Research Article

การพัฒนาและประเมินยาเม็ดไดโคลฟีแนคโซเดียมแตกตัวในปาก ที่เตรียมโดยสารช่วยเภสัชกรรมแบบผสมประเภทต่าง ๆ

กัมปนาท หวลบุตตา[1]*, Mohd. Fadli Asmani[2], Yugesvaran A/L Vedewellu[2], ธนิกานต์ แสงนิ่ม[1]

[1]อาจารย์ คณะเภสัชศาสตร์ มหาวิทยาลัยบูรพา ชลบุรี ประเทศไทย 20131

[2]อาจารย์ School of Pharmacy, มหาวิทยาลัย Management and Science, Shah Alam, มาเลเซีย 40100

*** ติดต่อผู้นิพนธ์:** กัมปนาท หวลบุตตา อาจารย์ คณะเภสัชศาสตร์ มหาวิทยาลัยบูรพา ชลบุรี ประเทศไทย 20131

โทรศัพท์: +6638102610 อีเมลล์: tanikan@go.buu.ac.th

บทคัดย่อ

การพัฒนาและประเมินยาเม็ดไดโคลฟีแนคโซเดียมแตกตัวในปากที่เตรียมโดยสารช่วยเภสัชกรรมแบบผสมประเภทต่าง ๆ

กัมปนาท หวลบุตตา[1]*, Mohd. Fadli Asmani[2], Yugesvaran A/L Vedewellu[2], ธนิกานต์ แสงนิ่ม[1]

ว. เภสัชศาสตร์อีสาน 2561; 14(1) : 45-57

รับบทความ : 5 พฤษภาคม 2560 **ตอบรับ :** 8 กุมภาพันธ์ 2561

งานวิจัยนี้มีจุดประสงค์เพื่อพัฒนาและประเมินยาเม็ดไดโคลฟีแนคโซเดียมแตกตัวในปากที่เตรียมด้วยสารช่วยทางเภสัชกรรมแบบผสมที่ผ่านกระบวนการปรับปรุง **วิธีการ**: เตรียมยาเม็ดแตกตัวในปากด้วยวิธีการตอกตรง ซึ่งเป็นวิธีการเตรียมยาเม็ดที่มีประสิทธิภาพและค่าใช้จ่ายในการผลิตต่ำ สารเพิ่มปริมาณที่ผ่านกระบวนการปรับปรุงสามชนิดที่มีอยู่ในท้องตลาดประกอบด้วย F-Melt® C, F-Melt® M และ Pearlitol Flash® ถูกนำมาใช้ในการเตรียมยาเม็ด โดยเปรียบเทียบกับ Mannitol ซึ่งเป็นสารเพิ่มปริมาณที่ใช้อยู่อย่างแพร่หลายในปัจจุบัน ยาเม็ดที่เตรียมได้ถูกประเมินสมบัติเชิงกายภาพหัวข้อต่างๆ เช่น ความแข็ง ความหนา เส้นผ่าศูนย์กลาง ความกร่อน การแตกตัวและการละลายของยา **ผลการทดลอง:** จากผลการทดสอบทุกสูตรตำรับพบว่ายาเม็ดแตกตัวในปากที่เตรียมจาก F-Melt® M ที่ตอกด้วยแรงอัด 1 ตัน เป็นเวลา 5 วินาที มีคุณสมบัติเชิงกลดีกว่าสูตรอื่น โดยมีความแข็งสูง (19.74±1.24 กก./ซม.^{2}) ยาเม็ดแตกตัวเร็วภายใน 53.4 ± 4.72 วินาที และละลายเร็วภายใน 3 นาที โดยปลดปล่อยยาร้อยละร้อยภายในสามนาทีแรก จากผลการศึกษาจึงสามารถสรุปได้ว่า F-Melt® M สามารถทำหน้าเป็นสารเพิ่มปริมาณในตำรับยาเม็ดแตกตัวในปากได้ดีและมีโอกาสที่จะพัฒนาในการผลิตในระดับอุตสาหกรรม

คำสำคัญ: ยาเม็ดแตกตัวในช่องปาก, สารช่วยทางเภสัชกรรมแบบผ่านขบวนการพัฒนา, การแตกตัว

Development and Evaluation of Diclofenac Sodium Oral Dispersible Tablet (ODT) Formulation using Different Types of Co-excipients

Kampanart Huanbutta[1]*, Mohd. Fadli Asmani[2], Yugesvaran A/L Vedewellu[2], Tanikan Sangnim[1]

[1]Lecturer, Faculty of Pharmaceutical Sciences, Burapha University, Chonburi, Thailand, 20131

[2]Lecturer, School of Pharmacy, Management and Science University, Shah Alam, Malaysia 40100

*** Corresponding author:** Kampanart Huanbutta**,** Faculty of Pharmaceutical Sciences, Burapha University, Chonburi, Thailand, 20131**,**

Tel: +6638102610, E-mail address: kampanart@go.buu.ac.th

Abstract

Development and Evaluation of Diclofenac Sodium Oral Dispersible Tablet (ODT) Formulation using Different Types of Co-excipients

Kampanart Huanbutta[1]*, Mohd. Fadli Asmani[2], Yugesvaran A/L Vedewellu[2], Tanikan Sangnim[1]

IJPS, 2018; 14(1) **:** 45**-**57

Received : 5 May 2017 **Accepted :** 8 February 2018

The aim of this study was to develop and evaluate diclofenac sodium as oral dispersible tablets (ODTs) using different types of co-excipients. **Methods:** The ODTs were prepared by direct compression technique as it is a favorable and cost effective way to produce tablets with sufficient structural integrity. Three different co-processed excipients were used including F-Melt® type C, F-Melt® type M and Pearlitol Flash® along with conventional excipient, mannitol, for comparative purpose of the study. The formulated tablets were evaluated for various physical tests such as hardness, thickness, diameter, friability, disintegration time and dissolution testing. Among all the evaluated formulation, the best condition of ODTs from each excipient formulation were selected for the in-vitro dissolution test. **Results:** Among all the formulation, the diclofenac sodium loaded ODTs prepared by using F-Melt M, co-processed excipient, with compression force of 1 ton for 5 sec was superior in term of mechanical strength, disintegration and dissolution profile compared to other formulations. The best drug loaded ODTs formulation prepared by F-Melt type M provides a tablet hardness of 19.74±1.24 kg/cm^2, disintegration time of 53.4±4.72 seconds, and 100% drug being released within the first 3 minutes. The results suggested that the co-processed excipient system F-Melt type M act as a satisfying combination of excipient with the active pharmaceutical ingredient (API), diclofenac sodium, in developing ODTs. Thus, scale studies can be performed for application at industrial sites.

