*Bull. Health Sci. Technol. **2018, 16(1): 39-49**. ISSN 0858-7531*

OPTIMUM CONTENT OF SUPERDISINTEGRANTS FOR PHENYTOIN SODIUM ORALLY DISINTEGRATING TABLETS BY SIMPLEX LATTICE DESIGN

Pienkit Dangprasirt[1*] and Moleephan Dangprasirt[2]

[1,*] Faculty of Pharmacy, Rangsit University, Thailand
[2]Institute of Nuclear Technology, Bangkok, Thailand

*Corresponding author : E-mail : pienkitd@yahoo.com

Abstract: Phenytoin sodium orally disintegrating tablets (ODT) were prepared by direct compression. A statistical experimental design, simplex lattice design, was applied to study the main effects and interactions of the contents of three superdisintegrants, sodium starch glycolate (Explotab®, SG), crospovidone (Polyplasdone® XL, CP) and croscarmellose sodium (Ac-Di-Sol®, CS) on ODT disintegration time in order to identify the optimum contents of the superdisintegrants which provided the fastest disintegration time. According to the simplex lattice design; the predetermined various ratios of SG, CP and CS were used as disintegrants resulting in 7 designed tablet formulations. Microcrystalline cellulose (Avicel® PH 102) and spray-dried lactose were employed as direct compressible diluents. Saccharin sodium, magnesium stearate and talcum were used as sweetener, lubricant and glidant, respectively. All the prepared tablet formulations provided disintegration times between 8 to 105 seconds. The tablet formulations containing 0:1:0 SG:CP:CS provided the fastest disintegration times of 8 seconds and met the USP requirement of not less than 85% drug dissolved at the 30th minute time interval. From the obtained tablet properties, the equations representing the relationships between disintegration time and friability as function of the SG, CP and CS ratios utilized in the tablet formulations were computed using the principle of a mixture design, the simplex lattice. From the predicted equations, the two batches of the validated formulation containing 0:0.9:0.1 SG:CP:CS were prepared and tested for tablet disintegration and dissolution. The predicted disintegration time and friability of the validated formulation were 8 seconds and 0.79%, respectively. While the observed disintegration times of 13 and 16 seconds and the observed friability of 0.86% and 0.74% were obtained from the two batches of the validated formulation. However, the ODT containing 0:0.9:0.1 SG:CP:CS failed to meet the USP dissolution requirement despite its fast disintegration time. Therefore, the optimum ratio of the superdisintegrants utilized in preparing the ODT was 0:1:0 SG:CP:CS. A tablet solubilizing agent, sodium lauryl sulfate, was incorporated into the tablet formulation containing 0:1:0 SG:CP:CS to improve the dissolution of the ODT. Inclusion of SLS resulted in the tablet disintegration time of 11 seconds and increased drug dissolution in the initial dissolution stage.

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

บทคัดย่อ: เตรียมยาเม็ดเฟนิโทอินโซเดียมชนิดแตกตัวในปาก (ODT) ด้วยวิธีตอกโดยตรง โดยใช้การออกแบบการทดลองทางสถิติชนิดsimplex lattice เพื่อศึกษาผลโดยตรงและปฏิกิริยาของ superdisintegrants สามชนิด คือ sodium starch glycolate (Explotab®, SG), crospovidone (Polyplasdone® XL, CP) และ croscarmellose sodium (Ac-Di-Sol®, CS) ที่มีต่อเวลาในการแตกตัวของ ODT เพื่อหาปริมาณที่เหมาะสมของ superdisintegrats ที่ทำให้ได้เวลาในการแตกตัวที่เร็วที่สุด กำหนดอัตราส่วนที่แตกต่างกันของ SG, CP และ CS ที่ใช้เป็นสารช่วยแตกตัวล่วงหน้าตามการออกแบบชนิด simplex lattice เป็นผลให้ได้ตำรับยาเม็ดที่ออกแบบจำนวน 7 ตำรับ ใช้ microcrystalline cellulose (Avicel® PH 102) และ spray-dried lactosel เป็นสารเพิ่มปริมาณชนิดตอกโดยตรง และใช้ saccharin sodium, magnesium stearate และ talcum เป็นสารแต่งรสหวาน สารหล่อลื่น และสารช่วยไหลตามลำดับ ยาเม็ดทุกตำรับให้เวลาในการแตกตัวระหว่าง 8 ถึง 105 วินาที ตำรับที่ประกอบด้วย 0:1:0 SG:CP:CS ให้เวลาในการแตกตัวที่เร็วที่สุด คือ 8 วินาที และเข้าตามข้อกำหนดของ USP ที่ให้ค่าการละลายของยาไม่น้อยกว่า 85% ที่ช่วงเวลา 30 นาที จากคุณสมบัติของยาเม็ดที่ตรวจวัดได้ สร้างสมการที่แสดงความสัมพันธ์ระหว่างเวลาในการแตกตัว และความกร่อนของยาเม็ดกับอัตราส่วนของ SG, CP และ CS ที่ใช้ในตำรับโดยใช้หลักการของ mixture design แบบ simplex lattice จากสมการที่ได้ทำการเตรียมตำรับยาเม็ดที่ประกอบด้วย 0:0.9:0.1 SG:CP:CS จำนวนสองรุ่นการผลิต เพื่อยืนยันความถูกต้องของสมการและนำไปทดสอบการแตกตัวและการละลายของยาเม็ด โดยเวลาในการแตกตัวและค่าความกร่อนที่ทำนายมีค่าเท่ากับ 8 วินาที และ 0.79% ตามลำดับ ในขณะที่ทั้งสองรุ่นการผลิตของตำรับที่ใช้ยืนยันความถูกต้องให้ค่าเวลาในการแตกตัวจริงคือ 13 และ 16 วินาที และให้ค่าความกร่อนจริงคือ 0.86% และ 0.74% อย่างไรก็ตาม ODT ที่ประกอบด้วย 0:0.9:0.1 SG:CP:CS ไม่เข้าตามข้อกำหนดของ USP เกี่ยวกับการละลายถึงแม้จะให้เวลาในการแตกตัวที่เร็ว ดังนั้นอัตราส่วนที่เหมาะสมของ superdisintegrants ที่ใช้ในการเตรียม ODT คือ 0:1:0

