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FORMULATION OF DIRECTLY COMPRESSED PHENYTOIN SODIUM ORALLY DISINTEGRATING TABLETS BY SIMPLEX LATTICE DESIGN USING AVICEL® PH 102 AND ERA-TAB® AS DILUENTS

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Abstract: The orally disintegrating tablets (ODT) consisted of phenytoin sodium (PS), a poorly water-soluble drug, were prepared by direct compression. According to simplex lattice design; the various ratios of the two direct compressible diluents, microcrystalline cellulose (Avicel® PH102) and spray-dried rice starch (Era-Tab®) utilized in the tablet formulations were predetermined. Cross-linked polyvinylpyrrolidone (crospovidone, Polyplasdone® XL) was used as disintegrant. Saccharin sodium, magnesium stearate and talcum were used as sweetening agent, lubricant and glidant, respectively. The prepared tablet formulations provided disintegration times between 4 to 107 seconds. The tablet formulation containing 1:0 Avicel® PH 102:Era-Tab® provided the fastest disintegration times of 4 seconds. From the obtained tablet disintegration times, the equation representing the relationship between disintegration time and the ratio of Avicel® PH 102 to Era-Tab® was constructed. From this equation, the validated formulations containing 0.17:0.33, 0.33:0.67 and 0.67:0.33 Avicel® PH102:Era-Tab® were prepared and tested for tablet disintegration. The tablet formulation yielded the observed and predicted disintegration times of 81, 51, 12 and 75, 51, 16 seconds, respectively. The tablet formulations containing 1:0 and 0.67:0.33 Avicel® PH 102:Era-Tab® which exhibited the fastest disintegration times were tested for tablet dissolution. Their percentages of drug dissolution at the 30th minute time interval were 69% and 87%, respectively. The tablet formulation containing 0.67:0.33 Avicel® PH 102:Era-Tab® met the USFDA disintegration time requirement for ODT and passed the USP criteria for prompt phenytoin sodium dissolution test.

Keywords: Orally disintegrating tablets, phenytoin sodium, simplex lattice design.

บทคัดย่อ: เตรียมยาเม็ดชนิดแตกตัวในปาก (ODT) ที่มีตัวยาเฟนิโทอินโซเดียมซึ่งละลายน้ำยากด้วยวิธีตอกโดยตรง โดยใช้การออกแบบการทดลองแบบ simplex lattice ในการกำหนดอัตราส่วนต่าง ๆ ของสารเพิ่มปริมาณชนิดตอกโดยตรงสองชนิด คือ microcrystalline cellulose (Avicel® PH 102) และ spray-dried rice starch (Era-Tab®) ที่ใช้ในตำรับยาเม็ด ใช้ cross-linked polyvinylpyrrolidone (crospovidone, Polyplasdone® XL) เป็นสารช่วยแตกตัว และใช้ saccharin sodium, magnesium stearate และ talcum เป็นสารแต่งรสหวาน สารหล่อลื่นและสารช่วยไหลตามลำดับ พบว่ายาเม็ดที่เตรียมให้เวลาในการแตกตัวระหว่าง 4 วินาที ถึง 107 วินาที พบว่าตำรับที่ประกอบด้วย Avicel® PH 102 และ Era-Tab® ในอัตราส่วน 1:0 ให้เวลาในการแตกตัวที่เร็วที่สุด คือ 4 วินาที นำผลเวลาการการแตกตัวของยาเม็ดมาสร้างสมการความสัมพันธ์ระหว่างเวลาในการแตกตัวของยาเม็ดกับอัตราส่วนของ Avicel® PH 102 ต่อ Era-Tab® จากสมการที่ได้ทำการเตรียมตำรับยาเม็ดที่ประกอบด้วย Avicel® PH 102 และ Era-Tab® ในอัตราส่วน 0.17:0.33, 0.33:0.67 และ 0.67:0.33 เพื่อยืนยันความถูกต้องของสมการ พบว่าให้เวลาในการแตกตัวจริงและตามการทำนายเท่ากับ 81, 51, 12 และ 75, 51, 16 วินาทีตามลำดับ เลือกตำรับที่ประกอบด้วย Avicel® PH 102 และ Era-Tab® ในอัตราส่วน 1:0 และ 0.67:0.33 ซึ่งให้เวลาในการแตกตัวที่เร็วที่สุดไปศึกษาการละลายของยาเม็ด พบว่าให้ปริมาณยาละลายจากยาเม็ดที่เวลา 30 นาที เท่ากับ 69% และ 87% ตามลำดับ พบว่าตำรับยาเม็ดที่ประกอบด้วย Avicel® PH 102 และ Era-Tab® ในอัตราส่วน 0.67:0.33 เป็นไปตามข้อกำหนดเกี่ยวกับเวลาในการแตกตัวของ USFDA สำหรับ ODT และผ่านการทดสอบเกณฑ์การละลายของเฟนิโทอินโซเดียมแบบปลดปล่อยทันทีตามมาตรฐาน USP