Keywords: oral dispersible tablets, co-processed excipients, disintegration

Introduction

Oral route of drug delivery is the most pleasing, convenient, essential and favored route for the administration of drug with ease of swallowing, self-medication, economic, and most importantly patient compliance. Compared to oral liquids, tablets are the most popular and preferred oral formulation available in the market because of its ease of manufacturing, convenience in administration, accurate dosing, and stable. In addition, tablets are more tamper proof than oral capsule (Joshi *et al.*, 2013).

Oral dispersible tablets (ODT) also acknowledged as orally disintegrating tablets, mouth-dissolving tablets, rapid dissolving tablets, fast-disintegrating tablets, and fast-dissolving tablets were developed in the late 80s and popularized to the market in the early 90s (Hirani *et al.*, 2009, Dey and Maiti, 2010). The oral dispersible tablets are termed as an uncoated tablet to be placed in the mouth where they dissolved rapidly before being swallowed. The kind of tablet can be taken without any liquid. The emerging of ODT in the pharmaceutical field is due to several problems that were encountered from the conventional oral dosage forms. Many patients experiences difficulty in swallowing (dysphagia) especially in the case of pediatric, geriatric, bedridden, travelling patients as well as patient undergoing chemotherapy or antipsychotic treatment (Bandari *et al*., 2008). Furthermore, it is very difficult to ensure mentally retarded, epileptic or unconscious patients to swallow medication despite their condition. Hence, these conventional dosage forms results in high incidence of noncompliance and treatment failures with respect to swallowing (Dey and Maiti, 2010). With the utilization of ODTs, rapid drug therapy intervention can be obtained, achieved increased bioavailability/rapid absorption through pregastric absorption of drugs from mouth, pharynx, and esophagus as saliva passes down. The good mouth feel property of ODTs helps to change the impression of medication as bitter pill, especially in pediatric patients (Parkash *et al.*, 2011).

There various techniques can be used in making oral dispersible tablets (ODTs) such as freeze drying or lyophilization, molding, sublimation, and compaction. Selection of ODT preparation techniques is depended on the physical properties of the ingredients incorporated in the formulation (Parkash *et al.*, 2011; Gryczke *et al.*, 2011) Nonetheless, most of the techniques required selective machines and time consuming. Furthermore, the hardness of ODT products was not enough to stand up for process of packaging and transportation. Among those techniques, direct compression is a favorable and cost effective way to produce tablets with sufficient structural integrity (Patel *et al.*, 2011). Pharmaceutical excipients play an important role for the development of a compelling formulation that fulfilled all the qualities of and ODT (Parker, 2009). Thus, co-processed excipient systems have been developed with the aim to ease ODTs manufacturing (Kanojia *et al*., 2013). The combination of two or more excipients designed to physically modify their properties in a manner not feasible by simple physical mixing and without significant chemical change (Marwaha *et al.*, 2010). In addition, there is no need for toxicological studies of the new material (Krupa *et al.*, 2012). These excipients have high functionalities as compared to individual excipients like better flow property, compressibility, reduced lubricant sensitivity (Kathpalia *et al.*, 2014). One of the crucial benefits of co-processed excipients is fixed and homogenous distribution of the components in the mixture that prevents from segregation (Mishra *et al.*, 2006). As presented in Table1, various co-processed system that are intended to form ODTs by direct compression includes F-Melt (Fuji Chemical Industry, Japan), Pearlitol Flash (Roquette, France), Pharmaburst (SPI Polyols, USA), Ludiflash (BASF, Germany), and Prosolv ODT (JRS, Germany). Basically, they are made up of polyols, disintegrants, and inorganic compounds. The ODTs are made up by easily dry blend the API with the excipient and lubricant, then directly compressed into tablets.

Table 1 Composition of various co-processed excipient

Co-processed Excipients	Manufacturer	Components	Claimed benefits
F-Melt® Type C	Fuji Chemical	D-Mannitol, xylitol, MCC, Crospovidone, and Fujicalin® (anhydrous dibasic calcium phosphate)	Directly compressible, pleasant mouth feel, high flowability
F-Melt® Type M	Fuji Chemical	D-Mannitol, xylitol, MCC, crospovidone, Neusilin® (Magnesium Aluminometasilicate)	Directly compressible, pleasant mouth feel, high flowability
Pearlitol Flash®	Roquette	Mannitol Maize starch	Pleasing taste, fast melting, easy direct compressibility
Ludipress®	BASF	Lactose monohydrate-93.4 Kolidon30- 3.2 Kollidon CL- 3.4	Low hygroscopicity, good flowability, constant tablet weight
Ludiflash®	BASF	Mannitol- 90 Kollidon® CL- SF-5 Kollicoat® SR30D- 5	Rapidly disintegrating, mechanically stable tablets
Avicel® CE-15	FMC	MCC- 85 Guar- 15	Less grittiness, improved tablet palatability

The aim of the present study is to compare the effectiveness of different co- processed excipient systems, including F- Melt (Type C & M) and Pearlitol Flash to form oral dispersible tablets (ODTs) by direct compression technique using diclofenac sodium as a model drug. Mannitol is also utilized to develop the ODTs for comparing with the ODTs made of co- processed excipients. Assessment of physicochemical properties of tablets included hardness, diameter, thickness, friability, tapped density, disintegration time measurement and dissolution studies were performed to optimize the formulation.

