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Development of diclofenac sodium orodispersible tablets using wet granulation technique

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บทคัดย่อ

การพัฒนายาเม็ดไดโคลฟิแนคโซเดียมชนิดกระจายเร็วในช่องปากโดยใช้เทคนิคการทำแกรนูลเปียก

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บทนำ: ยาเม็ดชนิดกระจายเร็วในช่องปาก (ODTs) หมายถึง ยาเม็ดที่มุ่งหมายให้วางในปากเพื่อกระจายอย่างรวดเร็วก่อนกลืน ไดโคลฟิแนคโซเดียม (DICL) เป็นยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ที่มีฤทธิ์แรงและมีรสขม การศึกษานี้มีวัตถุประสงค์เพื่อพัฒนา DICL ODTs โดยเทคนิคการทำแกรนูลเปียกที่ใช้พอลิเมอร์กลบรสและสารเจือจาง **วัสดุและวิธีการทดลอง:** เตรียมแกรนูลกลบรสที่มีสารเจือจางเป็น แลคโตสแอนไฮดรัส (LT) หรือไดเบสิกแคลเซียมฟอสเฟต (DP) โดยใช้ Eudragit® NE 40D เป็นสารยึดเกาะก่อนผสมกับแกรนูลเปล่าและตอกเม็ด ประเมิน ODTs ความแปรปรวนของน้ำหนัก ความแข็ง ความกร่อน เวลาแตกตัว เวลาเปียก การดูดซึมน้ำ ปริมาณยา ความขม และการปลดปล่อยนอกกาย **ผลการศึกษา:** DICL ODTs ทุกตำรับผ่านเกณฑ์ความสม่ำเสมอของน้ำหนักและความกร่อน ตำรับที่มี DP 50 mg มีเปอร์เซ็นความกร่อนสูง เมื่อเพิ่มปริมาณสารเจือจาง พบว่า เวลาเปียก การดูดซึมน้ำ และเวลาแตกตัว เพิ่มขึ้น ตำรับที่ใช้ LT มีเวลาเปียกสั้นกว่าแต่การดูดซึมน้ำสูงกว่าตำรับที่ใช้ DP ตำรับที่ใช้ LT แสดงบันทึกการละลายในสภาวะบัฟเฟอร์สูงกว่า **สรุปผล:** สามารถตั้งตำรับ DICL ODTs ได้โดยเทคนิคการทำแกรนูลเปียกที่ใช้ Eudragit® NE 40D เป็นพอลิเมอร์กลบรสและแลคโตสเป็นสารเจือจาง

คำสำคัญ: ยาเม็ดชนิดกระจายเร็วในช่องปาก, ไดโคลฟิแนคโซเดียม, Eudragit, สารเจือจาง, การทำแกรนูลเปียก

Abstract

Development of diclofenac sodium orodispersible tablets using wet granulation technique

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Introduction: Orodispersible tablets (ODTs) are defined as an uncoated tablet intended to be placed in the mouth where they disperse rapidly before being swallowed. Diclofenac sodium (DICL) is a potent nonsteroidal anti-inflammatory drug having bitter taste. The objective of this study was to develop DICL ODTs by wet granulation technique using a taste-masking polymer and a diluent. **Materials and methods:** Taste-masked granules containing lactose anhydrous (LT) or dibasic calcium phosphate (DP) as diluent were prepared by using Eudragit® NE 40D as binder before mixing with blank granules and tableting. The ODTs were evaluated for the weight variation, hardness, friability, disintegration time, wetting time, water absorption, drug content, bitterness, and *in vitro* release. **Results:** All DICL ODTs formulations were met the criteria of "uniform of weight" and "friability". The formulation with DP 50 mg showed high percentage of friability. The wetting time, water absorption and disintegration time of DICL ODTs was found to increase with the amount of diluent. The formulations using LT showed shorter wetting time but higher water absorption as compared with those using DP. The formulations using LT showed higher dissolution profiles in buffer stage. **Conclusion:** DICL ODTs could be successfully formulated by wet granulation technique using Eudragit® NE 40D as taste-masking polymer and lactose as diluent.

Key words: Orodispersible tablets, Diclofenac sodium, Eudragit, Diluent, Wet granulation

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Introduction

Orodispersible tablets (ODTs) are defined as an uncoated tablet intended to be placed in the mouth where they disperse rapidly before being swallowed (BP2009). There are many methods used in manufacturing ODTs such as freeze drying, molding, direct compression and wet granulation (Agarwal et al, 2007).

Diclofenac, an nonsteroidal anti-inflamatory drug (NSAID), is the most commonly used NSAID in Europe (Brunton et al, 2008). It is useful for short-term treatment of acute musculoskeletal pain and long-term treatment of rheumatoid arthritis. Diclofenac sodium (DICL) is available in immediate release and modified release dosage forms. DICL appears as a hygroscopic, crystalline powder with intensely bitter taste (Sweetman, 2009).

