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EFFECT OF EUDRAGIT® E PO QUANTITY ON BITTER TASTE-MASKING OF DICLOFENAC SODIUM IN ORALLY DISINTEGRATING TABLETS

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Abstract: Bitter taste-masking of diclofenac sodium (DS) was prepared by forming solid dispersion of drug and polymer using solvent method. Polymeric materials used were ethyl cellulose (EC) or polymethacrylates E PO (Eudragit® E PO). Drug and polymer ratios were varied in the range of 1:1, 1:2, 1:3, and 1:4. Drug dissolution of solid dispersion powders were tested in simulated saliva fluid (SSF). Comparing to the drug (DS), increasing amount of polymer in the preparations decreased drug dissolution and reduced the bitter taste of drug. Drug released was retarded due to drug entrapment in the polymer. Because of stickiness and difficulty for size reduction of EC preparations at the ratio of 1:2 and higher, Eudragit® E PO preparation was selected for tablet preparation. Orally disintegrating tablets (ODTs) of drug (DS ODTs) were prepared by direct compression. Effect of superdisintegrant type and quantity on disintegration time was studied. ODTs of 5% by weight of crosslinked polyvinylpyrrolidone (P5) showed the fastest disintegration time. ODTs with taste-masked DS (solid dispersion of drug to Eudragit® E PO, 1:3) were prepared in the same manner of P5 and gave faster disintegration time than DS ODTs (13.15 second and 22.57 second, respectively). The percentage of drug released from taste-masked DS ODTs was lower than that from DS ODTs in SSF. (39.13% and 91.26% at 5 minutes, respectively) *In vitro* taste-masking in 10 mL SSF was tested at 1, 3 and 5 minutes. Drug released of DS from taste-masked ODTs at various times were significant lower than those from DS ODTs (6.92, 9.48, 7.31 mcg/mL and 45.68, 67.40, 49.03 mcg/mL at 1, 3 and 5 minutes, respectively). Eudragit® E PO could be used for taste-masking of bitter drug powder and drug bitterness was reduced with the increasing in the amount of polymer in the preparation.

Keywords: Orally disintegrating tablets, Diclofenac sodium, Solid dispersion, Taste-masking, Eudragit® E PO

บทคัดย่อ: กลบรสขมของไดโคลฟีแนคโซเดียม (DS) โดยเตรียมในรูปโซลิดดิสเพอร์ชันของยากับพอลิเมอร์ด้วยวิธีใช้ตัวทำละลาย พอลิเมอร์ที่ใช้คือ เอธิลเซลลูโลส (EC) หรือ พอลิเมทาคริเลท อี พีโอ (Eudragit® E PO) ในอัตราส่วนยาต่อพอลิเมอร์ 1:1, 1:2, 1:3, และ 1:4 นำผงโซลิดดิสเพอร์ชันที่เตรียมได้ไปทดสอบการละลายในสารละลายน้ำลายจำลอง (SSF) การเพิ่มปริมาณพอลิเมอร์ในสูตรตำรับทำให้ยาละลายออกมาลดลงเมื่อเปรียบเทียบกับยาเดี่ยว (DS) ดังนั้นจึงสามารถกลบรสขมของยาได้ การที่ยาละลายออกมาลดลงเนื่องจากยาถูกห่อหุ้มอยู่ในพอลิเมอร์ สูตรตำรับที่ใช้ EC ในอัตราส่วนยาต่อพอลิเมอร์ตั้งแต่ 1:2 ขึ้นไปได้ฟิล์มที่มีลักษณะเหนียวและยากต่อการลดขนาด จึงเลือกเฉพาะสูตรตำรับที่ใช้ Eudragit® E PO มาเตรียมเป็นยาเม็ด เตรียมยาเม็ดแตกตัวเร็วในช่องปาก (ODTs) ของยา (DS ODTs) ด้วยวิธีตอกโดยตรง ศึกษาผลของชนิดและปริมาณสารช่วยแตกตัวยิ่งยวดต่อเวลาในการแตกตัวของยาเม็ด พบว่า ODTs ที่ใช้ครอสลิงค์โพลิไวนิลไพโรลิโดนร้อยละ 5 โดยน้ำหนัก (P5) ให้เวลาในการแตกตัวของยาเม็ดน้อยที่สุด เมื่อเตรียม ODTs ที่มี DS ที่ถูกกลบรส (โซลิดดิสเพอร์ชันของยาต่อ Eudragit® E PO ในอัตราส่วน 1:3) ด้วยวิธีการเตรียมเช่นเดียวกับ P5 พบว่าให้เวลาในการแตกตัวของยาเม็ดเร็วกว่า DS ODTs (13.15 วินาที และ 22.57 วินาที ตามลำดับ) ร้อยละการละลายของยาจาก taste-masked DS ODTs ใน SSF มีค่าน้อยกว่า DS ODTs (39.13% และ 91.26% ที่ 5 นาที ตามลำดับ) เมื่อทดสอบการกลบรสยาในหลอดทดลองโดยใช้ SSF 10 mL ที่เวลา 1, 3 และ 5 นาที พบว่า taste-masked ODTs ให้การละลายของยาออกมาน้อยกว่า DS ODTs อย่างชัดเจน (6.92, 9.48, 7.31 mcg/mL และ 45.68, 67.40, 49.03 mcg/mL ที่เวลา 1, 3, 5 นาที ตามลำดับ) Eudragit® E PO สามารถใช้ในการกลบรสขมของยาและกลบรสขมของยาได้ดีขึ้นเมื่อเพิ่มปริมาณของพอลิเมอร์ในสูตรตำรับ