2. Materials and methods

2.1 Materials

Diclofenac sodium was purchased from Amoli Organics Ltd. (India). Magnesium stearate and mannitol were obtained from Chemipan Co., (Thailand). The co-processed excipients, F-Melt type C and M were purchased from Fuji Chemical Industry Co., Limited (Japan). The Pearlitol Flash was purchased from Roquette Pharma (France).

2.2 Morphology of Co-Processed Excipients

Scanning electron microscopy (SEM), was utilized to envision the particle diameter, structural and surface morphology of the excipients powders. The different types of co-processed excipients powders; F-Melt (Type C & M) and Pearlitol Flash were mounted on double-faced adhesive tape and sputter-coated with a thin (approximately 10nm) layer of gold in Balzers SCD 050 (Balzers Union, Liechtenstein) coating unit at 20 mA using an argon gas purge. Then, the samples were examine using scanning electron microscope (LEO, 1450 VP, United Kingdom) operating at high vacuum with an accelerating voltage of 15 kV and a sample working distance of 10mm (Yang *et al.*, 2011).

2.3 Flow Properties and Compressibility of the Powders

The drug powders mixed with excipients were evaluated for flow property which includes angle of repose, bulk density, tapped density, Hausner' s ratio, and compressibility index (Carr's index) (Shah *et al.*, 2008).

2.3.1 Angle of Repose

The angle of repose was checked by using funnel method. Accurately weighed 25 gram of granules was allowed to pass through a funnel which was fixed to the retort stand 5 cm above from the base. The height and diameter of the cone pile was noted from which the angle of repose is calculated using the following equation (Sundaresan A, *et al*. 2014):

$$\theta = \tan^{-1}(h/r) \quad (1)$$

Where, θ = Angle of Repose

h = Pile height

r = Radius of pile

2.3.2 Bulk Density

The powder was filled into a graduated cylinder. The height was measured after the powders were leveled. The unsettled volume (V_o) was recorded. The bulk density was calculated using the following equation (Sundaresan *et al.*, 2017):

$$Bulk\ Density(\rho_0) = \frac{M}{V_0} \quad (2)$$

Where, M = Mass of powder taken; V_o = Apparent unsettled volume (Bulk volume).

2.3.3 Tapped Density

Tapped density of the granules was determined by tapping the measuring cylinder containing pre-weighed granules (M) gently on a wooden plane from 1 inch (h) above at regular intervals of 2 seconds for 500 times (Sundaresan *et al*., 2017):

$$Tapped\ Density(\rho_t) = \frac{M}{V_t} \quad (3)$$

Where, M = Weight of the granules; V_t = Tapped volume of granules in cm^3.

2.3.4 Hausner's Ratio

Tapped density and bulk density of the granules were used to calculate the Hausner's index *(*Joshi *et al*., 2013).

Hausner's index= D_t/D_b (4)

where, D_t is tapped density and D_b =is bulk density.

2.3.4 Carr's Index

Carr's Index was measured using the values of bulk density and tapped density. The following equation was used to find the Carr's Index (Sundaresan *et al.*, 2014):

Carr's Index (%) = $(D_t - D_b)/ D_t \times 100$) (5)

2.4 Preparation of ODT

In this study, oral dispersible tablets (ODTs) were prepared by using direct compression method with different compression force and duration. Total of eight formulations were made using different excipients; F-Melt type C, F-Melt type M, Pearlitol Flash and mannitol. The composition of each formulations are shown in table 2.

Table 2 Composition of diclofenac sodium oral dispersible tablet formulation

Component	F1	F2	F3	F4	F5	F6	F7	F8
Diclofenac Sodium (mg)	-	-	-	-	25.00	25.00	25.00	25.00
Excipients (mg)	F-Melt C	F-Melt M	Pearlitol	Mannitol	F-Melt C	F-Melt M	Pearlitol	Mannitol
	497.00	497.00	497.00	497.00	472.00	472.00	472.00	472.00
Magnesium stearate	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Total weight of each tablet (mg)	500	500	500	500	500	500	500	500

2.5 Evaluation of ODT

2.5.1 Hardness, diameter and thickness

The prepared tablets were evaluated for the uniformity of thickness, diameter and hardness by using (Erweka TBH 28, Frankfurt, Germany) apparatus according to USP22 tests.

2.5.2 Friability test

The friability tester (Erweka friabilator, A3R, Frankfurt, Germany) was used in this test. The procedure started with weighing 10 tablets and placing in the apparatus. After 100 revolutions, the tablets were de-dusted and weighed again. The test was determined from the expression;

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad (6)$$

2.5.3 Disintegration test

The disintegration test apparatus (Erweka, ZT4, Heusentsamn, Germany) was used to determine the disintegration time of six tablets. The process involves placing each tablet onto the tube of the basket rack assembly of the disintegration apparatus without disc. The disintegration media (distilled water) was maintained at 37.0±1ºC and time needed for complete disintegration of each tablet was recorded.

2.5.4 *In-vitro* Dissolution Study

From the physical evaluation, best condition of ODTs offering high hardness, rapid disintegration excellent flowability was selected from each formulation and further tested for *in-vitro* dissolution studies. The drug release from the formulated Diclofenac sodium ODTs were determined using USP type II, paddle dissolution apparatus. The dissolution test was performed using 900 mL of phosphate buffer solution, pH 6.8 at 37± 0.5ºC and 75 rpm of paddle speed. Then, 5 mL of the solution was collected from the dissolution apparatus at specific time intervals and the samples were replaced with same volume of the fresh dissolution medium. Each sample was analyzed by UV-spectrophotometer (UV-2900 Shimadzu) at wavelength of 298 nm (Kumar and Babu, 2014).

