Bulletin of Health,
Science and Technology
BHST
ISSN 0858-7531
Volume 15, Number 1, 2017 : 28-38

TASTE-MASKING AND DISSOLUTION ENHANCEMENT OF DICLOFENAC SODIUM ORODISPERSIBLE TABLETS USING SPRAY-DRYING TECHNIQUE

Kanokporn Burapapadh*

Faculty of Pharmacy, Rangsit University, Patumthani 12000 Thailand

*Corresponding author : E-mail : kanokporn.b@rsu.ac.th

Abstract: Diclofenac sodium is a potent non-steroidal anti-inflammatory drug with bitter taste and slightly water soluble properties. The aim of this study is to develop diclofenac sodium orodispersible tablet formulation which is taste-masked and enhanced dissolution rate by spray-drying method. Polyvinylpyrrolidone K30 (PVP K30) was used as a polymeric carrier in the drug/polymer ratios of 1:1, 1:2, and 1:4. The obtained particles were then characterized. The particles were spherical shape with wide range of size distribution. Diclofenac sodium was completely entrapped in the polymer cause masking of the drug taste. The solid stage of diclofenac sodium was changed from crystalline to amorphous state. The obtain particles which the drug/polymer ratios of 1:1 and 1:2 were further prepared as orodispersible tablets by direct compression method. Superdisintegrants consisted of cross-linked polyvinylpyrrolidone, sodium starch glycolate and cross-linked sodium carboxylmethylcellulose were used in various ratios. The formulation consists of 3% (w/w) cross-linked polyvinylpyrrolidone and 6% (w/w) cross-linked sodium carboxylmethylcellulose showed the most rapid disintegration time of 65 seconds and the dissolution rate was also enhanced. Diclofenac sodium from the formulation completely dissolved in 150 minutes while the formulation consists of untreated drug took more than 360 minutes to completely dissolve.

Keywords: diclofenac sodium, spray-drying, orodispersible tablets, taste-masking, dissolution enhancement

บทคัดย่อ: ไดโคลฟีแนคโซเดียม เป็นยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ที่มีฤทธิ์แรง มีรสขม และละลายน้ำยาก การศึกษาครั้งนี้มีวัตถุประสงค์เพื่อพัฒนาสูตรตำรับไดโคลฟีแนคโซเดียม ชนิดยาเม็ดกระจายตัวเร็วในช่องปาก (orodispersible tablets; ODTs) ซึ่งกลบรสและเพิ่มการละลายของตัวยาด้วยวิธีการทำแห้งแบบพ่นฝอย โดยใช้โพลีไวนิลไพโรลิโดน เค 30 (PVP K30) เป็นพอลิเมอร์ตัวพาในอัตราส่วนยาต่อพอลิเมอร์เท่ากับ 1:1, 1:2 และ 1:4 เมื่อนำอนุภาคที่เตรียมได้มาประเมินสมบัติทางกายภาพ พบว่าอนุภาคที่ได้มีรูปทรงกลมและมีการกระจายขนาดกว้างโดยพอลิเมอร์สามารถห่อหุ้มตัวยาไดโคลฟีแนคโซเดียมได้อย่างสมบูรณ์ ทำให้มีสามารถกลบรสได้ ไดโคลฟีแนคโซเดียมเกิดการเปลี่ยนแปลงสภาวะของแข็งจากรูปแบบสัณฐานเป็นรูปแบบอสัณฐาน จากนั้นนำอนุภาคที่เตรียมได้โดยใช้อัตราส่วนยาต่อพอลิเมอร์เท่ากับ 1 :1 และ 1:2 ไปเตรียมเป็นตำรับยาเม็ดชนิดกระจายตัวเร็วในช่องปากด้วยวิธีการตอกโดยตรงโดยใช้สารช่วยแตกตัวยิ่งยวดชนิดต่างๆ ได้แก่ ครอสลิงค์โพลีไวนิลไพโรลิโดน, โซเดียมสตาร์ชไกลโคเลต และครอสลิงค์โซเดียมคาร์บอกซีเมทิลเซลลูโลสในอัตราส่วนที่แตกต่างกัน พบว่าตำรับที่ประกอบด้วยครอสลิงค์โพลีไวนิลไพโรลิโดนร้อยละ 3 โดยน้ำหนัก ร่วมกับครอสลิงค์โซเดียมคาร์บอกซีเมทิลเซลลูโลสร้อยละ 6 โดยน้ำหนัก สามารถแตกตัวได้เร็วที่สุดภายในเวลา 65 วินาที และสามารถเพิ่มอัตราการละลายของไดโคลฟีแนคโซเดียมได้โดยตัวยาสามารถละลายออกมาอย่างสมบูรณ์ภายในเวลา 150นาที ในขณะที่ตำรับที่ประกอบด้วยตัวยาตัวยาไดโคลฟีแนคโซเดียมที่ไม่ได้ผ่านการทำแห้งแบบพ่นฝอยมีการละลายของยาออกมาสมบูรณ์เมื่อเวลาผ่านไปมากกว่า 360 นาที