คำสำคัญ: ยาเม็ดแตกตัวเร็วในช่องปาก ไดโคลฟีแนคโซเดียม โซลิดดิสเพอร์ชัน การกลบรสยา ยูดราจิท อี พีโอ

INTRODUCTION

Orally disintegrating tablets (ODTs) are tablets which disintegrate rapidly in the mouth without chewing and absence of water. Guidance for Industry from United States Food and Drug Administration indicated that ODTs are solid dosage forms that disintegrate rapidly in oral cavity with an *in vitro* disintegration time of approximately 30 seconds or less when using USP disintegration test method or equivalent and tablet weight should not exceed 500 mg (U.S. Department of Health and Human Services FDA, 2008).

Taste-masking of ODTs is necessary for ODTs containing bitter taste drug. Two methods used to mask the unpleasant-taste are addition of flavors or sweeteners in the formulation and preventing drug from coming in contact with the taste buds. Several techniques were used to prevent drug release in oral cavity including coating drug with polymers, solid dispersion, ion exchange resins, and inclusion complex.

Eudragit® E PO was used for masking bitter taste drug by various methods such as preparing microspheres by spray drying method (Yan et al., 2010), mass extrusion method (Kulkarni et al., 2012), and solid dispersion microparticles (Pradhan et al., 2016). It is pH dependent and soluble at pH below 5.5. When the ODTs are in the oral cavity, the polymer will act as a physical barrier around the bitter taste drug by preventing the drug release in saliva (pH 6.2) thus masking the bitterness of drug to contact with patient's taste buds. However, Eudragit® E PO will be dissolved in gastric fluids (pH 1.2) and active drug is then rapidly released in stomach.

Diclofenac sodium (DS) is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, antipyretic and analgesic drug. It was chosen as the model drug because of its intensely bitter taste. The objective of this study was to preliminary study of taste-masking bitter taste drug in the oral cavity by preventing drug release in simulated saliva fluid (SSF). Polymeric materials employed were ethyl cellulose (EC) and Eudragit® E PO (E PO). Taste-masking of drug was produced by solid dispersion technique. The effect of polymer amount on drug release in SSF was also investigated. ODTs of DS (DS ODTs) using various superdisintegrants were prepared by direct compression to evaluate the effect of type and amount of superdisintegrants on disintegration time of tablets. The ODT formulation that provided the fastest disintegration time and suitable physical properties of tablets was identified and selected for tablet production of taste-masked DS. Selected taste-masked DS solid dispersion was prepared and formulated into tablets. The resulted tablets were evaluated for physical properties, disintegration time and *in vitro* taste-masking compared to those of DS ODTs.