In order to develop DICL ODT, taste masking of DICL should be achieved before incorporating the taste masked drug into the tablet. Polymethacrylates are used as binders in both aqueous and organic wet-granulation processes. Eudragit® NE is an aqueous dispersion of poly(ethyl acrylate, methyl methacrylate) (2:1) It is used to form water-insoluble film. The neutral Eudragit NE grade does not have functional ionic groups. It swells in aqueous media independently of pH without dissolving.

The objective of this study was to develop DICL ODTs by using wet granulation technique. Eudragit® NE was selected as taste-masking polymer. Lactose anhydrous (LT) or dibasic calcium phosphate (DP) was used as diluent.

Materials and Methods

Materials: Diclofenac sodium (DICL; S. Tong Chemicals, Bangkok, Thailand), Eudragit® NE 40D (Eudragit), croscarmellose sodium (croscarmellose; Ac-Di-Sol®, a gift sample from Rama Production, Bangkok, Thailand), polyvinyl pyrrolidone K30 (PVP), microcrystalline cellulose (MCC; Avicel® PH101), saccharin sodium, dibasic calcium phosphate (DP; Emcompress®), lactose anhydrous (LT), mannitol, talcum, magnesium stearate (K.Science Center & Medical, Khon Kaen, Thailand)

Methods:

Preparation of ODTs

Granules A (taste-masked granules) and *Granules B* (blank granules) (**Table 1**) were prepared separately by using wet granulation technique. Ingredients were weighted and dry mixed with a cube mixer (Erweka AR400, Germany) for 5 min. After addition of binder (Eudragit or 10% PVP aqueous solution), wet mass was screened using sieve no. 16. Wet granules were dried in hot air oven at 60°C for 30 min, and subsequently screened using sieve no. 18. *Granules A* containing 25 mg of DICL were mixed with *Granules B* and croscarmellose for 5 min and then mixed with talcum and magnesium stearate for 3 min. A single punch tabletting machine (Yeo Heng, Bangkok, Thailand) equipped with flat faced punches with a die diameter of 11 mm, was employed to prepare tablets.

Evaluation of ODTs

Weight variation : Ten tablets were weighed individually using an electronic balance (L 420 S, Sartorius AG, Germany) (USP32-NF27). The mean weight was calculated and expressed in mg ± S.D.

Hardness : A hardness tester (VK 200, Agilent, CA) was used to measure the crushing strength of tablets. Ten tablets were analyzed. The mean hardness was calculated and expressed in kilopound (kp ± S.D.).

Friablility : The friability of 20 tablets was determined using a friabilator (Agilent, CA) at 25 r.p.m. for 4 min. The friability is expressed in terms of weight loss and is calculated in percentage (%) of the initial weight.

Disintegration time : The mean disintegration time of six tablets was determined in seconds using the disintegration test apparatus (QC-21, Hanson Research, CA). Deionized water kept at 37°C was used as a medium and the basket was raised and lowered at a constant frequency of 30 cycles/min.

Wetting time and water absorption : A weighed tablet was placed in a petri dish (i.d. 6.5 cm) containing a piece of filtered paper and 6 mL of water at room temperature. After complete wetting was attained, the wetting time was recorded and the wetted ODT was weighed. Water absorption was calculated based on the change in the weight with respect to initial weight of tablet (Schiermeier and Schmidt,2002; Sona and Muthulingam, 2011).

Drug content : A weighed tablet was dissolved in 70 mL of 95% ethanol, sonicated for 30 min and then

adjusted the volume to 100 mL. The DICL content was determined spectrophotometrically at 276 nm (UV-Vis spectrophotometer model UV-1201, Shimadzu, Japan).

Bitterness Evaluation : The bitterness of DICL ODTs was evaluated by authors and co-workers.

In vitro release of DICL : *In vitro* release of DICL ODT was investigated by paddle apparatus (apparatus 2, USP 32) using dissolution tester (VK 7000 Dissolution Apparatus, Agilent, CA). The DICL ODTs were placed in 750 mL of 0.1 N hydrochloric acid (37.0 ± 0.1 $^{\circ}$C). The paddle speed was set at 50 r.p.m. After 2 h, 250 ml of 0.2 M dibasic sodium phosphate was added and the medium was adjusted the pH to 6.8 by 2 N sodium hydroxide within 5 min. At predetermined time intervals, 10-mL medium was withdrawn and replaced with fresh medium. The concentration of DICL was determined spectrophotometrically.

Results and Discussion

Regarding the definition of ODTs, they have to disintegrate all within 3 min (BP2009). Therefore, suitable disintegrant must be chosen to formulate DICL ODTs. Sona and Muthulingam (2011) formulated DICL ODTs by using different disintegrants, croscarmellose and sodium starch glycolate. They reported that formulation using croscarmellose showed shorter disintegration time at same concentration. Croscarmellose was chosen as disintegrant in this study. Because of DICL's bitter taste, Eudragit (Eudragit® NE 40D) was selected as a taste masking agent. It swells in water without dissolving. The amount of Eudragit in taste-masked granules preparation was preliminary studied. It was found that 37.5 mg of Eudragit (containing dry polymer of 15 mg) was suitable for damp mass forming of taste-masked granules (*Granules A* in formulation Rx1 and Rx3). When the higher amount of diluent was added to taste-masked granules (*Granules A* in formulation Rx2 and Rx4), sufficient water was added to form damp mass. In preliminary study, taste-masked granules were mixed with other ingredients in powder form. After tablet performed, many variations such as weight and hardness were found. Blank granules composed of mannitol, saccharin sodium, MCC and croscarmellose were prepared and used instead of powder.