คำสำคัญ: ไดโคลฟีแนคโซเดียม วิธีการทำแห้งแบบพ่นฝอย ยาเม็ดกระจายตัวเร็วในช่องปาก การกลบรส การเพิ่มอัตราการละลาย

INTRODUCTION

Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic properties. It was classified by the biopharmaceutics classification system (BCS) as a class II drug based on its high permeability and low solubility (Amidon et al., 1995). Diclofenac sodium showed concentration dependent, highest bitterness intensity compared to other NSAIDs (Yoshida et al., 2014). Therefore, administration of diclofenac sodium via oral route is limited by its taste.

Orodispersible tablets (ODTs) are used in oral drug delivery system as a single-unit solid dosage form which rapidly disintegrates in the mouth. ODTs are increasingly used due to their advantages such as, convenient to handle, easy to swallow, and can be taken without water. Therefore, ODTs could enhance patient compliances, especially in children and elderly (Hanning et al., 2016). However, the formulation of ODTs is still faced challenging issues. As defined by US FDA and European Pharmacopeia, ODTs should rapidly disintegrate within 30 second (U.S. Food and Drug Administration, 2008) and 3 minutes (Council of Europe, 2010), respectively. Thus, ODTs should be ready to disintegrate in small amount of water but stable enough to handle. Moreover, since the drug administered by ODTs must be disintegrated in oral cavity, taste-masking becomes an important point.

Taste-masking is necessary for preparation of the ODTs containing an unpleasant-taste drug. Techniques used in taste-masking could be separated into three principles; functional, biochemical and physical masking (Nilesh et al., 2012). Functional taste-masking is the simplest method. Bitterness of drugs is suppressed by using of sweeteners, flavorings and other excipients (Lenik et al., 2016). However, this method could not successfully mask the taste of high-dose drugs. The biochemical method masks the taste of drugs by chemical modification including prodrugs or inclusion complex. The taste was masked by decreasing drug solubility in saliva and decreasing amount of drug particles exposed to taste buds (Sharma et al., 2010). Physical taste-masking by preventing release of drug in oral cavity is one of the best methods. Several techniques were used to coat drugs with polymers including, extrusion-spheronization (Petrovick et al., 2016), hot-melt extrusion (Maniruzzaman et al., 2012), granulation (Nishiyama et al., 2016), coacervation (Comunian et al., 2013), emulsion solvent diffusion (Gao et al., 2006), and spray-drying (Yi et al., 2014). Spray-drying technique is wildly used as it is one-step process, provides good final product stability, and easy to scale-up. The dissolution of the microparticles prepared from spray-drying are also improved (Wikarsa et al., 2008).

The aim of this study is to develop diclofenac sodium orodispersible tablet formulation which is taste-masked and enhanced dissolution rate by spray-drying method. Diclofenac sodium was incorporated in taste-masked microparticles, using polyvinylpyrrolidone K30 (PVP K30) as a carrier. The taste-masked microparticles were compressed into tablets by direct compression method using various disintegrants. The physicochemical characteristics, taste-masking efficiency and dissolution rate enhancement of diclofenac sodium were then evaluated.

MATERIALS AND METHODS

The following materials were purchased from commercial sources. Diclofenac sodium (Batch No. 8427) was obtained from Kairav Chemicals Ltd. PVP K30, spray-dried rice starch (Era-Tab®), mannitol, sodium starch glycolate (Explotab®), cross-linked polyvinylpyrrolidone (cross-linked PVP; Polyplasdone-XL®), cross-linked sodium carboxylmethylcellulose (cross-linked NaCMC; Ac-Di-Sol®), citric acid, saccharin sodium, talcum, colloidal silicon dioxide

(Aerosil®) and magnesium stearate were supplied by Pharmaceutical Science Ltd., Part., Thailand.

Preparation of taste-masked diclofenac sodium microparticles

Taste-masked diclofenac sodium microparticles were prepared by spray-drying technique using PVP K30 as a polymeric carrier. PVP K30 was dissolved in distilled water at the concentration of 15% (w/w). The accurate amount of diclofenac sodium was then dispersed in the PVP K30 solution to obtain the drug/polymer ratios of 1:1, 1:2 and 1:4. The prepared drug/polymer dispersions were dried using a spray-dryer (Mini spray dryer B-290, Buchi, Switzerland). The inlet air temperature, feed flow rate and aspiration rate were set at 160°C, 10 mL/min, and 85%, respectively. The nozzle orifice was 0.7 mm in diameter. The dried microparticles were collected and stored in a desiccator till further analysis.