MATERIALS AND METHODS

The following materials were purchased from commercial sources. Diclofenac sodium (Batch No.8427) was obtained from Kairav Chemicals Ltd. India. Ethyl cellulose E20 and Cross-linked polyvinylpyrrolidone (Polyplasdone XL®, Batch no. 20090510) were obtained from Onimax Co., Ltd., Thailand. Eudragit® E PO (Lot no. G140531533, Evonik Röhm GmbH, Germany) was a gift from Jabsen & Jessen Ingredients (T) Ltd. Thailand. Microcrystalline cellulose, Avicel® PH-102 (lot no. P211823634) was obtained from FMC BioPoltmer, USA. Spray-dried lactose (FlowLac®100), croscarmellose sodium (Ac-Di-Sol®), sodium starch glycolate (Explotab®), Colloidal silicon dioxide (Aerosil®) and magnesium stearate were supplied by Pharmaceutical Science Ltd., Part., Thailand.

Preparation of taste-masked diclofenac sodium solid dispersion

Taste-masking of diclofenac sodium was prepared by forming solid dispersion of drug and polymer using solvent method. EC or Eudragit® E PO was dissolved in 95% ethanol using magnetic stirrer until clear solution was obtained. The accurate amount of drug (drug to polymer ratios of 1:1, 1:2, 1:3 for EC and 1:1, 1:2, 1:3, 1:4 for Eudragit® E PO) was then dissolved in the polymer solution. The obtained solution was dried on water bath and the remaining of ethanol was removed by hot air oven at 55°C for 1 hour. The dried solid dispersion was sieved via sieve no. 40. The obtained powder was collected in amber plastic bag and kept in the desiccator for dissolution study and assay.

Dissolution and drug content

Dissolution: Drug dissolution was performed (n=3 for powder, n=6 for tablets) using Type 2 (paddle method) dissolution apparatus (Distek®, Model No.2100B, USA) at 50 rpm. The dissolution medium was 900 mL of simulated saliva fluid (SSF) pH 6.8 ± 0.1 at 37 ± 0.5°C. Samples of 7 mL were withdrawn at 3, 6, 9, 12, 15, 30, 45, 60 minutes, followed by addition of an equal volume of fresh medium in order to keep the constant volume of dissolution medium. Then, the samples were filtered and analyzed using UV-VIS spectrophotometer (Evolution 201 UV-VIS spectrophotometer, Thermo scientific, USA) at the wavelength of 267 nm.

Drug content: Accurately weight of DS-E PO solid dispersion equivalent to 25 mg DS was dissolved in 95% ethanol until the clear solution was obtained. The solution was appropriately diluted in SSF and filtered through 0.45 micron membrane filter. The filtrate was analyzed by spectrophotometer at 276 nm and calculated as percent drug content. Drug content of solid dispersion was determined in triplicate.

Preparation of diclofenac sodium orally disintegrating tablets (DS-ODTs)

Due to limitation of Eudragit® E PO quantity, ODTs of DS were prepared to study the effects of type and amount of superdisintegrants on disintegration time. Tablets were prepared by direct compression. Microcrystalline cellulose (Avicel® PH-102) and spray-dried lactose (FlowLac®100) were used as directly compressible diluents. Superdisintegrants were sodium starch glycolate (Explotab®), crosslinked sodium carboxymethylcellulose (Ac-Di-Sol®) and crosslinked polyvinylpyrrolidone (Polyplasdone® XL). Colloidal silicon dioxide (Aerosil®) and magnesium stearate were used as a glidant and lubricant, respectively. DS, directly compressible diluents and superdisintegrant were sieved through 40-mesh screen and mixed thoroughly by geometric dilution. Colloidal silicon dioxide and magnesium stearate were passed through 80-mesh screen and blended to the previous mixture for 2 minutes. The obtained mixture was compressed into tablets of 9 mm flat-faced punches in diameter by single stroke tableting machine (Kilian). Tablet hardness was controlled between 4-5 kg.

