5.9 %, and 25.7±3.4 %, respectively. Drug release from the AAP-CR100 formulation was most suppressed until 2 min. The DSC thermograms and XRPD patterns of AAP bulk powder and the AAP particles are shown in Fig. 2. In the DSC thermogram of AAP bulk powder (Fig. 2(a)A), a sharp peak was observed at 170°C. In the DSC thermograms of the particles (Fig. 2(a)B-D), the peak shifted towards a lower temperature (164 °C). From the XRPD patterns of AAP bulk powder (Fig. 2(b)A) and the AAP particles (Fig. 2(b)B-D), although the peak intensity decreased, the peak position of the AAP particles agreed with that of the AAP bulk powder. Furthermore, the XRPD patterns of the AAP particles showed increased amorphous trends compared with AAP bulk powder (Wang et al. 2011; Maniruzzaman et al. 2012). It was considered that microcrystals and amorphous AAP were present in the AAP particles. A concentrated aqueous solution of polyglycerol fatty acid ester is known to have a liquid crystal structure (Duerr-Auster et al. 2007; Yamaguchi et al. 2016). In the present study, when AAP ethanol solution and Eudragit and TGPR diethyl ether solutions were mixed, it was possible that TGPR formed micelles (Matsuoka et al. 2017). Then, because the ethanol and diethyl ether were subsequently evaporated to dryness, there is a possibility that TGPR formed a lamellar structure. The lamellar structure constructs the hydrophilic and hydrophobic part, and AAP was loaded into the hydrophilic part and microcrystalline AAP might grow. On the other hand, Eudragit might be loaded into the hydrophobic part of the lamellar structure. It was considered that the DSC peak of the AAP particles shifted to a lower temperature, because AAP formed a mixture with TGPR and Eudragit. The XRPD patterns of AAP-CR100 stored at 25 °C, 60 %RH are shown in Fig. 3. The peak intensity decreased slightly with time. This was thought to be due to the influence of moisture absorption. However, because the peak pattern did not change for four weeks, it was suggested that the crystal form of AAP was stable in the mixture.

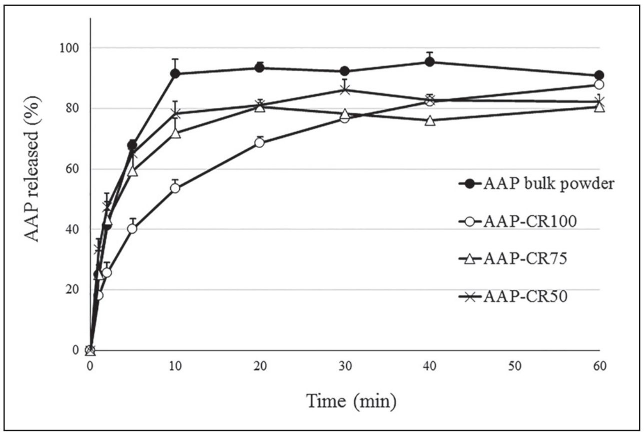

Fig. 1: Drug release profiles from taste masked particles of AAP. Each point represents the mean±S.D. (n=3).

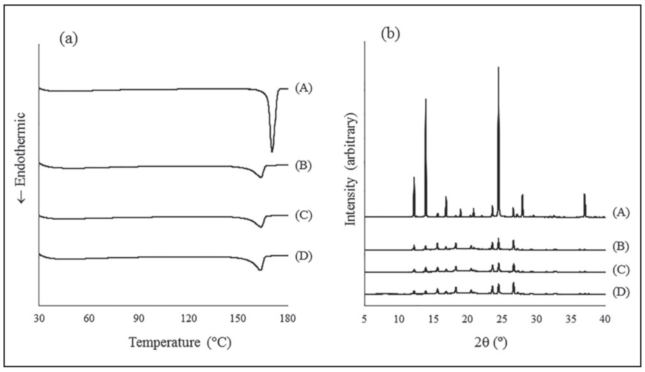

Fig. 2: (a) DSC thermograms and (b) XRPD patterns of: (A) AAP bulk powder, (B) AAP-CR100, (C) AAP-CR75, (D) AAP-CR50