Characterization of diclofenac sodium microparticles

Flowability study

The flowability of prepared microparticles was calculated from their bulk density and tapped density as Carr's index.

Morphology, size, and size distribution

The morphology, size, and size distribution of all microparticles was investigated by a scanning electron microscope (Maxim-2000, CamScan Analytical, England) for the structure. Microparticles samples were fixed on SEM stubs with double-sided adhesive tape and then coated in a vacuum with thin gold layer before investigation.

FT-IR spectroscopy

The functional group of the microparticles was tested by Fourier transform infrared (FT-IR) spectroscopy. The FT-IR spectra of all samples were obtained by a Nicolet 4700 FT-IR spectrophotometer (Thermo Electron Corporation, USA). Diclofenac sodium, PVP K30 and physical mixture of fixed drug/polymer ratios samples were prepared using the KBr disc method. The spectral values of the samples were obtained by scanning from 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1}. FT-IR spectral parameters of the samples were obtained using a software package (OMNIC FT-IR Software, version 7.2a, Thermo Electron Corporation, USA).

PXRD analysis

Powder X-ray diffraction (PXRD) analysis was used to investigate crystalline state of diclofenac sodium. PXRD patterns of diclofenac sodium in microparticles were obtained using the x-ray diffractometer (D8, Bruker, Germany) at 40 kV, 40mA over the range of 5°-45° 2θ using Cu Kα radiation wavelength of 1.5406 Å.

Loading capacity and loading efficiency

The loading capacity and loading efficiency of microparticles then were also investigated. An accurate amount of microparticles was weighed and dissolved in 95% ethanol. The drug amount of each sample was determined by a UV spectrophotometer (Evolution 201 UV-Visible spectrophotometer, Thermo scientific, USA) at the wavelength of 280 nm. The loading capacity and loading efficiency of microparticles then were calculated using the following equations.

$$\text{Loading capacity (\%)} = \frac{\text{Total amount of diclofenac sodium (mg)x 100}}{\text{Amount of microparticles (mg)}} \quad (1)$$

$$\text{Loading efficiency (\%)} = \frac{\text{Total amount of diclofenac sodium (mg)x 100}}{\text{Total amount of diclofenac sodium added initially (mg)}} \quad (2)$$

Preparation of taste-masked diclofenac sodium ODTs

The taste-masked microparticles prepared using suitable ratios of the drug and PVP K30, which are 1:1 and 1:2, were used in the preparation of ODTs. The diclofenac sodium ODTs were prepared by direct compression process using spray-dried rice starch and mannitol as diluents. Various types of disintegrant i.e., sodium starch glycolate, cross-linked PVP, and crossed-linked NaCMC were used. Citric acid and saccharin sodium were added in the formulations as flavoring agents. Each ingredient was screened through 40-mesh sieve before tumbling mixing. Talcum, colloidal silicon dioxide, and magnesium stearate as glidant, absorbent, and lubricant, respectively, were then passed through 80-mesh sieve and blended to the previous mixture for 2 minutes. The obtained mixture was compressed into tablets of 3/8-inch in diameter by a manual single stroke tableting machine (Viuhang Engineering, Thailand). The hardness of the tablets was controlled between 3-4 kg.

Table 1 presents the formulations of the taste-masked diclofenac sodium ODTs F-1, F-2, and F-3 were prepared using microparticles with drug/polymer ratio of 1:1 while F-4 contained microparticles with drug/polymer ratio of 1:2. F-5 is the controlled formulations, which contained the untreated diclofenac sodium as an active ingredient while F-6 is the formulation with no disintegrant added.

Table 1. Formulations of taste-masked diclofenac sodium ODTs

Ingredients	Amount					
	F-1	F-2	F-3	F-4	F-5	F-6
Diclofenac sodium (mg)					25	
Diclofenac sodium (as taste-masked microparticles) (mg)	62.75	62.75	62.75	93.70		62.75
Spray-dried rice starch (mg)	50	50	50	50	50	50
Mannitol (mg)	50	50	50	50	50	50
Sodium starch glycolate (%)	4	-	4	-	-	-
Cross-linked PVP (%)	-	3	3	3	3	-
Cross-linked NaCMC (%)	6	6	-	6	6	-
Citric acid (%)	7.5	7.5	7.5	7.5	7.5	7.5
Saccharin sodium (%)	1.5	1.5	1.5	1.5	1.5	1.5
Talcum (%)	3	3	3	3	3	3
Colliodal silicon dioxide (%)	2	2	2	2	2	2
Magnesium stearate (%)	1	1	1	1	1	1

Characterization of ODTs

Uniformity of weight

Uniformity of weight was tested on 20 tablets using an analytical balance (Sartorius, Model A200S analytical balance, Germany) according to BP2015 (The Department of Health, Great Britain, 2015).