SG:CP:CS และเมื่อเติมสารเพิ่มการละลายคือโซเดียมลอริลซัลเฟตลงในตำรับยาเม็ดที่ประกอบด้วย 0:1:0 SG:CP:CS เพื่อเพิ่มการลายของ ODT พบว่ายาเม็ดมีเวลาในการแตกตัวเท่ากับ 11 วินาที และให้ค่าการละลายของยาจากยาเม็ดที่เพิ่มขึ้นในช่วงแรกของการละลาย

คำสำคัญ: ยาเม็ดแตกตัวในปาก เฟนิโทอินโซเดียม การออกแบบการทดลองแบบ simplex lattice

INTRODUCTION

The United States Food and Drug Administration's Guidance for Industry: Orally Disintegrating Tablets (ODT) indicated that ODT 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, Rathod, Vadalla, 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. The basis for compressed ODT is the use of superdisintegrants, 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 was identified (Dangprasirt, 2015). In this study, the roles of the three superdisintegrants in preparing ODT consisted of a poorly water-soluble drug, phenytoin sodium (PS), was investigated.

A statistical experimental design, simplex lattice design, was applied to study the main effects and interactions of these superdisintegrants 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 formulation (Bolton S, 1986). According to the simplex lattice design of 3 variables, an observed response of the seven designed experimental trials is related to the levels of the independent variables by the following equation.

$$Y = B_a(X_1)+B_b(X_2)+B_c(X_3)+B_{ab}(X_1)(X_2)+B_{ac}(X_1)(X_3)+B_{bc}(X_2)(X_3)+B_{abc}(X_1)(X_2)(X_3)$$
$$(X_1) + (X_2) + (X_3) = 1.0$$

Where X_1, X_2 and X_3 are the ratios of the independent variables and Y is the predicted response. In this investigation, the effects of three superdisintegrants: SG, CP and CS, on tablet disintegration time and friability of the PS tablets prepared by direct compression were studied. The predicted equation as functions of the ratios of the employed disintegrants was computed by a multiple linear regression analysis. The optimum ratios of the three superdisintegrants providing the ODT of required tablet disintegration time and friability then were searched.

The aim of the present work is to find the optimum ratio of three superdistegrants, namely: sodium starch glycolate (Explotab®, SG), crospovidone (Polyplasdone® XL, CP) and croscarmellose sodium (Ac-Di-Sol®, CS) that provided the fastest disintegration time of Phenytoin sodium ODT.

MATERIALS AND METHODS

Phenytoin sodium was obtained from Sigma Aldrich corporation. Avicel® PH 102 (lot no. P211828634, FMC BioPolymer, USA), sodium starch glycolate (batch no. ASG/11/241111), crospovidone (Polyplasdone® XL-10EP6, batch no. 20090510, Nanhang Industrial Co. Ltd., China) and croscarmellose sodium (Ac-Di-Sol®, lot no. TN11822911) were supplied by Onimax Co. Ltd, Thailand. Spray dried lactose, sodium lauryl sulfate (Lot No.SEP50), 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 three formulation variables, the contents of sodium starch glycolate (SG), crospovidone (CP), and croscarmellose sodium (CS) on interested ODT properties, tablet disintegration time and friability. By this design, the overall 7 tablet formulations were established having the fix combined content of the 3 disintegrants in each tablet formulation. In this manner, the combined content of SG, CP and CS in each formulation is fixed at the amount of 12 mg per tablet.