Table 3: Composition of ODT containing taste masked particles of AAP

Formulation	Mannitol	HPC	CP	CMC	Mg-St	AAP-CR100 (50 mg as AAP)
	mg/Tab					
AAP-CR100-HPC(20)	246.0	20.0	-	-	4.0	86.4
AAP-CR100-CP(20)	246.0	-	20.0	-	4.0	86.4
AAP-CR100-CMC(20)	246.0	-	-	20.0	4.0	86.4
AAP-CR100-HPC(40)	226.0	40.0	-	-	4.0	93.7
AAP-CR100-CP(40)	226.0	-	40.0	-	4.0	93.7
AAP-CR100-CMC(40)	226.0	-	-	40.0	4.0	93.7

Table 4: Tensile strength and disintegration time of ODT

Formulation	Tensile strength* (N/mm^2)	Disintegration time** (s)
AAP-CR100-HPC(20)	0.70±0.06	230.3±3.3
AAP-CR100-CP(20)	0.63±0.01	28.3±0.9
AAP-CR100-CMC(20)	0.57±0.03	81.0±6.4
AAP-CR100-HPC(40)	0.58±0.03	210.3±8.6
AAP-CR100-CP(40)	0.59±0.02	22.3±1.7
AAP-CR100-CMC(40)	0.63±0.13	78.0±2.2

*: Each value represents the mean±S.D. (n = 4)
**: Each value represents the mean±S.D. (n = 3)

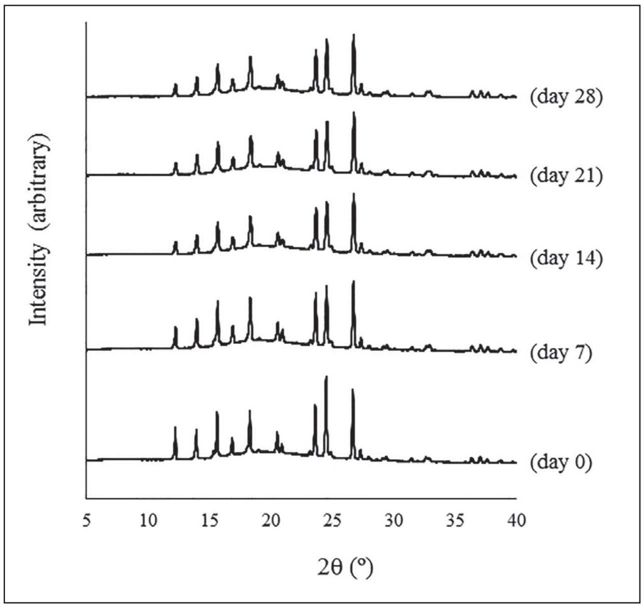

Fig. 3: XRPD patterns of AAP-CR100 stored at 25°C, 60%RH

2.2. *Characterization of ODT containing taste masked particles of AAP*

Since drug release from the AAP-CR100 formulation was most suppressed, AAP-CR100 was incorporated into ODT as for the taste masked particles of AAP. The compositions of ODT containing the taste masked particles of AAP are shown in Table 3. The content of AAP in the ODT was set at 50 mg. HPC, CP, or CMC was added as a disintegrant and the content was set at 20 mg or 40 mg. The tensile strength and disintegration time of ODT prepared are shown in Table 4. Regarding tensile strength, all formulations showed applicable hardness in handling. The formulation containing CP as a disintegrant showed the shortest disintegration time. Furthermore, the disintegration time of the formulation containing 40 mg of CP was shorter than that one containing 20 mg. The ODT formulations were placed in two types of containers and purified water was dropped into the containers.

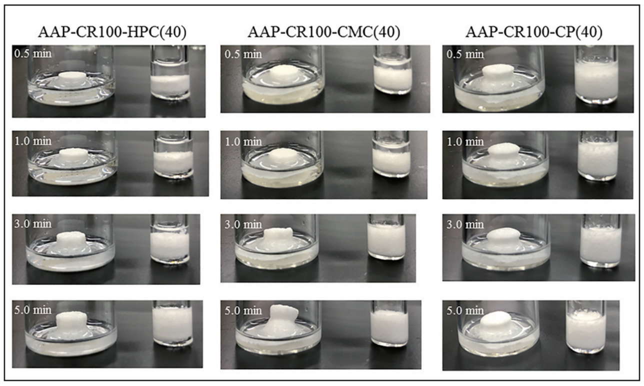

Fig. 4: Photographs of change over time of ODT placed in two types of containers after the addition of drops of purified water