Table 1 presents the formulations of DS-ODTs. The designation of formulations is capital letter (A, E, and P) with number (3, 5, and 8). A, E, or P is the formulation which used Ac-Di-Sol®, Explotab® and Polyplasdone® XL as superdisintegrant, respectively. The number 3, 5 and 8 represents 3%, 5% and 8% of superdisintegrant in the formulation.

Evaluation of DS ODTs

Uniformity of weight

Twenty tablets were sampled to evaluate uniformity of weight using analytical balance (Sartorius, Model A200S analytical balance, Germany) according to BP2015 (The Department of Health, Great Britain, 2015).

Table 1. Formulations of DS-ODTs.

Ingredients (mg)	P5	A5	E5	P5A3	P5E3	P8
Diclofenac sodium	25	25	25	25	25	25
Avicel® PH-102	100	100	100	100	100	100
Spray-dried lactose	100	100	100	100	100	100
Polyplasdone® XL	5%	-	-	5%	5%	8%
Ac-Di-Sol®	-	5%	-	3%	-	-
Explotab®	-	-	5%	-	3%	-
Aerosil®	0.75%					
Magnesium stearate	1%					

Hardness and thickness

Tablet hardness and thickness of each formulation were evaluated on 10 tablets using a hardness tester (Monsanto hardness tester, Standard Steel, USA) and micrometer (Mitutoyo).

Friability

Tablet friability of each formulation was tested according to USP37 NF32 using a friabilator (Roche® friabilator, K.S.L. Engineering Co. Ltd, Thailand) for 4 minutes at the speed of 25 rpm (The United States Pharmacopeia, 2014). The percentage of friability should be less than 1%.

Disintegration time

Six tablets were sampled to perform disintegration test by USP type disintegrator (K.S.L. engineering Co., Ltd., Thailand) using distilled water (37 ± 2^{o} C) as a medium. The disintegration time was tested without disc.

Wetting time

A five folds tissue paper was placed in a petri dish then 10 mL of dye solution was added. ODTs were carefully placed on the surface of the tissue paper. The time required for solution to reach the upper surface of the tablet is noted as the wetting time. This test was performed on 6 tablets for each formulation.

From DS-ODTs, the formulation (P5) which produced the fastest disintegration time and suitable tablet physical properties was used to prepare taste-masked ODTs. All ingredients in the formulation are shown in Table 2. Tablets of taste-masked ODTs were evaluated by the following tests; uniformity of weight, hardness, thickness, %friability, disintegration time, assay, dissolution and *in vitro* taste-masking. Tablet physical properties of taste-masked ODTs were compared to those of DS-ODTs (P5).

Table 2. Formulation of taste-masked DS-ODTs.

Ingredients (mg)	Taste-masked DS-ODTs
Diclofenac sodium (as taste masked)	100
Avicel® PH-102	100
Spray-dried lactose	25
Polyplasdone® XL	5%
Aerosil®	0.75%
Magnesium stearate	1%

***In vitro* taste-masking**

P5 (DS-ODTs) and taste-masked ODTs were sampled to evaluate for *in vitro* taste-masking. The experiment was adapted from *in vitro* evaluation of bitter taste drug (Sona et al., 2011). Each tablet was placed in a test tube containing 10 mL of SSF and then shaking in water bath (37±2^o C) at 50 rpm. At the end of time at 1, 3 and 5 minutes, the solution at the upper surface was withdrawn and filtered through 10 micron filters and the collected filtrate was analyzed by UV spectrophotometer at 276 nm. The tablets were tested in triplicate at each time interval.