Preparation of phenytoin sodium tablets

Seven PS tablet formulations, F1 to F7 (Table 1), according to the simplex lattice experimental design (Figure 1) were used for preparing 100 tablets per formulation by direct compression. The drug, direct compressible diluents, disintegrant(s), 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 tabletting machine (Viuhang Engineering, Thailand) with the hardness between 4 to 6 kg. Three additional extra formulations (F8-1, F8-2, and F2-S) were also prepared.

Test for tablet properties

Each tablet formulation was tested for wetting time, 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 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, 2015). 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).

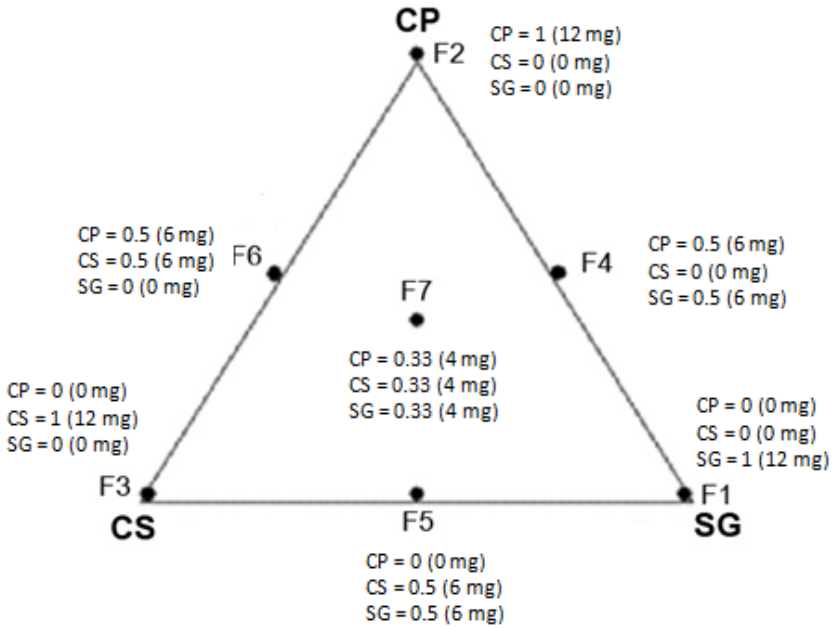

Figure 1. Simplex lattice design of 3 variables; SG, CP and CS ratios.
Note: SG+CP+CS = 1.0 (12.0 mg)

Table 1. Formulations of the prepared phenytoin sodium tablets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8-1	F8-2	F2-S
Phenytoin sodium	50	50	50	50	50	50	50	50	50	50
Avicel® PH 102	50	50	50	50	50	50	50	50	50	50
Sprayed dried lactose	100	100	100	100	100	100	100	100	100	100
Sodium starch glycolate	12	0	0	6	6	0	4	0	0	0
Crospovidone	0	12	0	6	0	6	4	10.8	10.8	12
Croscarmellose sodium	0	0	12	0	6	6	4	1.2	1.2	0
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Talcum	10	10	10	10	10	10	10	10	10	10
Saccharin sodium	1	1	1	1	1	1	1	1	1	1
Sodium lauryl sulfate	0	0	0	0	0	0	0	0	0	1.5

Wetting times

The wetting times of the PS tablets were studied (Battu, Repka, Majumdar, Rao, 2007). Five circular tissue papers were placed in a petri dish of 6.5 cm diameter. Six milliliters of distilled water containing a water-soluble dye was added to the petri dish. The dye solution was used to identify complete wetting of the tablet surface. A tablet was carefully placed on the surface of the tissue paper in the petri dish. The time required for water to reach the upper surface of the tablets and to completely wet then was noted as the wetting time. These measurements were carried out in replicate of five. Wetting time was recorded using a stopwatch.

Dissolution studies

Dissolution studies of the selected PS tablet formulations were also performed according to USP 37 and NF 32 (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°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, wetting time and disintegration time of the PS tablets prepared according to the simplex lattice design (F1-F7) are shown in Table 2. The percentages of tablet friability of the seven formulations varied from 0.58% to 0.91%. 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 were in the range of 8 to 105 seconds. Disintegration times of F2, F6 and F7 were less than 30 seconds, conforming to the definition of ODT (U.S. Department of Health and Human Services. Food and Drug Administration, 2008).