คำสำคัญ ยาเม็ดแตกตัวในปาก เฟนิโทอินโซเดียม การออกแบบการทดลองแบบ simplex lattice

INTRODUCTION

The United States Food and Drug Administration's Guidance for Industry: Orally Disintegrating Tablets (ODT) indicated that ODTs should have an in vitro disintegration time of approximately 30 seconds or less (using United States Pharmacopeia disintegration test or equivalent) and the tablet weight should not exceed 500 mg (U.S. Department of Health and Human Services. Food and Drug Administration, 2008). The ODT are considered as solid oral preparations that disintegrate rapidly in the oral cavity. This mode of administration eliminates the need to chew the tablet, swallow an intact tablet, or take the tablet with liquids; thus providing the benefit to pediatric and geriatric patients, to people with conditions related to impaired swallowing and the patients when compliances may be difficult. Current commercially available ODT technologies can be broadly categorized according to their method of manufacture as follows: lyophilized tablets, compressed tablets and other (including molded tablets, spray-dried powders, and sugar floss) (Hirani *et al*., 2009). This investigation intended to use direct compression to prepare ODT since this tableting method is a commonly practice utilized in the routine tableting process. Phenytoin sodium (PS), as the poorly water-soluble model drug, was incorporated into ODT by using various contents of microcrystalline cellulose (Avicel® PH 102) and spray-dried rice starch (Era-Tab®) as direct compressible diluents. The basis for compressed ODT is the use of super disintegrants, effervescent agents, or high aqueous soluble ingredients or combinations of each. The roles of various superdisintegrants; sodium starch glycolate (SG), crospovidone (CP) and croscarmellose sodium (CS) in preparing ODT consisted of a water-soluble drug, propranolol hydrochloride was previously investigated and a suitable tablet formulation consisted of CP as disintegrant was identified (Dangprasirt, 2015). Therefore, CP was chosen as tablet disintegrant in this study.

A statistical experimental design, simplex lattice design, was applied to study the main effects and interactions of two direct compressible diluents, Avicel® PH 102 and Era-Tab® on ODT disintegration time. Scheffe proposed the simplex lattice experimental design to study effects of the proportions of the components in a mixture on a mixture property (Scheffe, 1963). For pharmaceutical formulations, the simplex lattice method was demonstrated to search for an optimum tablet formula (Bolton S, 1986).

According to the simplex lattice design of 2 variables, an observed response of the three designed experimental trials is related to the levels of the independent variables by the following equation.

$$Y = B_1(X_1) + B_2(X_2) + B_{12}(X_1)(X_2)$$

$X_1 + X_2 = 1.0$

B_1 = the response at $X_1:X_2$ is 1:0

B_2 = the response at $X_1:X_2$ is 0:1

B_{12} = 4 (the response at $X_1:X_2$ is 0.5:0.5)–2(the response at $X_1:X_2$ is 1:0 + the response at $X_1:X_2$ is 0:1)

Where X_1 and X_2 are the ratios of the employed independent variables and Y is the predicted response. In this investigation, the effects of two direct compressible diluents, Avicel® PH 102 and Era-Tab® on disintegration times of the PS tablets prepared by direct compression were studied. The predicted disintegration time equation as function of the ratios of the employed disintegrants was computed. The optimum ratio of Avicel® PH 102 to Era-Tab® providing the ODT of satisfied disintegration time and dissolution rate was searched.