Hardness

The hardness of each formulation was carried on 10 tablets using a hardness tester (Monsanto hardness tester, Standard Steel, USA).

Friability

Tablet friability of each formulation was also tested according to USP 37 and NF 32 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).

Wetting time

Wetting time of ODTs was measured on 6 tablets. A five-folds tissue paper was placed in a petridish then 10 mL of water soluble dye solution was added. ODTs were carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time.

Disintegration test

Disintegration test was performed on 6 tablets per formulation by USP type disintegrator (K.S.L. Engineering Co., Ltd., Thailand) using 500 mL distilled water (37±2 °C) as disintegrating medium.

Dissolution

Dissolution studies of the ODTs were done in triplicate using a type II dissolution apparatus (Model NO.2100B, Distek, USA) with a speed of 50 rpm. The dissolution medium used in this study was 900 mL simulated intestinal fluid pH 6.8±0.1 at 37±0.5 °C. Samples were withdrawn from the dissolution vessels at 1, 5, 10, 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 360 minutes. Then, the analysis of diclofenac sodium content was done by a UV spectrophotometer (Evolution 201 UV-Visible spectrophotometer, Thermo scientific, USA) at the wavelength of 280 nm.

Taste-masking properties

The taste-masking properties of the ODTs were also investigated by dissolution method. According to FIP/AAPS Guidelines to Dissolution/in Vitro Release Testing of Novel/Special Dosage Forms (Siewert et al., 2003), the taste of a drug could be masked if ≤10% of drug dissolved in first 5 minutes. Therefore, the taste-masking properties of the ODTs will be noted if the *in vitro* drug release of the ODTs is not more than 10%.

RESULTS AND DISCUSSION

The taste-masked microparticles were prepared by spray-drying technique. The drug was entrapped in the matrix carrier thereby the contact of drug with taste buds is retarded (Shah et al., 2008). The diclofenac sodium taste-masked microparticles showed similar bulk density, tapped density and flowability in all drug/polymer ratios. The Carr's index of each formulation was between 37.53 and 42.95 (data not shown), indicating the poor flowability. Due to the fine characteristics, flowability of microparticles was decreased due to the cohesive force between particles (Tomas et al., 2009). From the flowability study, using of high efficiency glidants in tablet formulations should be considered.

From the SEM micrographs shown in Figure 1, all particles were in spherical shape with smooth surface and wide range of size distribution. The polymer ratio did not affect the morphology and size of the spray-dried microparticles. The size of microparticles in all

formulations was similar, i.e., around 5-30 µm. There is no diclofenac sodium crystal investigated in all formulations.

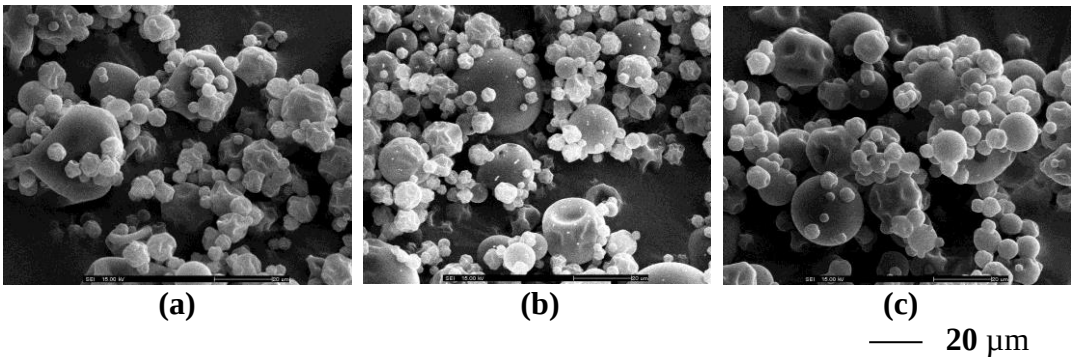

Figure 1. SEM images (1000x) of taste-masked diclofenac sodium microparticles prepared by various drug/polymer ratios **(a)** 1:1, **(b)** 1:2, and **(c)** 1:4

The possibility of drug-polymer interaction studies was established using FT-IR (Figure 2). The FT-IR spectrum of untreated diclofenac sodium showed the characteristic peak of the drug, which appeared at 3386.9, 1575.1, and 766.2 cm^{-1} representing NH stretching of secondary amine, C=O stretching of the carboxy ion, and C-Cl stretching, respectively. This is in agreement with the previously recorded spectra of the pure drug (Shivakumar et al., 2008). The FT-IR spectrum of PVP K30 displayed the C-H stretching peak at 2956.4 cm^{-1} and the C=O stretching at 1651.2 cm^{-1}. There was no new absorption peak or shifting found from the FT-IR analysis of microparticles, indicating no or minor interaction between diclofenac sodium and PVP K30 molecules after the formulations of microparticles. The FT-IR spectra of microparticles were similar to the spectrum of PVP K30 while the FT-IR spectra of physical mixture still presented the drug peaks. From the results, diclofenac sodium might be completely entrapped in PVP K30 in all formulations (Ajun et.al, 2009), even in formulation with low polymer ratio.