RESULTS AND DISCUSSION

Preparation of taste-masked diclofenac sodium solid dispersion

Solid dispersion of DS-EC was obtained as film with pale yellow in color and the yellow color intensity increases with the increasing in the amount of EC in the preparation. Drug released of DS from DS-EC solid dispersion in SSF was retarded with the higher amount of polymer (data not shown). However, EC solid dispersions at the ratio of drug to polymer 1:2 and higher ratio were sticky and difficult for size reduction. Thus, Eudragit® E PO was selected as a polymer to further prepare and mask the taste of drug.

Solid dispersion of DS-E PO was easeful to prepare by solvent method and obtained as white to pale yellow powder. Percentage of yield and assay of DS-E PO solid dispersion were 79.8-82.3% and 98.02-103.5%, respectively and shown in Table 3. Figure 1 shows the dissolution profiles of DS from solid dispersion powder. Drug released of DS powder at 3 minutes (Q_3) was 72.97% while increasing Eudragit® E PO in the preparation produced lower Q_3 in SSF (52.42%, 43.89%, 24.06% and 14.40% for the ratio of drug to polymer at 1:1, 1:2, 1:3 and 1:4, respectively). Drug released was retarded due to the entrapment of drug in the polymer and hence reducing drug contact with the taste buds and bitter taste-masking of drug were obtained. According to FIP/AAPS Guidelines to Dissolution/In Vitro Release Testing of Novel/Special Dosage Forms, the *in vitro* evaluation of the taste-masking properties could be performed to avoid organoleptic test in volunteers (Siewert et al., 2003). Delay released of drug (≤ 10%) in neutral pH medium at the early points of analysis e.g. ≤ 5 minutes may be recommended. From the powder dissolution test, Eudragit® E PO could be used for masking the unpleasant taste of drug with the increasing in the amount of polymer and at the ratio of 1:4 could almost mask the whole bitter taste of drug. Due to the limitation of Eudragit® E PO quantity, drug to polymer at the ratio of 1:3 was selected to prepare in sufficient amount for making ODTs.

Table 3. Appearance, %Yield and Assay of DS-E PO solid dispersion powder.

Formulations	Appearance	%Yield	Assay (%) mean ± SD
DS-E PO 1:1	White powder	81.5	99.12 ± 1.22
DS-E PO 1:2	White powder	82.3	103.50 ± 2.20
DS-E PO 1:3	Pale yellow powder	79.0	99.65 ± 5.13
DS-E PO 1:4	Pale yellow powder	79.8	98.02 ± 6.33