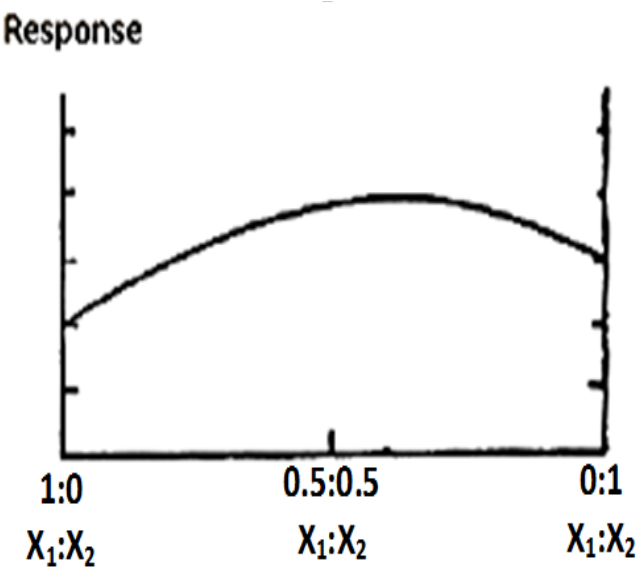

Figure 1. Simplex lattice design of 2 variables; Avicel® PH 102 and Era-Tab® ratios
Note: X_1 (Avicel® PH 102) + X_2 (Era-Tab®) = 1.0 (150 mg)

MATERIALS AND METHODS

Phenytoin sodium was obtained from Sigma Aldrich corporation, USA. Avicel® PH 102 (lot no. P211828634, FMC BioPolymer, USA), and croscarmellose sodium (Ac-Di-Sol®, lot no. TN11822911) were supplied by Onimax Co. Ltd, Thailand. Spray dried rice starch (Era-Tab®) was bought from Erawan Pharmaceutical Research and Laboratory Co, Thailand. Magnesium stearate, talcum and saccharin sodium (Lot No.090623) were purchased from Pharmaceutical Science Ltd., Part., Thailand.

Experimental design

The simplex lattice design as shown in Figure 1 was used to study the effects of two formulation variables, the contents of microcrystalline cellulose (Avicel® PH 102) and spray-dried rice starch (Era-Tab®) on interested ODT properties, tablet disintegration time and friability. By this design, the overall 3 tablet formulations were established having the fix combined content of the two diluents in each tablet formulation. In this manner, the combined content of Avicel® PH 102 and Era-Tab® in each formulation was fixed at the amount of 150 mg per tablet. Figure 1 illustrates the employed simplex lattice design.

Preparation of phenytoin sodium tablets

Three PS tablet formulations, F1 to F3 (Table 1), according to the simplex lattice experimental design (Figure 1) were prepared by direct compression. The drug, direct compressible diluents, disintegrant and saccharin sodium were passed through a 40 mesh sieve while magnesium stearate and talcum were screened through an 80 mesh sieve. Then the tablet ingredients were dry mixed and compressed into tablets of 9 mm in diameter by a single stroke tableting machine (Viuhang Engineering, Thailand) with the hardness between 4 to 6 kg. Three additional extra formulations (F4, F5, and F6) were also prepared.

Table 1. Formulations of the prepared phenytoin sodium tablets

Formulation	F1	F2	F3	F4	F5	F6
X_1:X_2 ratio	1:0	0.50:0.50	0:1	0.17:0.83	0.33:0.67	0.67:0.33
Phenytoin sodium (mg)	50	50	50	50	50	50
Avicel® PH 102 (X_1) (mg)	150	75	0	25	50	100
Era-Tab® (X_2) (mg)	0	75	150	125	100	50
Crospovidone® XL (mg)	12	12	12	12	12	12
Saccharin sodium (mg)	1	1	1	1	1	1
Magnesium stearate (mg)	3	3	3	3	3	3
Talcum (mg)	10	10	10	10	10	10
Total (mg)	226.0	226.0	226.0	226.0	226.0	226.0

Test for tablet properties

Each tablet formulation was tested for hardness, friability, weight variation and disintegration time. Five tablets from each formulation were tested for tablet hardness (Dr.Schleuniger Co., Type THP-4M hardness tester, Switzerland). Tablet friability of each formulation was tested according to USP 37 and NF 32 (The United States Pharmacopeia, 2014) using a Roche friabilator for 4 minutes at the speed of 25 rpm. Tablet weight variation was tested on 20 tablets using an analytical balance (Sartorius, Model A200S analytical balance, Germany) according to BP 2015 on the test for uniformity of weight (The Department of Health, Great Britain, 2008). Disintegration test was performed on 6 tablets per formulation by USP type disintegrator (K.S.L. Engineering Co., Ltd., Thailand) using distilled water (37 ± 2^{o}C) as medium according to USP 37 and NF 32 (The United States Pharmacopeia, 2014).