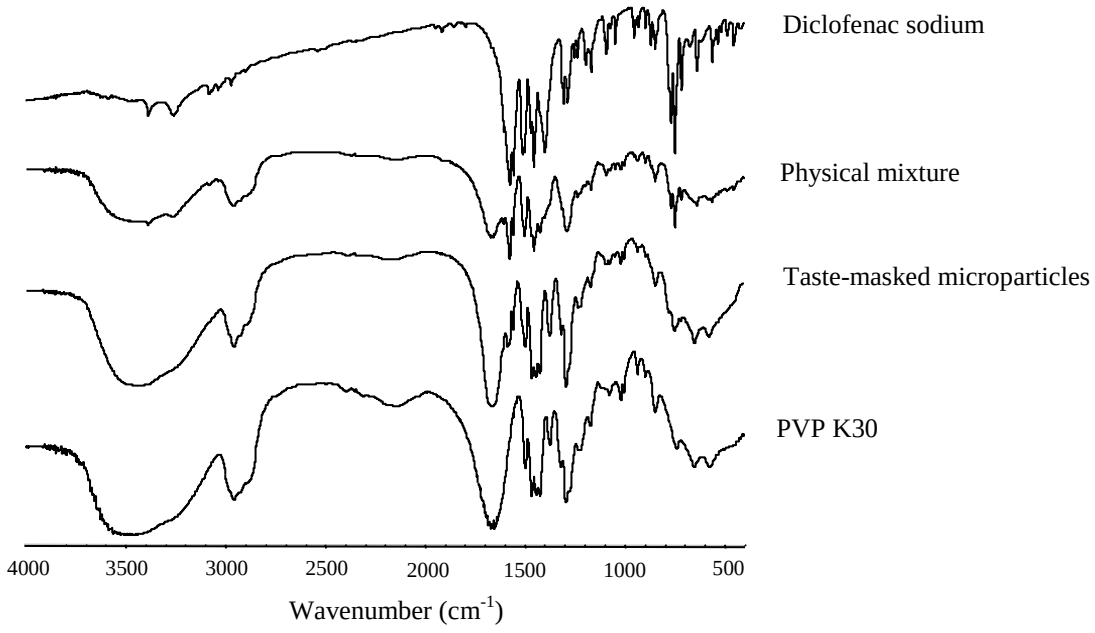

Figure 2. FT-IR spectra of diclofenac sodium, physical mixture of diclofenac sodium and PVP K30 in the ratio of 1:1, taste masked microparticles prepared using drug/polymer ratio of 1:1 and PVP K30

The PXRD patterns of microparticles compared to untreated drug, PVP K30, and physical mixture are shown in Figure 3. Untreated diclofenac sodium showed peaks associated with crystallinity while the halo-pattern of amorphous solid was observed in the case of PVP K30. Preparation of the taste-masked microparticles by spray-drying caused the significant change of PXRD pattern compared to the physical mixture in all drug/polymer ratios. After spray-drying, the halo-type PXRD pattern was clearly observed, indicating the molecularly dispersion of diclofenac sodium in PVP K30 or the change of solid state from crystalline to amorphous (Hollouard et al., 2016).

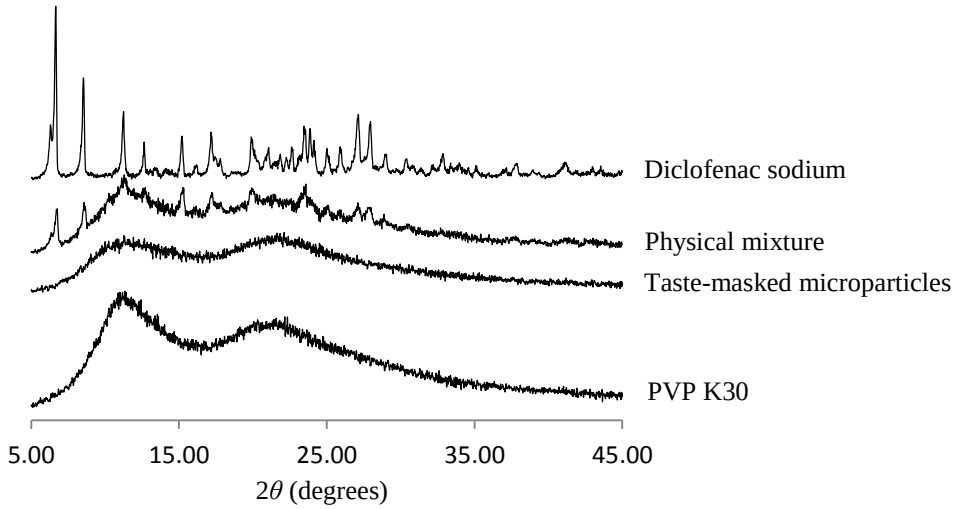

Figure 3. PXRD pattern of diclofenac sodium, physical mixture of diclofenac sodium and PVP K30 in the ratio of 1:1, taste-masked microparticles prepared using drug/polymer ratio of 1:1 and PVP K30