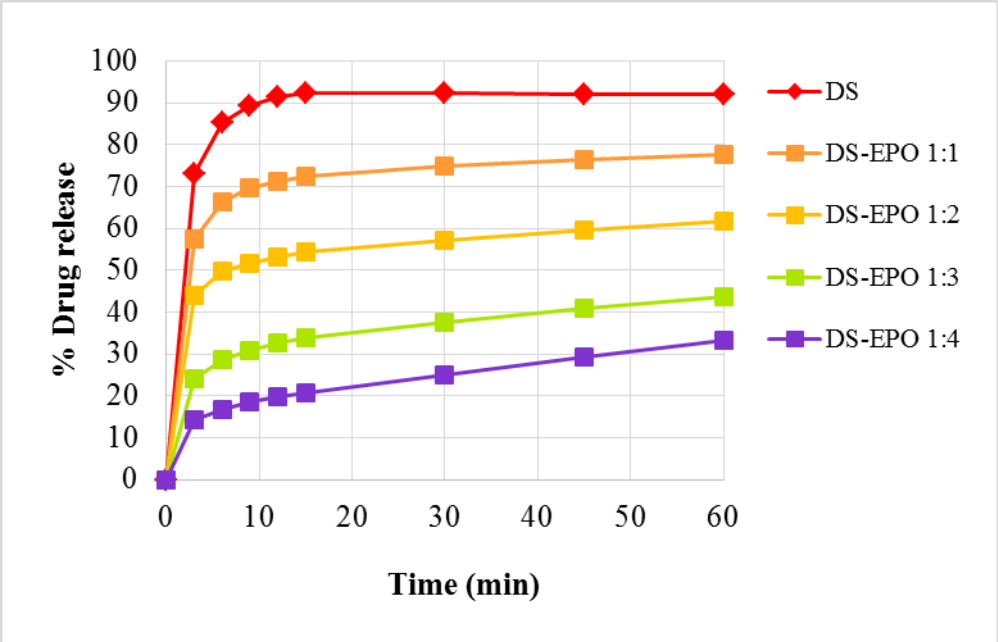

Figure 1. Dissolution profiles of DS-E PO solid dispersion powder in SSF.

Preparation and evaluation of DS-ODTs

DS-ODTs were prepared by direct compression. Avicel® PH-102 and FlowLac®100 were used as directly compressible diluents. Explotab®, Ac-Di-Sol® and Polyplasdone® XL were used as a single or in combination. Aerosil® and magnesium stearate were used as a glidant and lubricant, respectively. The disintegration times of obtained tablets were determined to study the effect of superdisintegrants used in formulations and the selected ODT formulation with the shortest disintegration time was used to prepare taste-masked ODTs.

Table 4 presents tablet physical properties of DS-ODTs. The average weight of all formulations was similar and gave the tablet weight between 240.8-248.3 mg. All DS-ODTs formulations passed the requirement of uniformity of weight (British pharmacopoeia, 2015) and provided good tablet properties. Hardness of all tablets was well-controlled around 4-5 kg and gave % friability lower than 1% which complied with the standard (The United States Pharmacopeia, 2014). The disintegration time determination provided the result correlated with the study of wetting time. Tablets using Polyplasdone® XL at 5% w/w (P5) as a single superdisintegrant showed the most rapid wetting time and disintegration time of 10.38 seconds and 22.57 seconds, respectively while the other (A5 and E5) gave the much longer times. Then Polyplasdone® XL at 5% w/w was used as the main disintegrant in combination with Explotab® or Ac-Di-Sol® in the concentration of 3% w/w. The wetting time and disintegration time of tablets with combined superdisintegrant were similar to those of tablets

with 5% Polyplasdone® XL (P5). The effect of Polyplasdone® XL quantity was further investigated, DS-ODTs with Polyplasdone® XL at 8% w/w (P8) were prepared and their wetting time and disintegration time were similar to those of P5. Therefore, the formulation using Polyplasdone® XL at 5% w/w was selected and used in preparing taste-masked ODTs.

Preparation and evaluation of Taste-masked ODTs

Taste-masked ODTs was prepared using the same composition as P5 that is shown in Table 2. The amount of spray-dried lactose was reduced for controlling the tablet weight around 240 mg. Tablet physical properties of taste-masked ODTs are presented in Table 5. All tablet physical properties were well controlled and complied with required standards. Wetting time and disintegration time of taste-masked ODTs were lower than those of P5. All tablets passed the criteria of FDA that indicated ODTs would have the disintegration time of approximate 30 seconds or less when using USP disintegration apparatus or equivalent (U.S. Department of Health and Human Services FDA, 2008). This rapid disintegration time of taste-masked ODTs was due to the swelling of Eudragit® E PO when contact with the medium and caused tablets to rapidly disintegrate.

Table 4. Physical properties of DS-ODTs.