Dissolution studies

Dissolution studies of the selected PS tablet formulations were also performed according to the USP criteria for the prompt phenytoin sodium dissolution test (The United States Pharmacopeia, 2014) using a type I dissolution apparatus (Pharma Test Co., Model PTWS 1200, Hamburg, Germany). The basket was adjusted to rotate at 50 rpm. Nine hundred milliliters of distilled water was employed as dissolution medium. Six tablets from each formulation were tested for dissolution at 37 ± 0.5^{o}C. Five milliliters of dissolution medium was withdrawn at predetermined time intervals up to 1 hour and assayed for drug content by UV spectrophotometer (Thermo Scientific, Model Evolution 201, U.S.A.) at the wavelength of 238 nm.

RESULTS AND DISCUSSION

Tablet hardness, friability, weight variation and disintegration time of the PS tablets prepared according to the simplex lattice design (F1 to F3) are shown in Table 2. All the prepared tablet formulations met the requirements on tablet friability (The United States Pharmacopeia, 2014) and uniformity of weight (The Department of Health, Great Britain, 2015). The tablet disintegration times of F1, F2 and F3 were 4.67, 30.26 and 107.21 seconds.

The disintegration time of F1 (4.67 seconds) was less than 30 seconds (0.5 minute), which conformed to the definition of ODT (U.S. Department of Health and Human Services. Food and Drug Administration, 2008).

By using the simplex lattice design to study the effects of Avicel® PH 102 and Era-Tab® contents on disintegration time of the PS tablets; the equation representing the relationship between disintegration time in seconds (DT) and the ratios of Avicel® PH 102 (X_1) and Era-Tab® (X_2) utilized in the tablet formulation were calculated as the following.

$DT = 4.67X_1+107.21X_2-102.72X_1X_2$

$X_1+X_2 = 1.00$

From tablet disintegration study (Figure 2), the PS tablet consisted of Era-Tab® as single diluent (F3) provided the slowest disintegration time (107.21 seconds). While the PS tablet contained Avicel® PH 102 (F1) provided the fastest disintegration time (4.67 seconds). However, the disintegration time of 30 seconds was obtained from the PS tablets consisted of 0.5:0.5 Avicel® PH 102:Era-Tab® (F2). Microcrystalline cellulose is regarded as a direct compressible diluent. Tablets of microcrystalline cellulose prepared by direct compression and with no other excipients present are self-disintegrating when put into aqueous media. Levels in excess of 10% w/w may be required to ensure adequate disintegration. Microcrystalline derives in disintegrating activity through a combination of wicking and disruption of the particle bonds due to the presence of water (Moreton, 2008). Decreasing amount of Avicel® PH 102 in F2 resulted in its slower disintegration time.

In order to verify the predicted DT equation, three additional PS tablet formulations consisted of Avicel® PH 102:Era-Tab® in the ratio of 0.17:0.83 (25:125 mg per tablet, F4), 0.33:0.67 (50:100 mg per tablet, F5) and 0.67:0.33 (100:50 mg per tablet, F6) were prepared as the validated formulations. The computed predicted disintegration times of these validated formulations were 75.85, 50.20 and 15.80 seconds, respectively. While their observed disintegration times were 81.19, 50.65 and 11.64 seconds, respectively. This result indicates the validity of the predicted disintegration time equation was quite satisfied since the predicted and observed responses were not much different.