From tablet disintegration study, the PS tablet consisted of CP (F2) provided faster disintegration time (8 seconds) than those consisted of SG (105 seconds, F1) or CS (49 seconds, F3). While the PS tablet containing CS provided faster disintegration time than the PS tablet containing SG. When these three disintegrants were used in the PS tablets as combined disintegrants, the disintegration times in the range of 18 to 47 seconds were obtained. The application of 0.5:0.5 CP:CS (F6, 18 seconds) as combined disintegrants yielded faster disintegration time than those of 0.5:0.5 SG:CP (F4, 43 seconds) and 0.5:0.5 SG:CS (F5, 47 seconds). When SG, CP and CS were employed as combined disintegrants in F7, the disintegration time was 23 seconds.

Table 2. The observed and predicted properties of the PS tablet formulations.

	SG:CP:CS ratio	Hardness ±SD (kg)	Average Weight ±SD (mg)	Wetting time ±SD (minute)	Observed Disintegration Time ±SD seconds (minutes)	Observed Friability (%)	Predicted Disintegration Time (minutes)	Predicted Friability (%)
F1	1:0:0	4.72± 0.33	225.4±2.01	4.15±0.50	105.28±7.13 (1.75±0.12)	0.68	1.75	0.68
F2	0:1:0	4.30±0.23	224.8±2.20	0.21±0.02	8.13±1.21 (0.14±0.02)	0.77	0.14	0.77
F3	0:0:1	4.70±0.23	223.6±1.38	4.28±0.39	49.02±9.38 (0.82±0.11)	0.78	0.82	0.78
F4	0.5:0.5:0	4.90±0.12	225.1±1.89	0.60±0.15	43.72±25.91 (0.73±0.43)	0.58	0.80	0.58
F5	0.5:0:0.5	4.30±0.23	226.1±1.06	4.78±0.06	47..40±3.27 (0.79±0.05)	0.91	0.79	0.91
F6	0:0.5:0.5	4.70±0.27	226.1±1.45	0.86±0.16	18.18±3.23 (0.30±0.05)	0.82	0.30	0.82
F7	0.33:0.33:0.33	4.70±0.32	225.4±1.55	1.45±0.11	22.50±3.84 (0.38±0.10)	0.79	0.41	0.79
F8-1	0:0.9:0.1	4.22± 0.56	221.2±3.27	0.46±0.12	13.10±5.75 (0.26+0.05)	0.86	0.14	0.79
F8-2	0:0.9:0.1	4.30±0.45	231.1±4.32	0.41±0.09	15.70±3.17 (0.22+0.10)	0.74	0.14	0.79
F2-S*	0:1:0	4.82±0.20	227.5±2.30	0.28±0.03	10.55±2.24 (0.18±0.04)	0.78	0.14	0.77

F2-S* = Formulation 2 with sodium lauryl sulfate

The simplex lattice design was used to study the effects of SG, CP, CS contents on disintegration time and friability of the PS tablets. The two equations representing the relationships between disintegration time in minutes (DT) and percentage of tablet friability (F) as function of the ratios of SG (X_1), CP (X_2) and CS (X_3) utilized in the tablet formulation were computed, using the principle of a mixture experimental design, the simplex lattice.

According to the simplex lattice design of 3 variables, an observed response of the seven designed experimental trials is related to the levels of the independent variables by the following equation (Jain, Nirmal, Khar, Bolton, 2013).

$Y = B_1(X_1)+B_2(X_2)+B_3(X_3)+B_{12}(X_1)(X_2)+B_{13}(X_1)(X_3)+B_{23}(X_2)(X_3)+B_{123}(X_1)(X_2)(X_3)$

Whereas

$(X_1) + (X_2) + (X_3) = 1.0$

Where

X_1, X_2 and X_3 are the independent variables and Y is the predicted response.

$B_1 = Y_1$, response at 100%A

$B_2 = Y_2$, response at100%B

$B_3 = Y_3$, response at 100%C

$B_{12}= 4(Y_{12}) – 2(Y_1+Y_2)$ and Y_{12} is the response at 50%A-50%B

$B_{13}= 4(Y_{13}) – 2(Y_1+Y_3)$ and Y_{13} is the response at 50%A-50%C

$B_{23}= 4(Y_{23}) –2 (Y_2+Y_3)$ and Y_{23} is the response at 50%B-50%C

$B_{123}= 27(Y_{123}) – 12(Y_{12}+Y_{13}+Y_{23}) + 3(Y_1+Y_2+Y_3)$

and Y_{123} is the response at 1/3A, 1/3B and 1/3C

The calculated DT and F equations were as the following.