Loading capacity and loading efficiency of the taste-masked microparticles were measured. The microparticles had a loading capacity and loading efficiency of 15.57-40.42% and 77.85-80.84%, respectively. The microparticles prepared using drug/polymer ratio of 1:1 gave the highest loading capacity and loading efficiency due to low amount of polymer used in the formulations. Therefore, the taste-masked microparticles with drug/polymer ratios of 1:1 and 1:2 were then used in ODTs.

Table 2. Loading capacity and loading efficiency of taste-masked microparticles

Drug/polymer ratio of taste-masked microparticles	Loading capacity (%)	Loading efficiency (%)
1:1	40.42	80.84
1:2	26.68	80.05
1:4	15.57	77.85

Properties of taste-masked diclofenac sodium ODTs are presented in Table 3. All ODTs prepared from each formulation mentioned above showed good tablet properties. The hardness of all tablets was well-controlled. All formulations met pharmacopoeial requirements of uniformity of weight (The Department of Health, Great Britain, 2015) and friability (The United States Pharmacopeia, 2014). The average weight of F-1, F-2, F-3, F-4, and F-6 was similar (between 200-235 mg) while that of F-5 was 153 ± 4.02 mg. Thus, the difference in

values of disintegration time and dissolution of F-5from other formulations due to the difference of average weight could occur.

Table 3. Properties of taste-masked diclofenac sodium ODTs

Formulation	Uniformity of weight	Hardness (kg)	Friability (%)	Wetting time (minutes)	Disintegration time (minutes)
F-1	Passed	3.8 ± 0.2	0.4853	>15	3.58 ± 0.64
F-2	Passed	3.7 ± 0.2	0.4513	2.85 ± 0.54	1.07 ± 0.30
F-3	Passed	3.8 ± 0.3	0.7735	3.86 ± 0.23	1.69 ± 0.22
F-4	Passed	3.8 ± 0.3	0.2380	>15	8.19 ± 1.95
F-5	Passed	3.7 ± 0.2	0.6675	1.66 ± 0.15	0.40 ± 0.06
F-6	Passed	3.7 ± 0.4	0.7028	>15	9.53 ± 3.88

The wetting time analysis showed the influence of disintegrant type and PVP K30 on wetting properties of the ODTs. The formulation with untreated drug (F-5) showed the most rapid wetting time of 1.66 ± 0.15 minutes. The wetting time of other formulations was retarded due to the presence of PVP K30. The formulation consists of microparticles with drug/polymer ratio of 1:1 using 3% (w/w) cross-linked PVP and 6% (w/w) cross-linked NaCMC as disintegrants (F-2) showed wetting time of 2.85 ± 0.54 minutes while increasing of polymer ratio in the microparticles caused much longer wetting time (F-4). Combination of sodium starch glycolate and cross-linked PVP as co-disintegrants (F-3) also showed short wetting time. However, using of sodium starch glycolate in combination with cross-linked NaCMC (F-1) caused more than 15 minutes wetting time, similar to the formulation without disintegrant (F-6).

The disintegration time determination showed the correlated result with the wetting time study. ODTs with untreated diclofenac sodium showed the most rapid disintegration within 0.40 minutes. Presenting of PVP K30 increased the disintegration time of taste-masked ODTs due to its good binding properties (Nagadivya, 2012). Type of disintegrant also played the important role in ODTs disintegration. While the ODTs prepared by F-1 showed average disintegration time of 3.58 minutes, ODTs formulated by F-2 and F-3 could completely disintegrate within 1.07 and 1.69 minutes, respectively. Therefore, using of cross-linked PVP and cross-linked NaCMC as combined disintegrants in the taste-masked ODT formulations would be suggested from the result. Using high amount of PVP K30 in microparticles could inhibit ODT disintegration. As in F-4, which consisted of two-times higher PVP K30 amount than F-2, the average disintegration time was increased to over seven-folds, compared to that of F-2. Consequently, taste-masked microparticles prepared using drug/polymer ratio of 1:1 are more suitable for further ODT preparations.