3. Result and discussion

3.1 Morphology of Co-processed Excipients

The SEM images of the co-processed excipients of F-Melt type M, type C, Pearlitol Flash and mannitol are illustrated in Fig. 1, 2, 3, and 4 respectively. The F-Melt M showed porous agglomerates and their particle sizes were ranging from 2-100 µm. While the F-Melt C particle size was larger than those of type M. The Pearlitol Flash also having the same range of particle size with the F-Melt M granules but Pearlitol Flash agglomerates were less spherical than F-Melt. However, the particle size distribution was more uniform in case of Pearlitol Flash compared to F-Melt granules. This can be explained by the different solid forms of the granules. The Pearlitol Flash is in crystalline solid form and F-Melt excipients are in amorphous solid form. The crystalline and amorphous solid forms are different in term of their arrangement order in which the crystalline forms are arranged in orderly geometric pattern, where as the amorphous solid have their particles distributed without any long-range pattern (Hancock and Zografi, 1997). Surface analysis of the both co-processed excipients showed that the Pearlitol Flash granules surface was rougher compared to the F-Melt granules. For mannitol, they are in crystalline form and their size are around 3-16 µm.

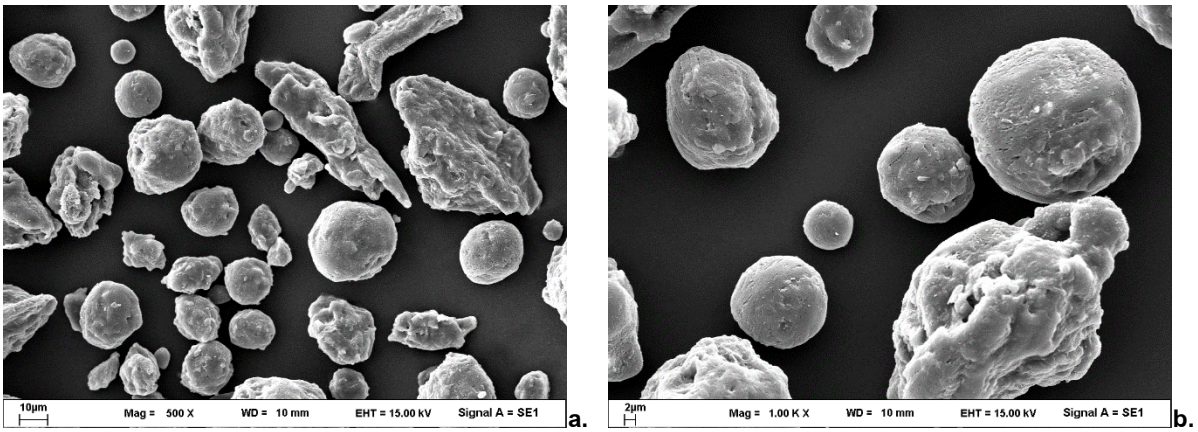

Figure 1 SEM pictures of co-processed excipient F-Melt type M at magnification of (a.) 500x and (b.) 1000x.

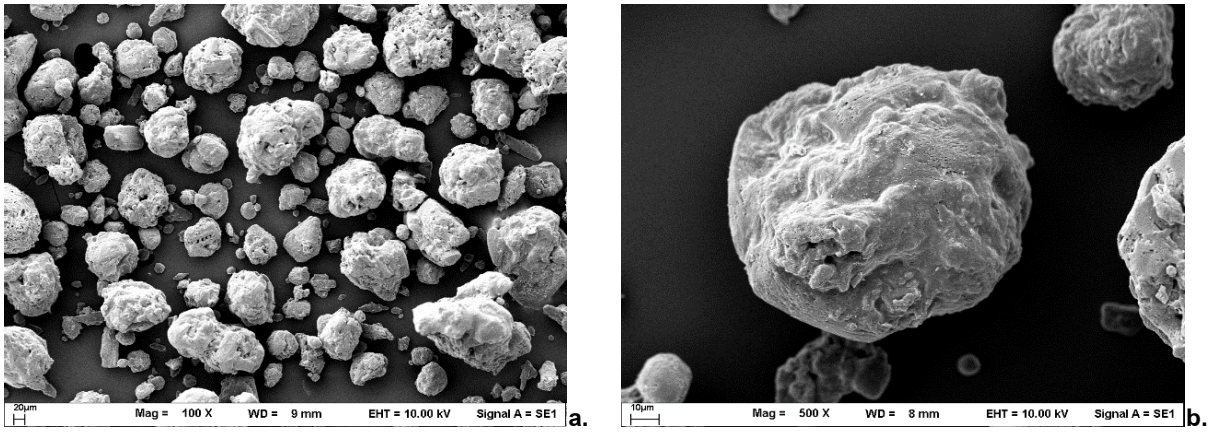

Figure 2 SEM pictures of co-processed excipient F-Melt type C at magnification of (a.) 100x and (b.) 500x.