$DT = 1.755X_1+0.136X_2+0.817X_3-0.566X_1X_2-1.983X_1X_3-0.694X_2X_3 -3.612X_1X_2X_3$

$F = 0.680X_1+0.770X_2+0.780X_3 -0.580X_1X_2+0.720X_1X_3+0.180X_2X_3-0.300X_1X_2X_3$

Consideration on the predicted DT equation, the several PS tablet formulations that exhibited the required predicted disintegration times of less than 30 seconds (0.5 minute) could be identified as shown in Table 3. Therefore, an additional PS tablet formulation consisting of SG:CP:CS in the ratio of 0:0.9:0.1 (0:10.8:1.2 mg per tablet), which showed the predicted satisfied tablet disintegration time of 8.13 seconds (0.14 minute) in Table 3, was chosen as a validated formulation. The computed predicted tablet friability (F) of this validated formulation was 0.79% which met the tablet friability requirement of less than1% (The United States Pharmacopeia, 2014). Two batches of the validated tablet formulation, F8-1 and F8-2, having the identical ingredients were prepared as the validated tablet formulations in order to study the reproducibility of the tablet formulation. The observed tablet disintegration times and percentages of friability were found to be 0.26, 0.22 minute and 0.86%, 0.74% for F8-1 and F8-2, respectively. While the predicted tablet disintegration time and friability were 0.14 minute and 0.79%, respectively. This result indicates the validity of the predicted disintegration time and friability equations was quite satisfied even though there was some difference in the predicted and observed responses.

The three PS tablet formulations yielding the required fast disintegration times (<30 seconds) were F2 (8 seconds), F6 (18 seconds) and F7 (23 seconds). Wetting times of F2, F6 and F7 were 13, 52 and 87 seconds (0.21, 0.86 and 1.45 minutes) as listed in Table 2. Therefore, these three formulations provided similar ranking in tablet disintegration times and wetting times. The presence of CP in the tablet formulations caused rapid wetting times as demonstrated in Table 2 for F2, F4, F6 and F7. The absence of CP in F1, F3 and F5 resulted in slow wetting times. Slower wetting times were observed when the ratios of CP in the combined disintegrant system decreased as evident by the wetting times of F2 (0.21 minute), F4 (0.60 minute), F6 (0.86 minute) and F7 (1.45 minutes).

Table 3. The SG:CP:CS ratios in the PS tablet formulations predicted to have the required fast disintegration times.

SG ratio (content)	CP ratio (content)	CS ratio (content)	Predicted Disintegration time (minute)	Predicted Friability (%)
0 (0 mg)	0.9 (10.8 mg)	0.1 (1.2 mg)	0.14	0.79
0.1 (1.2 mg)	0.8 (9.6 mg)	0.1 (1.2 mg)	0.22	0.73
0 (0 mg)	0.7 (8.4 mg)	0.3 (3.6 mg)	0.19	0.81
0.1 (1.2 mg)	0.9 (10.8 mg)	0 (0 mg)	0.25	0.71
0.1 (1.2 mg)	0.7 (8.4 mg)	0.2 (2.4 mg)	0.21	0.76