Characteristics of DICL ODTs containing different type and amount of diluent were shown in **Table 1**. Formulation Rx1 and Rx2 showed comparable weight when compared to formulation Rx3 and Rx4, respectively. All formulations were met the criteria of "uniform of weight". They had similar hardness. Almost formulations showed low friability, except formulation Rx4 which contained 50 mg of DP per tablet showed high friability.

Table 1 Composition and characteristics of DICL ODTs formulations.

Ingredients		Formulation			
		Rx1	Rx2	Rx3	Rx4
Granules A	**DICL**	25	25	25	25
	LT	25	50	-	-
	DP	-	-	25	50
	Eudragit (dry)	15	15	15	15
Granules B	**Mannitol**	48			
	Saccharin sodium	1			
	MCC	152			
	Croscarmellose	4			
	PVP	19			
Extra-granule	**Croscarmellose**	5			
	Magnesium stearate	3			
	Talcum	3			
Weight (mg)		304 ± 6	327 ± 3	303 ± 7	328 ± 7
Hardness (kp)		2.9 ± 0.3	3.1 ± 0.2	3.2 ± 0.3	3.0 ± 0.4
Friability (%)		0.87	0.50	0.45	1.34

The wetting time and water absorption of ODTs containing different type and amount of diluent was measured and shown in **Figure 1**. It was found that the formulation using LT showed significantly shorter wetting time but significantly greater water absorption when compared to that using DP ($p<0.05$). It is well known that LT is a water soluble substance which could exhibit hygroscopicity at high relative humidities (Rowe *et al.*, 2009). When LT was used, its hydrophilic surface was easy to wet resulting in short wetting time and high water absorption. In contrast to LT, DP is a water insoluble substance. When it was used, its hydrophobic surface might prevent the tablet from wetting resulting in long wetting time and low water absorption. When the amount of diluent was increased, the wetting time and the water absorption of both diluents were increased with comparable values (9-10 s, 18-20 %, respectively). This may be the effect of tablet weight that increased from 300 to 325 mg.

The disintegration time of ODTs containing different type and amount of diluent was evaluated and shown in **Figure 1**. Surprisingly, changing of diluent from LT to DP had no effect on disintegration time. From previous studies, ODT containing LT can be wet easily and higher amount of water was absorbed. These could be affected to disintegration time. When LT was used, some part of water that wet tablet might be bound with LT. So, this tablet might have to use higher amount of water when compared to tablet containing DP. The time to disintegrate of ODT containing LT might be extended to equivalent time as ODT containing DP. When the amount of diluent was increased, the disintegration time was also increased. This may be the effect of tablet weight that increased.

The bitterness of DICL ODT was evaluated by authors and co-workers. It was revealed that all formulation showed slightly bitterness. ODT with higher amount of diluents showed less bitterness.

Prior to do the release study, the drug content in each formulation has to be measured. It was found that all formulations showed percentage labeled amount of 95-105%. The release-time profiles are shown in **Figure 2**. The formulations using lactose showed higher dissolution profiles in buffer stage. Most of LT may be dissolved and produced pores on granules' surface. However, changing in amount of LT showed no effect on release profile.

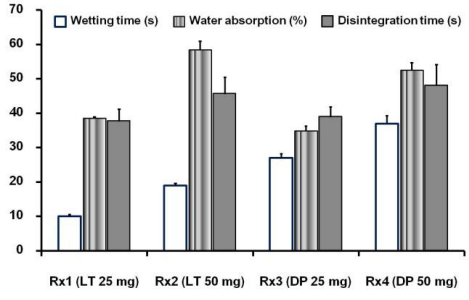

Figure 1 Effects of type and amount of diluent on wetting time, water absorption (n=3) and disintegration time (n=6) of DICL ODTs (mean ± SE).

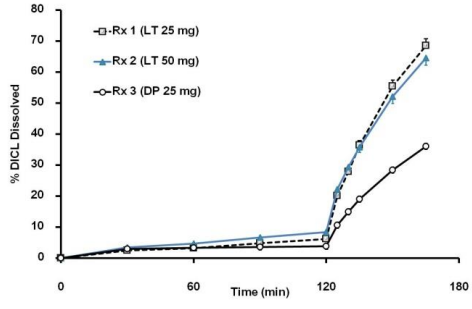

Figure 2 Effects of type of diluent on percentage release-time profile of DICL ODTs (n=6, mean ± SE).

Conclusion

It can be concluded that DICL ODTs could be formulated by wet granulation technique using Eudragit® NE 40D as taste-masking polymer and lactose as diluent.

Acknowledgements

The authors are grateful to Division of Pharmaceutical Technology, Faculty of Pharmaceutical

Sciences, Khon Kaen University (Khon Kaen, Thailand) for its technical facilities.

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