Formulation	Average Weight (mg) mean ± SD	Hardness (kg) mean ± SD	Friability (%)	Wetting time (seconds) mean ± SD	DT (seconds) mean ± SD
P5	244.3 ± 1.67	4.6 ± 0.4	0.76	10.38 ± 1.55	22.57 ± 3.49
A5	242.8 ± 1.56	4.8 ± 0.2	0.69	54.78 ± 8.87	30.27 ± 2.63
E5	240.8 ± 1.65	4.9 ± 0.1	0.69	38.83 ± 3.21	37.07 ± 1.83
P5A3	246.4 ± 0.86	5.2 ± 0.3	0.60	17.52 ± 2.78	25.04 ± 1.93
P5E3	248.3 ± 1.69	4.5 ± 0.4	0.62	15.15 ± 1.45	22.70 ± 1.39
P8	247.4 ± 2.30	5.0 ± 0.2	0.83	10.24 ± 1.10	25.17 ± 0.66

Table 5. Physical properties of Taste-masked ODTs and DS-ODTs (P5)**.**

Formulation	Average Weight (mg) mean ± SD	Hardness (kg) mean ± SD	Friability (%)	Wetting time (seconds) mean ± SD	DT (seconds) mean ± SD	Assay (%) mean ± SD
P5	244.3 ± 1.67	4.6 ± 0.4	0.76	10.38 ± 1.55	22.57 ± 3.49	105.9 ± 1.05
Taste-masked ODTs	243.8 ± 3.68	4.8 ± 0.3	0.58	9.75 ± 1.85	12.81 ± 2.94	100.5 ± 3.98

Drug dissolution profiles are depicted in Figure 2. Percent drug release of DS from P5 was about 79% and 99% at 3 and 5 minutes, respectively. Therefore, drug promptly dissolved in saliva and showed intensely bitter taste immediately when put on the tongue. Taste-masked ODTs gave the lower drug release than P5 ODTs which were 35% and 39% at 3 and 5 minutes, respectively. Thus, the usage of Eudragit® E PO for preparing solid dispersion could mask the bitter taste due to the entrapment of drug in the polymer matrix and lowering drug release from the solid dispersion. However, the ratio of drug to polymer at 1:3 could not mask

the whole bitter taste of drug because drug release was greater than 10% in the early points of analysis of dissolution profile (3 or 5 minutes) (Siewert et al., 2003 and Lai et al., US 2009/0263480).

DS-ODTs and taste-masked ODTs were evaluated for *in vitro* taste-masking. The investigation method was adapted from Sona et al. (2011). Drug releases of DS from taste-masked ODTs at various times (Figure 3) were significant lower than those from DS ODTs (6.92, 9.48, 7.31 mcg/mL and 45.68, 67.40, 49.03 mcg/mL at 1, 3 and 5 minutes, respectively). According to the determination of bitterness threshold concentration of diclofenac sodium, the lowest concentration at which a drug continues to provoke a bitter sensation after 30 seconds was 20 mcg/mL (Sona et al., 2011). From the data of *in vitro* taste-masking, drug release of taste-masked ODTs at all of time interval was lower than the bitterness threshold, therefore it was anticipated that the bitter taste masked would be achieved in *in vivo* organoleptic measurement. However, *in vivo* taste-masking evaluation is needed to be performed.