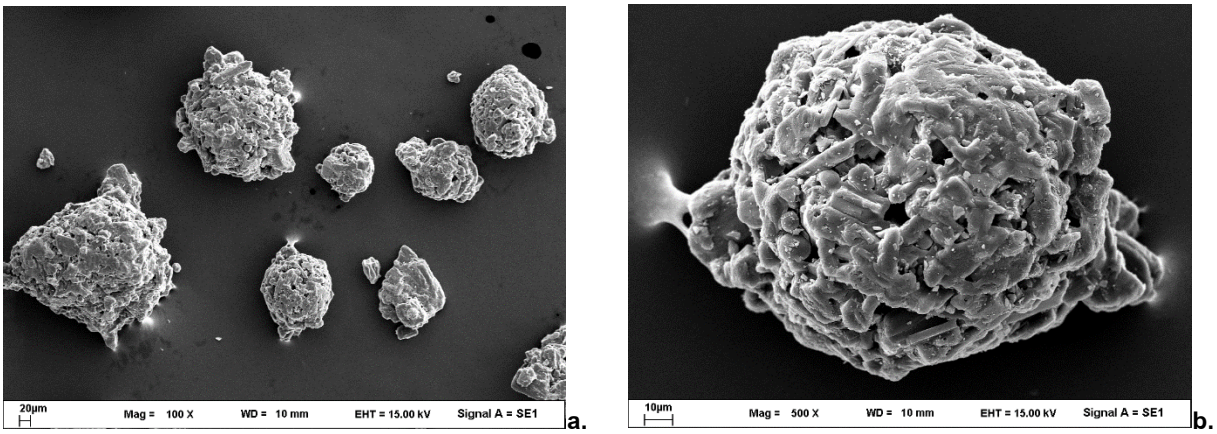

Figure 3 SEM pictures of co-processed excipient Pearlitol Flash at magnification (a.) 100x and (b.) 500x.

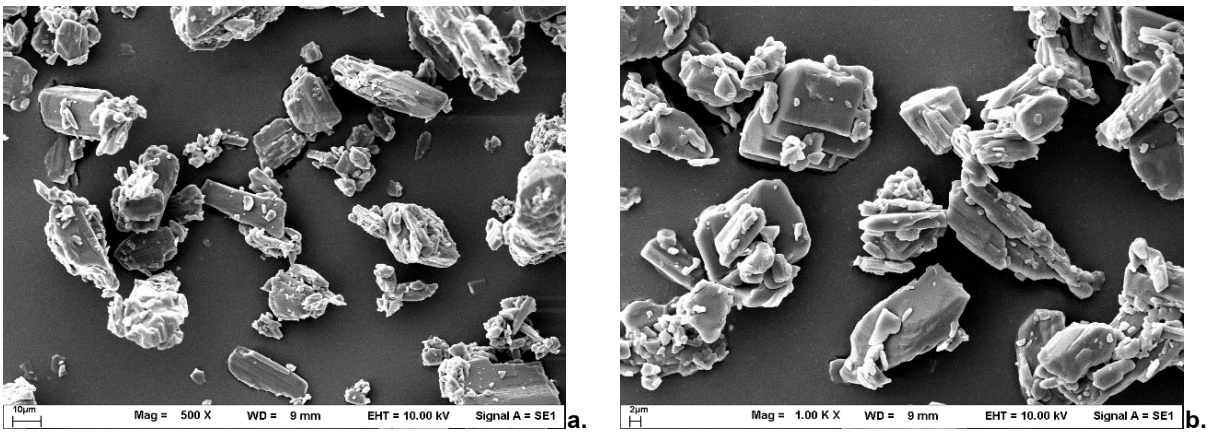

Figure 4 SEM pictures of mannitol at magnification (a.) 500x and (b.) 1000x.

3.2 Flow Properties and Compressibility of the Powders

All the formulations were prepared by direct compression method. The data obtained from pre-compression parameters such angle of repose, bulk density, tapped density, Hausner's ratio and Carr's index are shown in Table 3. Angle of repose are used to measure the inter-particulate friction or resistance towards the movement between powder particles. Based on the result, the angle of repose of all formulation without drug containing co-processed excipients, F-Melt C (F1), F-Melt M (F2) and

Pearlitol (F3) were 25.79, 25.82 and 25.72, respectively indicating excellent powder flow. However, formulation containing mannitol F4 and F8 performed poor flow properties. As per the pharmacopoeia standards, angle of repose ranging from 25-30 degree indicates excellent flow for powders. Bulk density is calculated because the interparticles interactions not only influencing bulking characteristic of the powder but also interfering with powder flow. All the formulation having bulk and tapped densities values closer to each other which determines very less interparticles interaction between the powders. As indicating in USP, the compressibility index (Carr's index) ranging more than 26 and Hausner's ratio more 1.35 shows poor flowability for powders. From the observation, formulation containing co-processed excipient Pearlitol Flash having an excellent powder flow characteristic in both non-drug loaded formulation (F3, Carr's index 12.36) and the one containing the active drug (F7, Carr's index 16.41). Due to its non-hygroscopic nature, mannitol is a versatile excipient used in formulating Pearlitol Flash together with maize starch by spray-drying method provide better flowability compared to the individual excipient, mannitol which have very poor flow property. This can further explain the effectiveness of co-processed excipients compared to individual excipient system. The powder flow characteristic declines in the following orders of the formulations; F3 > F2 > F7 > F1 > F5 > F6 > F4 > F8.

Table 3 Flow properties of powders

FORMULATION	ANGLE OF REPOSE (degrees)	BULK DENSITY (g/cm^3)	TAPPED DENSITY (g/cm^3)	CARR'S INDEX (g/cm^3)	HAUSNER'S RATIO
F1 (F-Melt C)	25.79 ± 0.68	0.56 ± 0.00	0.67 ± 0.01	17.56 ± 0.80	1.21 ± 0.01
F2 (F-Melt M)	25.82 ± 0.75	0.54 ± 0.01	0.62 ± 0.01	13.91 ± 2.68	1.16 ± 0.04
F3 (Pearlitol)	25.72 ± 0.79	0.42 ± 0.01	0.48± 0.01	12.36 ± 0.87	1.14 ± 0.01
F4 (Mannitol)	41.57 ± 1.12	0.43 ± 0.00	0.73± 0.02	41.75 ± 2.21	1.72 ± 0.07
F5 (F-Melt C)*	25.05 ± 0.64	0.55 ± 0.01	0.78 ± 0.05	29.40 ± 4.53	1.42 ± 0.09
F6 (F-Melt M)*	25.08 ± 0.82	0.56 ± 0.01	0.87 ± 0.01	36.27 ± 2.01	1.57 ± 0.05
F7 (Pearlitol)*	25.40 ± 0.74	0.56± 0.01	0.67± 0.01	16.41 ± 1.52	1.20 ± 0.02
F8 (Mannitol)*	41.43 ± 0.78	0.42 ± 0.01	0.77 ± 0.01	45.53 ± 1.80	1.84 ± 0.06