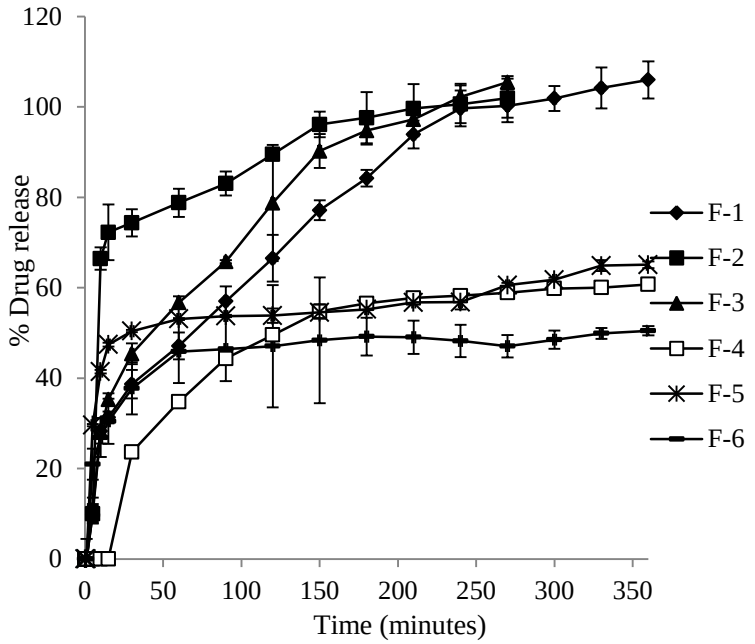

Figure 4. Dissolution profiles of diclofenac sodium from ODTs

Figure 4 shows the dissolution profiles of diclofenac sodium from ODTs. Most of formulations contained the taste-masked microparticles could enhance dissolution of diclofenac sodium. The enhancement of dissolution rate clearly depended on disintegration time. The dissolution of ODTs prepared from F-1, F-2, and F-3 showed significantly improvement compared to that of the ODTs contained untreated drug (F-5). This is due to the changing of drug crystalline state to amorphous solid during microparticles preparation process, as supporting by the PXRD study.

Among these ODTs, the tablets prepared by F-2 showed the most rapid dissolution which the drug could completely dissolved within 150 minutes. The F-1 and F-3 formulations required 240 minutes to completely dissolve. Increasing of PVP K30 ratio in microparticles preparation (F-4) inhibited the dissolution of diclofenac sodium. The drug release was retarded until 30 minutes and the total release was only 60% even after 360 minutes. This may due to an increasing of polymer thickness, which acts as a barrier to drug diffusion and inhibits the penetration of water to the drug (Maderuelo et al., 2011). Hence, the drug release was hindered.

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 done to avoid organoleptic test in volunteers (Siewert et al., 2003). The delay in drug release in first 5 minutes is long enough for the drug to pass through the oral cavity, typically ≤10% dissolved in 5 minutes was recommended. Therefore, it could be concluded that all the ODT formulations in this study could mask the drug taste due to their low dissolution in first 5 minutes.

CONCLUSION

Taste-masking and dissolution enhancement of diclofenac sodium could be achieved by entrapping the drug with PVP K30 using the spray-drying technique. The masking of taste occurred by completely entrapment of the amorphous drug in the polymer. Hence, the dissolution of the drug is first retarded before rapidly increase after a period of time. The taste-masked microparticles could be used to prepare ODTs by direct compression method.

However, use of high concentration polymer could limit the drug disintegration and thus affected the dissolution rate. Disintegrants played an important role on the disintegration of ODTs. The ODTs consisted of 3% (w/w) cross-linked PVP and 6% (w/w) cross-linked NaCMC seemed to be the promising formulation as it provided rapid disintegration time and dissolution rate along with desirable taste-masking properties.

ACKNOWLEDGMENTS

The author would like to acknowledge the department of Manufacturing Pharmacy, Faculty of Pharmacy, Rangsit University for material and equipment support. The author would also like to thank pharmacy students, Nuttaporn Kaewchai and Sayamon Lattimon, for their help. The thanks also go to Prof. Dr. Pornsak Sriamornsak for his advice and encouragement.

REFERENCES

Ajun W, Yan S, Li G, Huili L. 2009. Preparation of aspirin and probucol in combination loaded chitosan nanoparticles and in vitro release study. *Carbohydr Polym.* 75: 566-574.

Amidon GL, Lennernas H, Shah VP, Crison JR. 1995. A theoretical basis for a biopharmaceutic drug classification: The correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharm Res.* 12: 413-420.

Comunian TA, Thomazini M, Alves A, Matos Jr FE, Carvalho Balieiro JC, Favaro-Trindade CS. 2013. Microencapsulation of ascorbic acid by complex coacervation: Protection and controlled release. *Food Res Int.* 52: 373-379.

Council of Europe. 2010. *European pharmacopoeia*. 7th Strasbourg: Council of Europe.

Gao Y, Cui F, Guan Y, Yang L, Wang Y, Zhang L. 2006. Preparation of roxithromycin-polymeric microspheres by the emulsion solvent diffusion method for taste masking. *Int J Pharm.* 318: 62-69.