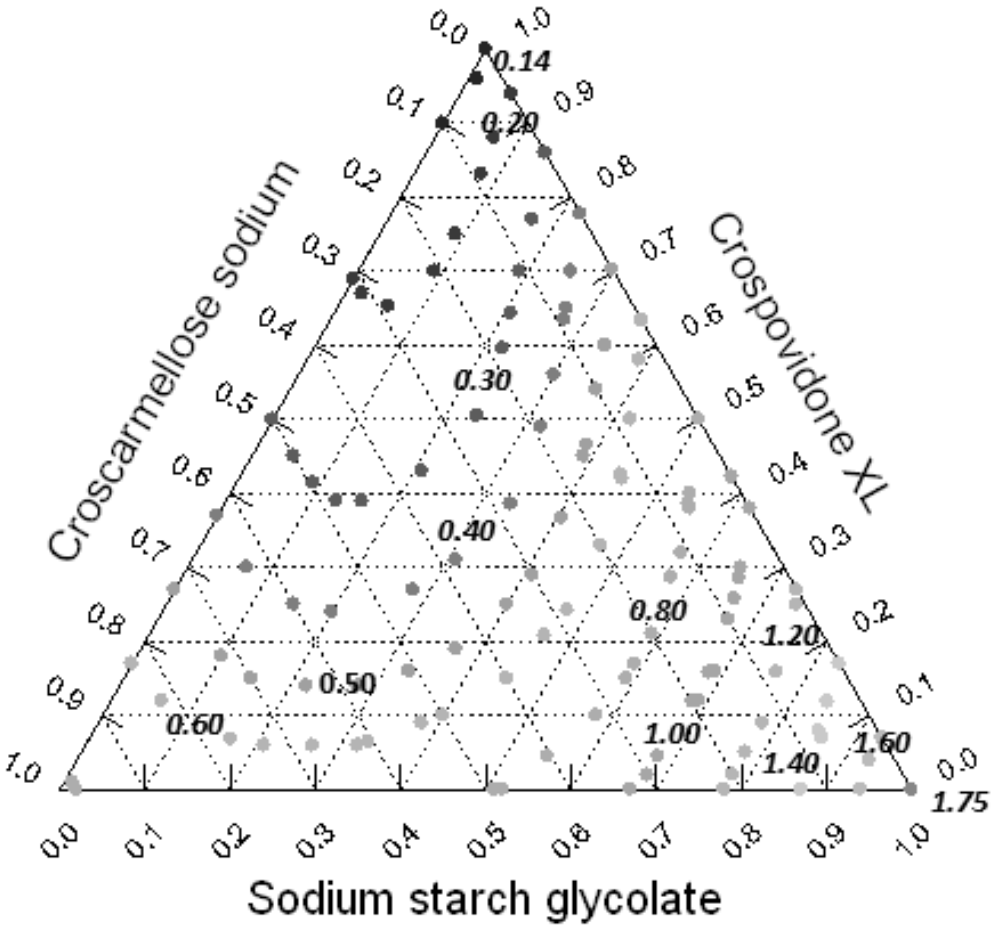

Figure 2. Triangular contour plot of disintegration time (minute) as function of SG:CP:CS ratios.

From the predicted disintegration time equation, the triangular contour plots of tablet disintegration time (Figure 2) as function of the employed ratios of SG, CP and CS was constructed. The presence of the three disintegrants in the PS tablets provided the predicted disintegration times in the wide range as demonstrated in Figure 2. By examining the contour plot, the various ratios of SG:CP:CS resulting in the predicted disintegration times of 0.50 minute or less can be obtained. It is clearly demonstrated in the triangular contour plot that the predicted disintegration time of less than 0.5 minute cannot be obtained by using the SG ratio of approximately more than 0.4 in the combined disintegrant system. The content of CP employed in the combined disintegrant system is the main factor in decreasing tablet disintegration time. The tablet disintegration time decreases as the ratio of CP increases. The usage of SG or CS as single disintegrant provided the tablet disintegration time of more than 0.5 minute. While the application of CP alone yielded the tablet disintegration time of less than 0.5 minute. If CP is not employed, the utilization of SG and CS cannot provide the tablet disintegration time of less than 0.5 minute. However, the required disintegration time (<0.5 minute) can be obtained when SG or CS is omitted and the remained combined disintegrants (CP and SG, CP and CS) are used as shown in Figure 2 and Table 4. For the system of three disintegrants, their optimum ratios are necessary to provide the PS tablets of less than 0.5 minute in disintegrating time, as demonstrated in the triangular contour plot.