All values expressed as mean ±SD from three experimental runs

* Drug loaded formulation

3.3 Evaluation of ODT

3.3.1 Hardness, diameter and thickness

The physical evaluation of developed drug loaded and non-drug loaded ODTs (1 ton/5 seconds compression time) using different co-processed excipients; F-Melt C, F-Melt M and Pearlitol Flash and mannitol are showed in table 4 which expresses that co-processed excipients of F-Melt types C and M were quite similar and having better hardness compared to the Pearlitol co-processed excipient and mannitol systems. The conventional excipient mannitol having weak mechanical strength as the hardness is only 4.83 ± 0.48 kg/cm^2. From Figure 5, the maximum hardness of F-Melt type M and C were at 20 seconds of compression time. However from 5 seconds over the tablet hardness was slightly increase. For mannitol and Pearlitol, they reached the highest tablet hardness at 5 seconds. At 60 seconds, tablet hardness from F-Melt type C was slightly higher than F-Melt type M and for F-Melt group, they was harder than those of Pearlitol Flash and mannitol, respectively. This might be because F-Melt type C contain Fujicalin® which

is dibasic calcium phosphate anhydrous enhancing hardness properties of the tablet structure (Camblin *et al.*, 2016). An ideal ODT should have sufficient hardness level in order to withstand the tablet's firmness during packaging and transportation. Whereas, thickness and diameter of all the formulation are within the acceptable limits, as reported in Table 4.

Table 4 Physical evaluation of the ODTs (1 ton/5 seconds compression time)

FORMULATION	HARDNESS (kg/cm^2)±S.D	THICKNESS (mm) ±S.D	DIAMETER (mm) ±S.D	IN-VITRO DISINTEGRATION TIME (s)±S.D	Friability (%)
F1 (F-Melt C)	21.05 ± 8.20	3.03 ± 0.03	22.97 ± 0.02	20.20 ± 3.49	-
F2 (F-Melt M)	20.07 ± 1.55	3.02 ± 0.01	22.98 ± 0.01	24.20 ± 0.84	-
F3 (Pearlitol F)	6.00 ± 1.15	3.02 ± 0.01	23.00 ± 0.00	19.80 ± 0.84	-
F4 (Mannitol)	4.83 ± 0.48	3.04 ± 0.01	22.94 ± 0.01	16.40 ± 1.14	-
F5 (F-Melt C)	20.23 ± 1.99	3.03 ± 0.03	22.93 ± 0.04	84.60 ± 18.43	0.20 ± 0.01
F6 (F-Melt M)	19.74 ± 1.24	3.06 ± 0.04	22.82 ± 0.01	53.40 ± 4.72	0.39 ± 0.04
F7 (Pearlitol F)	6.28 ± 0.54	3.10 ± 0.02	22.88 ± 0.01	36.80 ± 0.83	3.61 ± 0.12
F8 (Mannitol)	7.14 ± 0.47	2.91 ± 0.08	22.84 ± 0.01	42.80 ± 0.84	1.38 ± 0.11

All values are expressed as mean ± SD, n=5

F5-F8 are drug loaded formulation

Among the four blank ODTs formulation, it can be concluded that both the F-Melt C and F-Melt M co-processed excipients were better in term of mechanical strength and *in-vitro* disintegration time compared to Pearlitol Flash co-processed excipient and mannitol. The studies were further carried out to investigate the effectiveness of the co-processed excipients system with the active drug; diclofenac sodium in identifying a better and viable ODTs formulation.

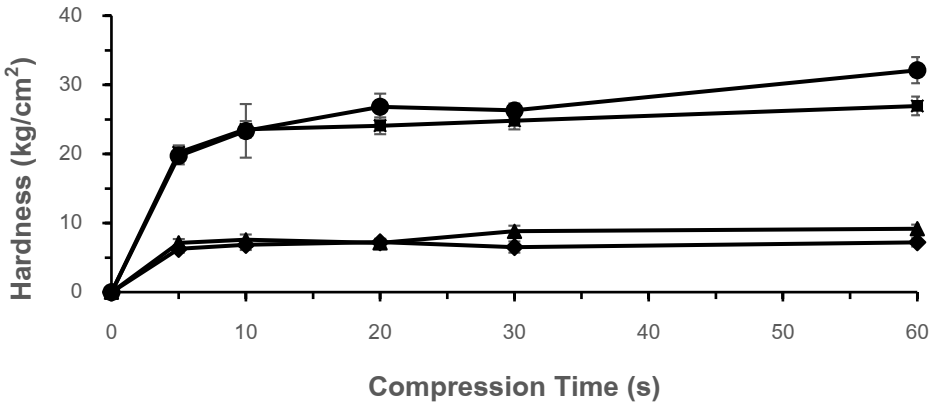

Figure 5 Relationship between hardness and compression time of diclofenac sodium ODTs using F-Melt C (●), F-Melt M (■), Pearlitol Flash (♦) and mannitol (▲) as major excipient