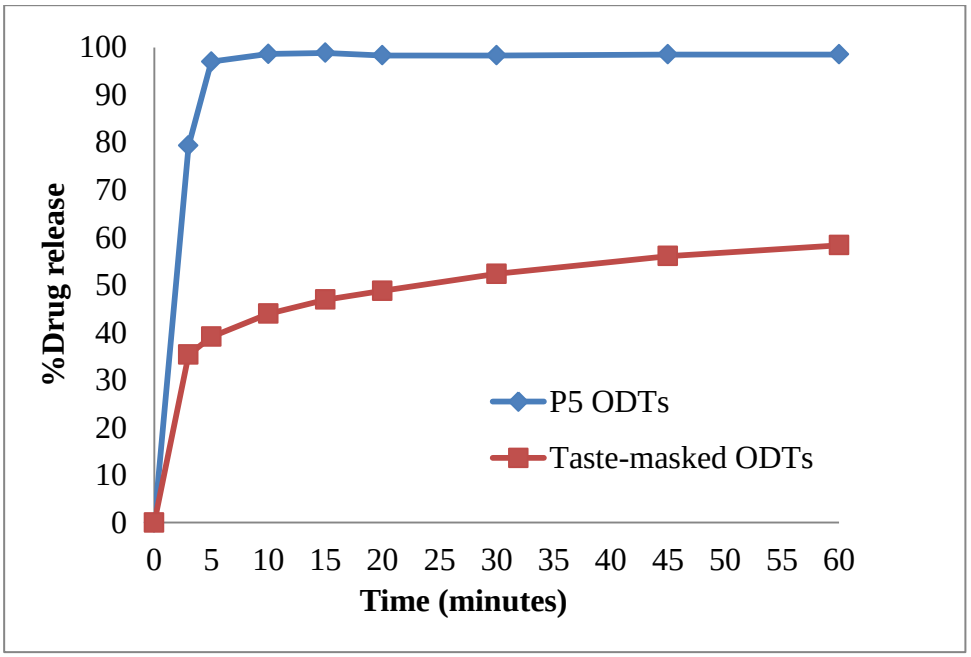

Figure 2. Dissolution profiles of P5 ODTs and Taste-masked ODTs.

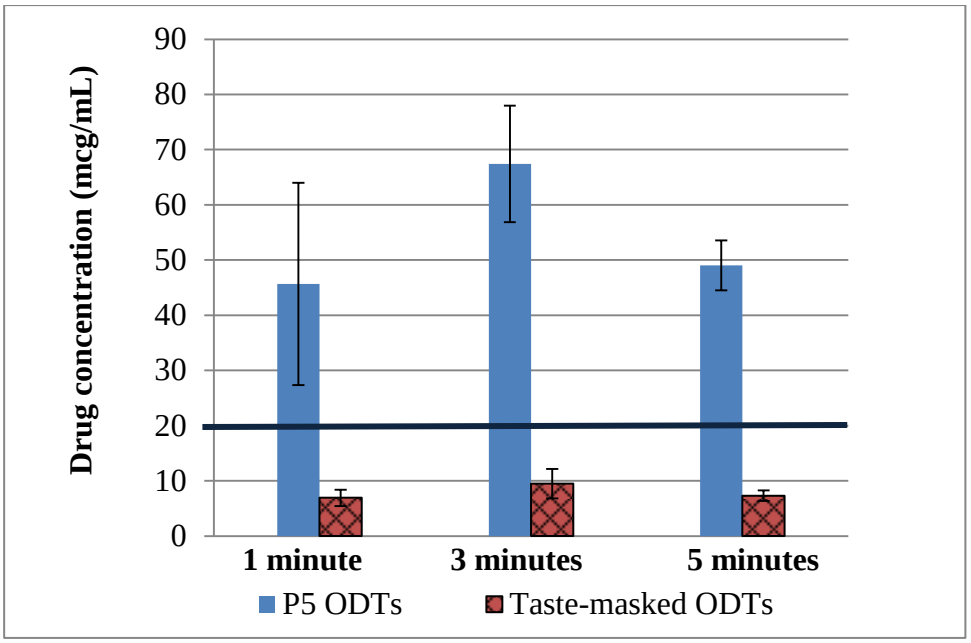

Figure 3. *In vitro* taste-masking of P5 ODTs and Taste-masked ODTs in SSF.

CONCLUSION

Taste-masking of diclofenac sodium could be achieved by forming a solid dispersion using Eudragit® E PO. Drug was entrapped in the polymer therefore the dissolution of drug was retarded in simulated saliva fluid. The bitter taste of drug was reduced when the quantity of polymer in the preparation was increased. Taste-masked ODTs using 5% w/w Polyplasdone® XL gave the fastest disintegration time. From *in vitro* taste-masking and drug dissolution test in SSF, it could be concluded that bitter taste of drug would be masked and reduced by solid dispersion technique.

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