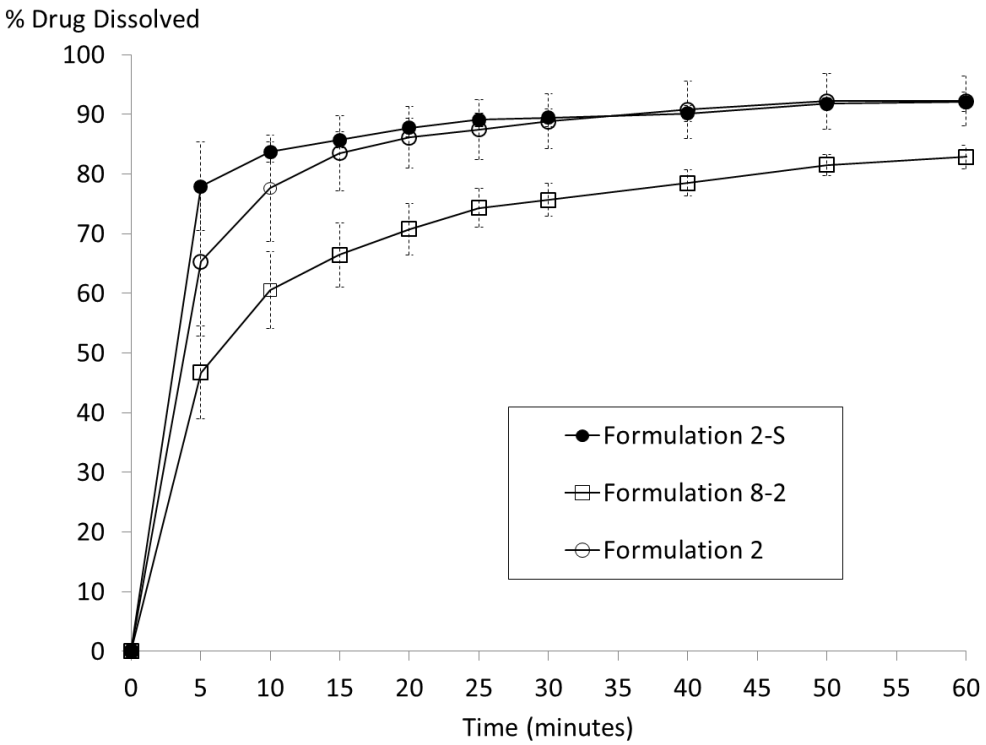

Figure 3. Dissolution profiles of the PS orally disintegrating tablets (F2, F8-2 and F2-S).

Table 4. The predicted SG:CP:CS ratios in the PS tablet formulations resulting in the required disintegration times of less than 0.5 minutes when SG or CS was omitted.

SG ratio (mg)	CP ratio (mg)	CS ratio (mg)	Predicted Disintegration time (minute)	Predicted Friability (%)
0 (0 mg)	0.90 (10.8 mg)	0.10 (1.2 mg)	0.14	0.79
0 (0 mg)	0.80 (9.6 mg)	0.20 (2.4 mg)	0.16	0.80
0 (0 mg)	0.7 (8.4 mg)	0.3 (3.6 mg)	0.19	0.81
0 (0 mg)	0.6 (7.2 mg)	0.4 (4.8 mg)	0.24	0.82
0 (0 mg)	0.5 (6.0 mg)	0.5 (6.0 mg)	0.30	0.82
0 (0 mg)	0.4 (4.8 mg)	0.6 (7.4 mg)	0.34	0.82
0 (0 mg)	0.3 (3.6 mg)	0.7 (8.4 mg)	0.47	0.81
0 (0 mg)	0.25 (3.0 mg)	0.75 (9.0 mg)	0.52*	0.81
0 (0 mg)	0.2 (2.4 mg)	0.8 (9.6 mg)	0.57*	0.81
0.10 (1.2 mg)	0.90 (10.8 mg)	0 (0 mg)	0.25	0.71
0.20 (2.4 mg)	0.80 (9.6 mg)	0 (0 mg)	0.37	0.66
0.3 (3.6 mg)	0.7 (8.4 mg)	0 (0 mg)	0.50*	0.62
0.4 (4.8 mg)	0.6 (7.2 mg)	0 (0 mg)	0.65*	0.69

*unacceptable values

The two PS orally disintegrating tablet formulations exhibiting the fastest disintegration times (F2 and F8-2) were chosen to test for tablet dissolution. Their dissolution profiles are shown in Figure 3. Disintegration times of PS tablets obtained from F2 and F8-2 were 8 and 16 seconds, respectively. Dissolution profile of F2 was faster than that of F8-2. The tolerance of phenytoin sodium tablet dissolution states that the drug is dissolved not less than 85% at the 30^{th} minute time interval (The United States Pharmacopeia, 2014). The percentages of drug release at the 30^{th} minute time interval (Q_{30}) of F2 and F8-2 were found to be 90.6% and 76.9%, respectively. Therefore, the dissolution profile of F2 met the requirement of the PS tablet (The United States Pharmacopeia, 2014).

From Figure 3, F8-2 provided slower drug dissolution rate than did F2 even though the disintegration times of the two PS tablet formulations were comparable, 8 and 16 seconds for F2 and F8-2, respectively. F2 consisted of CP while F8-2 consisted of CP and CS in the ratios of 0.9:0.1. Therefore, the usage of the CP as single disintegrant resulted in faster drug dissolution rate from the PS tablet than that of CP and CS as combined disintegrants. Augsburger et al (Botzolakis, Augsburger, 1988) has shown the mechanism of action of disintegrants such as croscarmellose sodium, crospovidone and corn starch by rapid liquid absorption and swelling of disintegrant particles which fills the void spaces and cause the compact to disintegrate rapidly. CP uses a combination of swelling, wicking and deformation mechanism for rapid disintegration of tablets, swells rapidly in water without forming gel. While CS absorbs water rapidly and swells in water to the extent of 200-300% (Kumar, Nirmala, 2012). However, CP forms a viscous gel layer on contact with water (Moreton, 2008).