3.3.2 Disintegration test

The *in-vitro* disintegration time of all tablets were between 16.4±1.14 to 84.6±18.43 seconds as presented in Table 4. Comparing between the drug loaded ODT (F5-F8) and the non-drug loaded ODT (F1-F4), disintegration times of the ODT containing drug were longer than the non-drug loaded formulations. This might be because hydrophobicity of diclofenac sodium is higher than the excipient leading to retard of water penetration into the tablet (Huanbutta *et al.*, 2011). According to the pharmacopoeia standards, the dispersible tablet must disintegrate within 2 minutes. And all the formulated batches of ODTs diclofenac sodium with different compression force have shown rapid disintegration time between 36.80±0.83 to 84.60±18.43 seconds indicating suitability for fast dissolving tablets. For disintegration time of the blank ODT, mannitol was slightly faster than those of Pearlitol Flash, F-Melt type M and C, respectively. However, friability of Pearlitol Flash and mannitol were higher than 1% which is not acceptable as shown in Table 4. The relationship between hardness and disintegration time of the non-drug loaded ODT prepared from the several excipients is revealed is in Figure 6. This depicts that physical properties such as disintegration time and hardness of mannitol and Pearlitol Flash ODTs are quite similar. Physical properties of F-Melt M and C are also analogous but higher than those of mannitol and Pearlitol Flash. This because the co-excipient, Pearlitol Flash, mainly composes of mannitol. Maize starch is also added in Pearlitol Flash in to improve binding properties while group of F-Melt is comprised of mannitol, xylitol, MCC, crospovidone and Fujicalin® (Magnesium Aluminometasilicatel; F-Melt M)/ Neusilin® (anhydrous dibasic calcium phosphate; F-Melt C). Consequently, the added MCC and crospovidone substantially ameliorate hardness of the tablet.

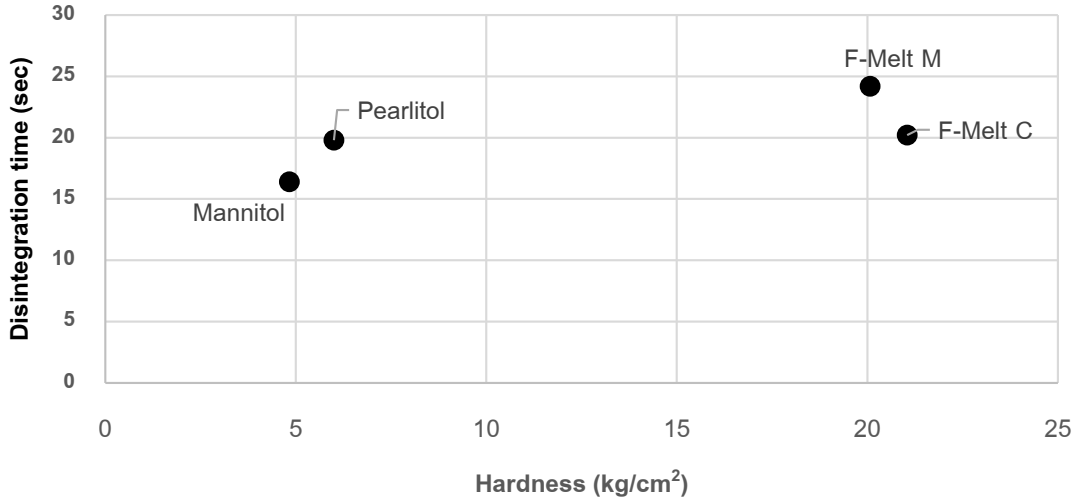

Figure 6 Relationship between hardness and disintegration time of the non-drug loaded ODTs using different excipients

3.3.3 Friability test

Friability percent of the drug loaded ODT prepared from different excipient were from 0.20 to 3.61% as shown in Table 4. Even though Pearlitol Flash and mannitol offered fast disintegration, they have high friability percent (more than 1%) indicating poor strength of the tablets. To improve friability property, intervention have been made for ODTs prepared by Pearlitol Flash and mannitol excipients in which the compression force (2.0, 2.5 and 3.0 tons) were increased by maintain a fixed 5 seconds of force applied. The results of the intervention shown in Table 5 indicating better friability properties. However, disintegration times were longer than 3 minutes when applied compression force was greater than 2.0 ton.

Table 5 Physical evaluation of ODTs loaded diclofenac sodium

FORMULATION	HARDNESS (kg/cm^2)±S.D	IN-VITRO DISINTEGRATION TIME (sec)±S.D	FRIABILITY (%)
F7 (Pearlitol F)			
1.5 ton/5sec	11.27 ± 1.40	58.6 ± 6.34	1.59
2.0 ton/5sec	16.03 ± 0.96	63.8 ± 8.17	1.00
2.5 ton/5sec	16.98 ± 1.32	OT	0.89
3.0 ton/5sec	20.11 ± 0.63	OT	1.01
F8 (Mannitol)			
1.5 ton/5sec	9.52 ± 0.25	60.6 ± 4.93	1.2
2.0 ton/5sec	10.95 ± 1.79	68.8 ± 8.70	1.59
2.5 ton/5sec	13.18 ± 2.25	OT	1.25
3.0 ton/5sec	16.70 ± 0.79	OT	1.12

All values are expressed as mean ± SD, n=5; friability test, n=10
OT: disintegration time is over than 180 sec

3.3.4 *In-vitro* Dissolution Study

The optimized compression condition of each ODT excipient including F-Melt type C (F5) and M (F6) compressed at 1 ton for 5 seconds, the drug loaded Pearitol Flash and mannitol ODT compressed at 2 ton for 5 seconds were evaluated in the *in-vitro* dissolution test as presented in Figure 7, all the ODTs formulation have shown more than 80% of drugs being released within 5 minutes in 0.2 M phosphate buffer, pH 6.8. From the observation, ODTs formulation that made up of both the F-Melt types co-processed excipients have achieved drug release more than 100% within 3 minutes whereas ODTs prepared from Pearlitol Flash and mannitol maximally able to achieve 80% drug release within 3 minutes. This particular comparison can be concluded that ODTs diclofenac sodium prepared by F-Melt types co-processed excipients have slightly better release of the active drug component compare to the ones prepared by Pearlitol Flash and mannitol. This might be because of higher compression force aimed to lessen friability in those of Pearlitol Flash and mannitol retard drug dissolution.