Table 2. Tablet properties of the prepared PS tablets

Formulation	Weight±SD (mg)	Hardness±SD (kg)	Friability (%)	Observed Disintegration time ±SD (seconds)	Predicted Disintegration time (seconds)
F1	226.1±6.70	5.20±0.84	0.30	4.67±0.45	-
F2	222.9±4.63	4.72±0.90	0.54	30.26±5.38	-
F3	229.2±7.27	5.80±1.27	0.55	107.21±40.95	-
F4	228.4±7.29	4.42±0.53	0.95	81.19±14.53	75.28
F5	224.0±4.41	4.40±0.55	0.54	50.65±9.74	50.66
F6	226.1±3.08	4.92±0.80	0.33	11.64±2.81	15.80

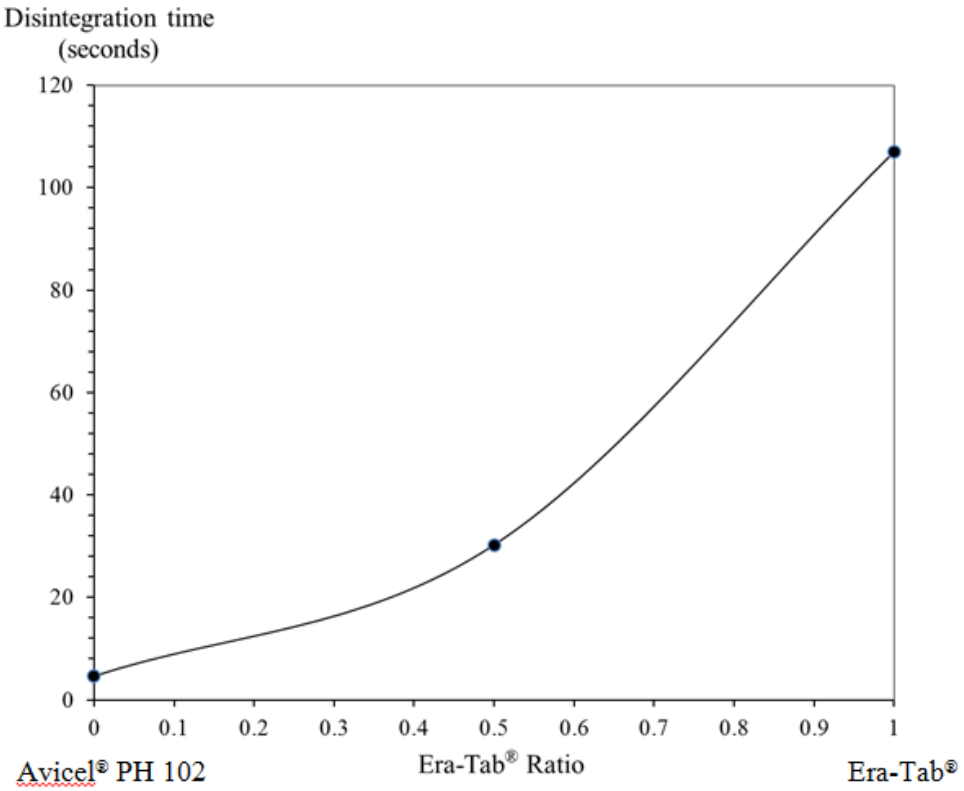

Figure 2. Plot of disintegration time (seconds) as function of two variables, Avicel® PH 102 and Era-Tab® ratios