The photographs of change over time of ODT after dropping on purified water are shown in Fig. 4. From the photographs, AAP-CR100-CP(40) absorbed water most quickly and collapsed from the bottom of the tablet by its own weight. On the other hand, AAP-CR100-HPC(40) and AAP-CR100-CMC(40) absorbed water moderately and swelled gradually. Onuki et al. (2018) tested various disintegrants in order to understand the disintegration actions, and measured the interaction of the disintegrant particles with water by pulse NMR. The T_2 is an index to estimate the interaction between the disintegrant and water, and shorter T_2 indicates the water molecular mobility is restricted more tightly by the interaction with the disintegrant particles. As a result of T_2 measurements, the longest T_2 value was observed for CP. Hence, it was suggested that CP had a weaker interaction with water molecules. In this study, AAP-CR100-CP(40) absorbed water most quickly and collapsed by its own weight. It was considered that although CP in AAP-CR100-CP(40) could absorbed water, the tablet could not hold water due to the weak interactions with water. As a reason why AAP-CR100-CP(40) showed the shortest disintegration time, the influence of physicochemical properties of CP, the weaker interactions with water molecules, was suggested.

The drug release profiles from ODT and the commercial AAP tablet are shown in Fig. 5. AAP-CR100-CP(40) with the shortest disintegration time was used as ODT in the drug release experi-

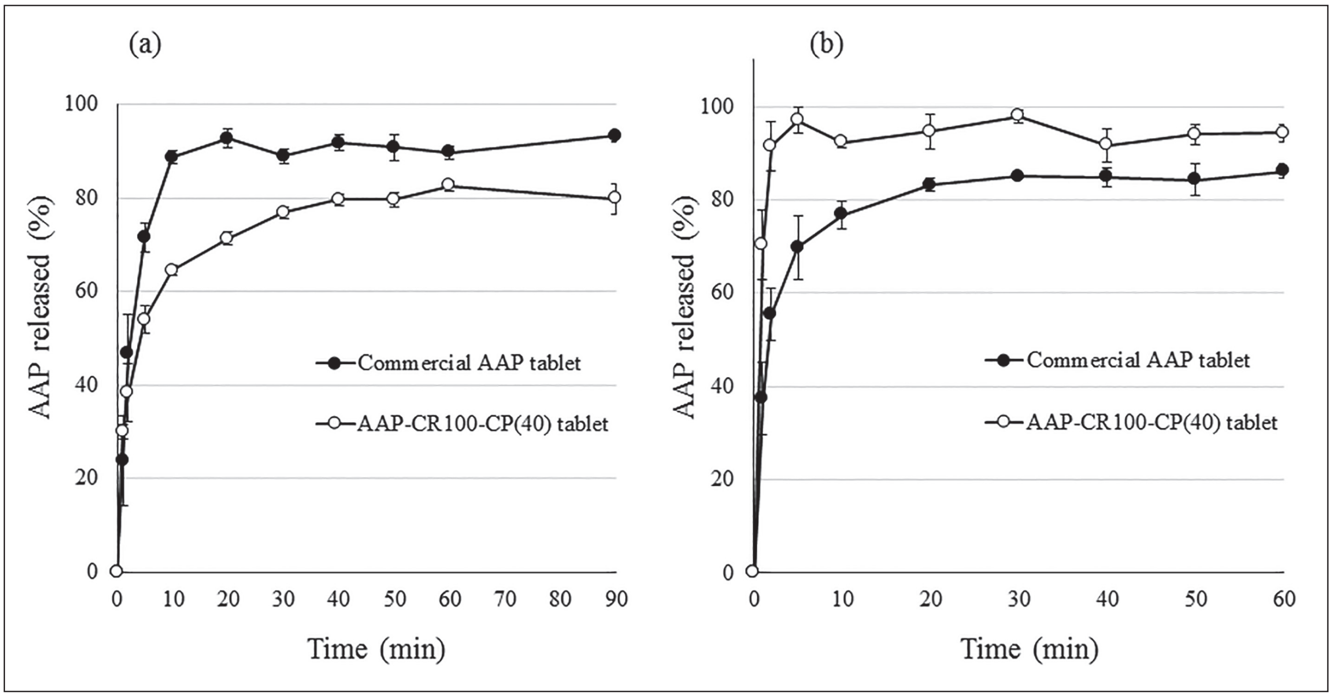

Fig. 5: Drug release profiles from ODT and commercial AAP tablets; (a) pH 6.8 test solution and (b) pH 1.2 test solution. Each point represents the mean±S.D. (n=3).