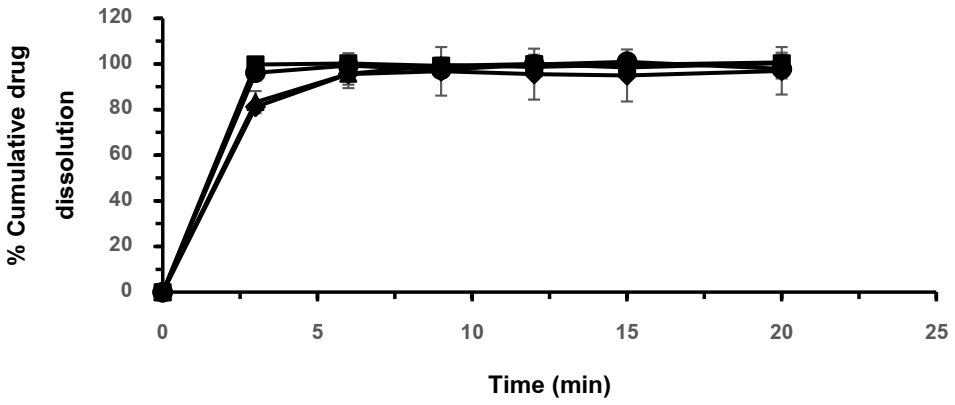

Figure 7 In-vitro drug dissolution profiles of diclofenac sodium ODTs formulation prepared from various co-process excipients including F-Melt C (●), F-Melt M (■), Pearlitol Flash (♦) and mannitol (▲)

Conclusion

In conclusion, oral dispersible tablets (ODTs) of diclofenac sodium are successfully made by using direct compression method. Among all the ODTs formulation evaluated, undoubtedly co- processed excipients system were way effective in producing an ideal ODT requirement compare to the individual excipient. The co- processed excipients have high functionalities as compared to individual excipients like better flow property, compressibility, reduced lubricant sensitivity. However, several factors may affect the mechanical strength, disintegration time and in- vitro drug release of the ODTs which are the compression force and time. Not all the co-processed excipients display same favorable physical profile when incorporating with the active pharmaceutical ingredient (API), diclofenac sodium. It can be concluded that ODTs diclofenac sodium prepared using F- Melt type M with compression force of 1ton/ 5sec are superior in term of mechanical strength, disintegration and dissolution profile compared to other formulation. Scale studies can be performed for application at industrial site.

Acknowledgements

The authors acknowledge the Faculty of Pharmaceutical Science, Burapha University for providing the grant and adequate laboratories facilities in the execution of this study.

References

Bandari S, Mittapalli RK, Gannu, Rao YM. Orodispersible Tablets: An Overview. *J Chem Pharm Res* 2008; 1: 163-177.

Dey P, Maiti S. Orodispersible Tablets: A New Trend in Drug Delivery. *J. Nat. Sci Biol Med* 2010; 1(1): 2-5.

Gryczke A, Schminke S, Maniruzzaman M, Beck J, Douroumis D. Development and evaluation of orally disintegrating tablet (ODTs) containing Ibuprofen granules prepared by hot melt extrusion. *Colloid and Surfaces B: Biointerfaces* 2011; 86: 275-284.

Handcook BC Zografi and G. Characteristics and significance of the amorphous state in pharmaceutical systems 1997; 86(1): 1-12.

Huanbutta K, Sriamornsak P, Limmatvapirat S, Luangtana-anan M, Yoshihashi Y, Yonemochi E, Terada K, Nunthanid J. Swelling kinetics of spray-dried chitosan acetate assessed by magnetic resonance imaging and their relation to drug release kinetics of chitosan matrix tablets. *Eur J Pharm Biopharm* 2011; 77(2): 320-326.

Joshi Y, Chaudhary R, Teotia UVS. Formulaion and Evaluation of Diclofenac Sodium Sustained Release Matrix Tablets Using Aegle Marmelos Gum. *Int J Cur Trend Pham Res* 2013; 1(3): 174-180.

Kanojia N, Kaur L, Nagpal M, Bala R. Modified Excipients in Novel Drug Delivery: Need of The Day. *J. Pharm Tech Res Man* 2013; 1: 81-1074.

Kathpalia H, Jogi K. Co-processed Excipients: A Review. *World J Pham Res* 2014; *3*(3): 3863-3885.

Krupa A, Jachowicz R, Pedzich Z, and Wodnicka K. The Influence of the API Properties on ODTs Manufacturing from Co-processed Excipient Systems. *AAPS PharmaSciTech* 2012; 13(4): 1120-1129.

Kumar UM and Babu KM. Design and evaluation of fast dissolving tablets containing diclofenac sodium using fenugreek gum as natural superdisintegrant. *Asian Pac J Trop Biomed* 2014; 4(1): S329-S334.

Mishra DN, Bindal M, Singh SK, Kumar SKV. Spray Dried Excipient Base: A Novel Technique for The Formulaion of Orally Disintegrating Tablets. *Chem Pharm Bul* 2006*; 54*(1): 99-102.

Parkash V, Maan S, Deepika, Yadav S K, Hemlata, Jogpal V. Fast Disintegrating Tablets: Oppurtunity in Drug Delivery System. *J. Adv Pharm Technol Res* 2011; 2(4): 223-235.

Parker A. Focus on Excipients. *Chemistry Today* 2009: 27(1): 5-7.

Shah R, Tawakkul M, Khan M. Comparative Evaluation of Flow Properties for Pharmaceutical Powders and Granules. *AAPS Pharm Sci Tech* 2008; *9*(1): 250-258.

Sundaresan A, Niveditha R, Padmanabhan S, Vedha H.B.N, Ramyadevi D. Oro-dissolving Systems of Papaya Extract-Liquisolid Compacts and Lozenges. *Int J Pharm Tech Res* 2014; 6(7): 2083-2091.