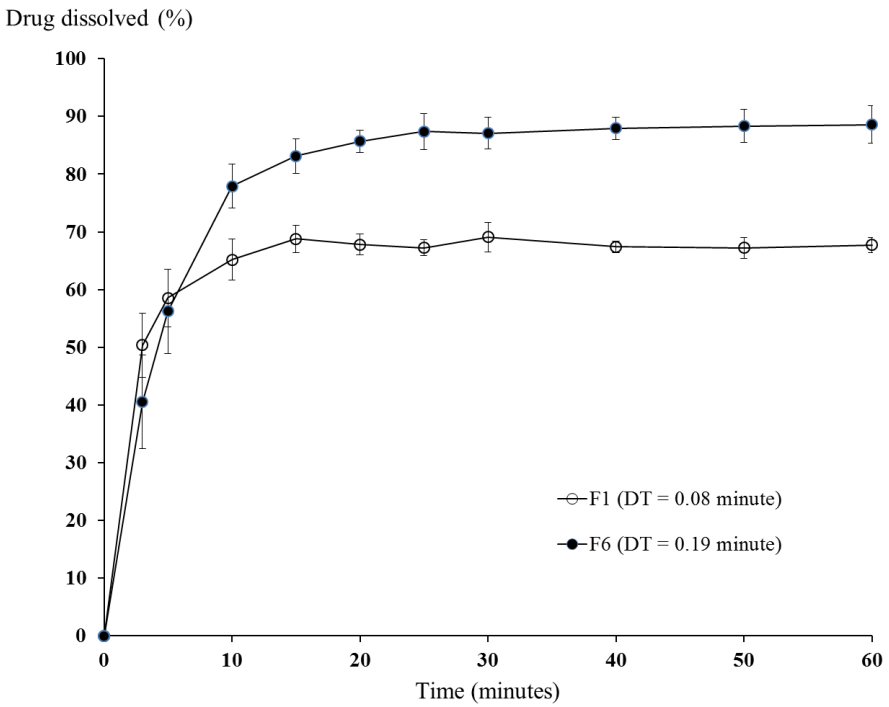

Figure 3. Dissolution profiles of the PS orally disintegrating tablets, F1 and F6.

The two PS tablet formulations providing the required fast disintegration times (<30 seconds) were F1 (4.67 seconds) and F6 (11.64 seconds). These formulations were chosen to

test for tablet dissolution. Their dissolution profiles are shown in Figure 3. Dissolution profile of F6 was faster than that of F1. The USP criteria for the prompt phenytoin sodium dissolution test states that the drug is dissolved not less than 85% at the 30th minute time interval (The United States Pharmacopeia, 2014). The percentages of drug release at the 30th minute time interval (Q_{30}) of F1 and F6 were 69.1% and 87.1%, respectively. Therefore, the dissolution profile of F6 met the requirement for the prompt phenytoin sodium dissolution test (The United States Pharmacopeia, 2014).

From Figure 3, the dissolution profiles of F1 and F6 were different as indicated by the value of the calculated similarity factor (f2) of 39.73 which was lower than 50. F1 provided slower drug dissolution rate than did F6 even though their disintegration times were comparable, 4.67 and 11.64 seconds for F1 and F6, respectively. F1 consisted of microcrystalline cellulose (Avicel® PH 102) as single diluent. Microcrystalline cellulose was water insoluble diluent (Rowe, 2009) and its application as direct compressible diluent in high amount for an insoluble drug might cause dissolution retardation. Incomplete drug dissolution is demonstrated in Figure 3 as only 70% of drug dissolution was obtained. In this situation, there was a portion of the disintegrated drug particles that was completely covered by insoluble microcrystalline cellulose particles remained in the dissolution medium resulting in the incomplete drug dissolution. When the utilized content of Avicel® PH 102 was decreased as in F6 the more complete drug dissolution (90%) was obtained since less drug particles was entrapped within the insoluble Avicel® PH 102 particles.

In this study, the fastest tablet disintegration time was obtained by using the system of 1:0 Avicel® PH 102:Era-Tab® as direct compressible diluents. Increasing ratio of Avicel® PH 102 to Era-Tab® utilized in the PS tablet formulations resulted in faster tablet disintegration time, as shown in Figure 2. However, the poor tablet dissolution was observed when Avicel® PH 102 was used as single diluent (F1). When an optimum content of Era-Tab® was added into the diluent system (0.67:0.33 Avicel® PH 102:Era-Tab®, F6), the increased tablet disintegration time was observed. However, the required fast dissolution profile of almost complete drug dissolution (90% drug dissolved) was obtained from this formulation since less content of Avicel® PH 102 was utilized.

CONCLUSION

The PS orally disintegrating tablets having the required disintegration times of less than 30 seconds were successfully prepared by direct compression using the optimum ratio of two direct compressible diluents, Avicel® PH 102 and Era-Tab®. Increasing Avicel® PH 102:Era-Tab® ratio, utilized in preparing the PS tablets, caused improving in tablet disintegration time. However, tablet dissolution retardation was observed when Avicel® PH 102 was used as single diluent. Therefore, the optimum ratio of Avicel® PH 102:Era-Tab® was an important factor in preparing the ODT consisted of the poorly water-soluble drug, PS, yielding the ODT of required fast disintegration time and satisfied rapid drug dissolution.

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