Hanning SM, Lopez FL, Wong I, Ernest TB, Tuleu C, Gul MO. 2016. Patient centric formulations for paedriatris and geriatrics: Similarities and differences. *Int J Pharm.* 512(2): 355-359.

Hollouard F, Mehenni L, Lahiani-Skiba M, Anouar Y, Skiba M. 2016. Solid dispersions for oral administration: An overview of the methods for their preparation. *Curr Pharm Des.* 22: 1-17.

Joshi S, Petereit HU. 2013. Film coatings for taste masking and moisture protection. *Int J Pharm.* 457: 395-406.

Lee H, Kim J, Park S, Rhee Y, Park C, Park E. 2017. Controlled-release oral dosage forms containing nimodipine solid dispersion and hydrophilic carriers. J Drug Deliv Sci Technol. 37: 28-37.

Lenik J, Wesoly M, Ciosek P, Wroblewski W. 2016. Evaluation of taste masking effect of diclofenac using sweeteners and cyclodextrin by a potentiometric electronic tongue. *J Electroanal Chem.* 780: 153-159.

Maderuelo C, Zarzuelo A, Lanao JM. 2011. Critical factors in the release of drugs from sustained release hydrophilic matrices. *J Control Rel.* 154: 2-19.

Maniruzzaman M, Boateng JS, Bonnefille M, Aranyos A, Mitchell JC, Douroumis D. 2012. Taste masking of paracetamol by hot-melt extrusion: An in vitro and in vivo evaluation. *Eur J Pharm Biopharm.* 80: 433-442.

Nagadivya P, Ramakrishna R, Sridhar G, Bhanushashank R. 2012. Solid dispersions for oral administration: An overview of the methods for their preparation. *Int J Res Pharm Sci.* 3(1): 12-16.

Nilesh MR, Shivaji DM, Rameshrao KD. 2012. Taste masking methods and agents in pharmaceutical formulations. *IRJP*. 3(8): 67-70.

Nishiyama T, Ogata T, Ozeki T. 2016. Preparation of bitter taste-masking granules of lafutidine for orally disintegrating tablets using water-insoluble/soluble polymer combinations. J Drug Deliv Sci Technol. 32: 38-42.

Petrovick GF, Breitkreutz J, Pein-Hackelbusch M. 2016. Taste-masking properties of solid lipid based micropellets obtained by cold extrusion-spheronization. *Int J Pharm.* 506: 361-370.

Siewert M, Dressman J, Brown CK, Shah VP. 2003. FIP/AAPS Guidelines to dissolution/in vitro release testing of novel/special dosage forms. *AAPS Pharm Sci Tech*. 4(1): Article 7.

Shah PP, Mashru SA. 2008. Formulation and evaluation of primaquine phosphate taste-masked rapidly disintegrating tablet. *J Pharm Pharmacol.* 60: 1279-1285.

Sharma V, Chopra H. 2010. Role of taste and taste masking of bitter drugs in pharmaceutical industries-An overview. Int J Pharm Pharm Sci. 2(4); 14-18.

Shivakumar HN, Desai BG, Deshmukh G. 2008. Design and optimization of diclofenac sodium controlled release solid dispersions by response surface methodology. *Indian J Pharm Sci.* 70(1): 22-30.

Tomas J, Kleinschmidt S. 2009 Improvement of flowability of fine cohesive powders by flow additives. *Chem Eng Technol.* 32(10): 1470-1483.

The Department of Health, Great Britain. The Department of Health, Social, Services and Public Safety, Northern Ireland. 2015. *British Pharmacopoeia. Volume V.* London: The Stationary Office. Appendix XII C V-371.

The United States Pharmacopeia. The National Formulary. 2014. *USP 37 and NF 22*. *Volume 1.2*. Rockville: The United States Pharmacopeial Convention, Rockville.

U.S. Food and Drug Asministration, Center for Drug Evaluation and Research (CDER). 2008. Guidance for Industry: Orally Disintegrating Tablets. Retrieved from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070578.pdf, accessed Feb. 24, 2017.

Wikarsa S, Durand D, Delarbre JL, Baylac G, Batalie B. 2008. The Improvement of Ibuprofen Dissolution Rate Through Microparticles Spray Drying Processed in an Aqueous System. Drug Dev Ind Pharm. 34(5): 485-491.

Yi E, Kim J, Rhee Y, Kim S, Lee H, Park C, Park E. 2014. Preparation of sildenafil citrate microcapsules and in vitro/in vivo evaluation of taste masking efficiency. *Int J Pharm.* 466: 286-295.

Yoshida M, Haraguchi T, Uchida T. 2014. Bitterness evaluation of acidic pharmaceutical substances (NSAIDs) using a taste sensor. *Chem Pharm Bull.* 62(12): 1252-1258.