ment. Because the pH of saliva is usually close to neutral, a pH 6.8 test solution was used as the drug release medium in order to predict the drug release into saliva in the oral cavity. In Fig. 5(a), the drug release from AAP-CR100-CP(40) was suppressed compared with the ordinary AAP tablet. The drug release percentage up to 2 min was 38.3±6.2 % for AAP-CR100-CP(40) and 46.7±8.3 % for the ordinary AAP tablet, respectively. The disintegration time (mean±S.D., n=3) was 22.3±1.7 s for AAP-CR100-CP(40) and 95.3±6.6 s for the ordinary AAP tablet, respectively. Hence, it was suggested that although AAP-CR100-CP(40) disintegrates quickly in the oral cavity, drug release was suppressed compared with ordinary AAP tablets. The drug release from AAP-CR100-CP(40) into the pH 1.2 test solution was rapid in Fig. 5(b), and 90 % or more of the drug was released in 2 min. From these results, it is suggested that drug release from AAP-CR100-CP(40) is suppressed in the oral cavity, and the drug is released promptly in the stomach. Hence, AAP-CR100-CP(40) may be a useful ODT for AAP with suppressed drug release in the oral cavity.

3. Experimental

3.1. *Materials*

AAP and magnesium stearate (Mg-St) was purchased from FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan). TGPR (SY-Glyster CR-310) was supplied by Sakamoto Yakuhin Kogyo (Osaka, Japan). Eudragit was obtained from Evonik Japan Co., Ltd. (Tokyo, Japan). Mannitol (Mannogem® EZ Spray Dried) was from Asahi Kasei Corporation (Tokyo, Japan). HPC (NBD-021) was from Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). CP (Kollidon® CL-F) was obtained from BASF Japan Ltd. (Tokyo, Japan). CMC (AcDiSol®) was supplied by Wilbur-Ellis Japan (Tokyo, Japan). As a commercially available AAP tablet, acetaminophen tablet 200 mg [JG] was purchased from Choseido Pharmaceutical Co., Ltd. (Tokushima, Japan). All other chemicals were obtained commercially at the highest purity grade available.

3.2. *Preparation of taste masked particles of AAP*

The composition of the taste masked particles of AAP is shown in Table 1. The particles were prepared as follows: AAP was dissolved in 5 ml ethanol using a recovery flask, and Eudragit and TGPR were dissolved in 15 ml diethyl ether. The Eudragit and TGPR solution was added to the AAP ethanol solution, and the mixture was agitated. The ethanol and diethyl ether were subsequently evaporated from the mixture using a rotary evaporator. The residue mixture in the recovery flask was peeled and sieved (mesh size = 425 mm). The sieved particles were obtained as the taste masked particles of AAP.

3.3. *Drug content ratio and drug recovery*

The drug content ratio in the particles was calculated as follows;

$$\text{Drug content ratio (\%)} = W_d / W_p \times 100 \qquad (1)$$

The drug recovery was calculated as follows;

$$\text{Drug recovery (\%)} = W_d / W_{id} \times 100 \qquad (2)$$

where W_d is the amount of AAP in the particles, W_p is the amount of the particles, and W_{id} is the amount of initial AAP. The amount of AAP in the particles was determined by high-performance liquid chromatography (HPLC). The HPLC system consisted of a LC-20AD pump and a SCL-10A VP system controller (Shimadzu, Kyoto, Japan) equipped with a Capcell Pak C18 MG II column (4.6 × 250 mm, Shiseido Co., Ltd., Tokyo, Japan) and an SPD-20A UV detector (Shimadzu). Chromatography was carried out at 40°C. The mobile phase comprised 25% (v/v) acetonitrile in 2.8 mmol/l phosphoric acid solution. The flow rate was 1 ml/min, and the detection wavelength was 254 nm (Kubo et al. 2003).