Combination of CP and CS disintegration actions might be the reason for the slower drug dissolution rates. Upon swelling of CS, the rate of gel formation was faster than the dissolution rate of the poorly water-soluble drug, phenytoin sodium, causing viscous environment around the drug particles. Slow diffusion of dissolved drug through the viscous environment was responsible for the retardation of drug dissolution. Recent study revealed

that the ODT consisted of a water-soluble drug, propranolol hydrochloride, and an optimum ratio of CP:CS provided faster drug dissolution than that consisted of CP (Dangprasirt, 2015). Propranolol hydrochloride dissolved rapidly prior to the gel formation of CS hence the diffusion of the drug took place rapidly through the expanded pathway causing by swelling action of CS.

The small content (0.75%, 1.5 mg per tablet) of a tablet solubilizing agent, sodium lauryl sulfate (SLS), was incorporated into F2 in order to improve the dissolution of the orally disintegrating tablet of poorly water-soluble drug, phenytoin sodium. This formulation (F2-S) yielded the tablet disintegration time and friability of 11 seconds and 0.78% while those of F2 were 8 seconds and 0.77%, respectively. Therefore the inclusion of 0.75% SLS in F2 did not significantly affect the tablet disintegration time and friability. Dissolution profile of this formulation (F2-S) is shown in Figure 3. It appeared that F2-S provided faster drug dissolution than did F2 for the initial period of drug dissolution. The percentages of drug release at the 5^{th} minute time interval of F2 and F2-S were found to be 65.3% and 77.9% which exhibited a significant difference according to the t-test (α = 0.01). The F2-S formulation also met the dissolution requirement for the PS tablet (The United States Pharmacopeia, 2014). The Q_{30} of F2 and F2-S were 90.6% and 89.4%, respectively.

CONCLUSION

The PS orally disintegrating tablets having the required disintegration times of less than 30 seconds were successfully prepared by direct compression using various ratios of three superdisintegrants; SG, CP and CS. By the simplex lattice design, the equation and triangular contour plot of the disintegration time as function of the contents of the three disintegrants were constructed and the optimum ratios of SG:CP:CS utilized as combined disintegrants in preparing the ODT were identified. High ratio of CP in the combined disintegrant system was necessary in obtaining the ODT. The presence in high ratio of SG in the combined disintegrant system could lead to failure to produce the ODT. The ODT prepared by using CP as single disintegrant met the tablet dissolution requirement. Inclusion of the surfactant, SLS, into this formulation improved drug dissolution in the initial stage.

REFERENCES

Battu SK, Repka MA, Majumdar S, Rao MY. 2007. Formulation and evaluation of rapidly disintegrating fenoverine tablets: Effect of superdisintegrants. *Drug Dev. Ind. Pharm.* 33:1225–1232.

Bolton S. 1986. Statistical applications in the pharmaceutical sciences. In: Lachman L, Liberman HA, Kanig JL editors. *The theory and practice of industrial pharmacy.* 3rd ed. Philadelphia: Lea&Febiger; pp. 283-285.

Botzolakis JE, Augsburger LL. 1988. Disintegrating agents in hard gelatin capsules. Part I: Mechanism of action, *Drug Dev. Ind. Pharm*. 14(1):29-41.

Dangprasirt P. 2015. Formulation of propranolol hydrochloride orally disintegrating tablets by direct compression using simplex lattice design. *Bul. Health. Sci. Tech.* 13(2): 39-46.

Hirani JJ, Rathod DA, Vadalla KR. 2009. Orally Disintegrating Tables: A Review. *Trop. J. Pharm. Res.* 8(2): 161-172.

Jain N, Nirmal J, Khar RK, Bolton S. 2013. Pharmaceutical statistic and optimization. In: Khar RK, Vyas SP, Ahmand F, Jain GK, editors. *The theory and practice of industrial pharmacy.* 4th ed. Hyderabad: CRS Publisher & Distributors; pp. 357-361.

Kumar GP, Nirmala. R. 2012. Fundamental aspects of superdisintegrants: a concise review. *Journal of Global Pharma Technology.* 4(02): 1-12.

Moreton RC. Disintegrants in Tableting. In: Ausburger LL, Hoag SW, editors. *Pharmaceutical dosage forms: tablets.* 3rd ed. New York: Informa Healthcare; pp 243.

Scheffe H. 1963. Simplex-centroid design for experiments with mixtures. *J. R. Stat. Soc. B.* 25: 235-263.

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 32. Volume 1.1. Volume 1.3 Volume 3.2*. Rockville: The United States Pharmacopeial Convention.

U.S. Department of Health and Human Services. Food and Drug Administration. 2008. *Guidance for Industry: Orally Disintegrating Tablets*. Rockville: Center for Drug Evaluation and Research.