3.4. *Drug release from taste masked particles of AAP*

Because the pH of saliva is usually close to neutral with a pH of 6.49–7.28, drug release experiments were performed using pH 6.8 phosphate buffer (2nd fluid, described in the Dissolution Test in the Pharmacopoeia of Japan 17 [JP17]) as the dissolution media in accordance with the paddle method in the Dissolution Test (JP17). A dissolution tester (NTR-VS3, Toyama Sangyo Co., Ltd.) was used. AAP bulk powder (20 mg) or sieved taste masked particles of AAP (mesh size = 425 mm) equivalent to 20 mg AAP were placed in a sinker and immersed in 900 ml of dissolution medium pre-warmed to 37±0.5 °C, and the paddle was rotated at 50 rpm. One-milliliter samples of the dissolution media were taken at predetermined time points and filtered using a fine filter (5 µm pore size). One milliliter of fresh medium was added immediately after each sample was taken. The filtrate was analyzed using an UV spectrophotometer (UV-1800, Shimadzu Corporation) at 244 nm to determine the amount of the drug released.

3.5. *Differential scanning calorimetry*

The thermal properties of the particles were determined using differential scanning calorimetry (DSC, Thermo plus EVO II DSC8230, Rigaku Corporation). Samples weighing approximately 2 mg were heated in a sealed aluminum pan at a constant heating rate of 10°C/min from 30°C to 180°C under a nitrogen purge (100 ml/min).

3.6. *X-ray powder diffraction*

X-ray powder diffraction (XRPD) patterns of the particles were obtained using a 9 kW SmartLab Rigaku diffractometer (Rigaku Corporation) with a rotating anode at room temperature. The voltage and amperage were set at 45 kV and 200 mA, respectively. Each sample was scanned between 5° and 40° in 2° with a step size of 0.02 and scan speed of 2°/min.

3.7. *Storage test*

AAP-CR100 was stored at 25 °C with a relative humidity (RH) of 60% for 4 weeks. During storage, XRPD patterns of the particles were measured over time.

3.8. *Preparation of ODT containing taste masked particles of AAP*

The compositions of ODT containing the taste masked particles of AAP are shown in Table 3. The content of AAP in the ODT was set at 50 mg. AAP-CR100 was prepared according to the composition of Table 1, and the preparation of AAP-CR100 particles was repeated 12 times. The particles were mixed and used for the ODT containing 20 mg of the disintegrants. Other AAP-CR100 particles prepared by 12 repetitions were used for the ODT containing 40 mg of the disintegrants. The ODT were formulated as follows. The AAP-CR100 particles, mannitol and disintegrants were sealed in a plastic bag and mixed by shaking for 2 min. Mg-St was added to the powder and mixture by shaking for a further 1 min. The one tablet weight of powder mixture was put into a mold made of stainless steel (diameter, 10 mm) for tableting. Using a hand press (SSP-10A, Shimadzu Corporation), tablets were formed by compression with a force of 2 kN for 1 s.

3.9. *Characterization of ODT*

3.9.1. *Tensile strength of ODT*

The thickness of the tablets was determined using vernier calipers. The hardness of the tablets was determined using a Monsanto hardness tester (Kayagaki Irika Kogyo, Ltd., Tokyo, Japan). Tablet tensile strength (T) was calculated using Eq. (3),

$$T = 2F/pdt, \qquad (3)$$

where F, d and t denote the diametral crushing force, tablet diameter and tablet thickness, respectively.

3.9.2. *Disintegration test*

The disintegration time of each ODT formulation was determined using a disintegration tester (NT-60H, Toyama Sangyo Co., Ltd., Japan) in accordance with the disintegration test of the JP17. The time was recorded when the tablet had fully disintegrated and no residue remained in the sample holder.

3.9.3. *Drug release test*

Drug release experiments for ODT were performed using pH 6.8 phosphate buffer (2nd fluid) and pH 1.2 NaCl-HCl solution (1st fluid), as described in the Dissolution Test in the JP17. The paddle method for dissolution tests in JP17 was employed and the paddle was rotated at 50 rpm. The AAP-CR100-CP(40) formulation and the commercial acetaminophen tablet 200 mg [JG] were placed in a sinker and immersed in 900 ml of dissolution medium pre-warmed to 37±0.5 °C. One-milliliter samples of the dissolution media were taken at predetermined time points and filtered using a fine filter (5 µm pore size). One milliliter of fresh medium was added immediately after each sample was taken. The filtrate was diluted and analyzed using an UV spectrophotometer at 244 nm to determine the amount of the drug released. Other conditions were same as the drug release test of the taste masked particles of AAP.

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