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TASTE MASKING OF DIRECTLY COMPRESSED PHENYTOIN SODIUM ORALLY DISINTEGRATING TABLETS BY SOLID DISPERSION TECHNIQUE

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Abstract: Phenytoin sodium (PS) orally disintegrating tablets were prepared by direct compression using various contents of spray-dried lactose and microcrystalline cellulose (Avicel® PH 102) as direct compressible diluents. Crospovidone (Polyplasdone® XL), magnesium stearate and talcum were used as disintegrant, lubricant and glidant, respectively. Mannitol or sorbitol and saccharin sodium were also utilized as sweetening agents to mask the bitter taste of PS. The orally disintegrating tablet formulation that provided the fastest disintegration time and provided the satisfied drug dissolution was selected as the optimum formulation. A solid dispersion technique, coprecipitation method, was applied as an attempt to mask the bitter taste of PS from the optimum orally disintegrating tablet formulation using mannitol or sorbitol as carrier. The orally disintegrating tablets prepared by PS-sorbitol and PS-mannitol solid dispersions provided better taste than those prepared by PS-sorbitol and PS-mannitol physical mixtures. However, the dissolution of orally disintegrating tablet prepared by PS-sorbitol solid dispersion was slower than that of the orally disintegrating tablet prepared by PS-sorbitol physical mixture and did not meet the USP requirement of not less than 85% drug dissolved at the 30th minute time interval. The orally disintegrating tablets prepared by PS-mannitol solid dispersion and physical mixture exhibited comparable satisfied disintegration times of 0.13 and 0.20 minutes, respectively. Their dissolution profiles were also similar and met the USP requirement. Inclusion of menthol in the orally disintegrating tablet consisted of PS-mannitol solid dispersion improved the tablet taste due to the additional cooling sensation. The drug dissolution from this orally disintegrating tablet formulation met the USP requirement. However, the reduction in tablet dissolution rate was observed in the initial period of drug dissolution.

Keywords: Orally disintegrating tablets, phenytoin sodium, solid dispersion.

บทคัดย่อ : เตรียมยาเม็ดเฟนิโทอินโซเดียม (PS) ชนิดแตกตัวในปากด้วยวิธีตอกโดยตรง โดยใช้ spray-dried lactose และ microcrystalline cellulose (Avicel® PH 102) ในปริมาณต่าง ๆ เป็นสารเพิ่มปริมาณชนิดตอกโดยตรง และใช้ cross-linked polyvinylpyrrolidone (crospovidone, Polyplasdone® XL), magnesium stearate และ talcum เป็นสารช่วยแตกตัว สารหล่อลื่นและสารช่วยไหลตามลำดับ นอกจากนั้นใช้ mannitol หรือ sorbitol และ saccharin sodium เป็นสารแต่งรสหวานเพื่อกลบรสขมของ PS จากนั้นเลือกตำรับยาเม็ดชนิดแตกตัวในปากที่ให้เวลาในการแตกตัวที่เร็วที่สุด และให้การละลายของยาที่น่าพอใจเป็นตำรับที่เหมาะสม ทำการกลบรสขมของยาจากตำรับที่เหมาะสมที่คัดเลือกโดยเทคนิคโซลิดดิสเพอร์ชันด้วยวิธีการตกตะกอนร่วมโดยใช้ mannitol หรือ sorbitol เป็นตัวพา ยาเม็ดชนิดแตกตัวในปากที่เตรียมจากโซลิดดิสเพอร์ชันของ PS-sorbitol และ PS-mannitol มีรสชาติที่ดีกว่ายาเม็ดชนิดแตกตัวในปากที่เตรียมจากสารผสมทางกายภาพของ PS-sorbitol และ PS-mannitol อย่างไรก็ตามพบว่าการละลายของยาจากยาเม็ดชนิดแตกตัวในปากที่เตรียมจากโซลิดดิสเพอร์ชันของ PS-sorbitol ช้ากว่าที่ได้จากยาจากยาเม็ดชนิดแตกตัวในปากที่เตรียมจากสารผสมทางกายภาพของ PS-sorbitol และไม่เข้าตามข้อกำหนดของ USP ที่ให้ยาละลายออกมาไม่น้อยกว่า 85% ที่ช่วงเวลา 30 นาที ในขณะที่ยาเม็ดชนิดแตกตัวในปากที่เตรียมจากโซลิดดิสเพอร์ชันและสารผสมทางกายภาพของ PS-mannitol ให้เวลาในการแตกตัวที่เป็นที่น่าพึงพอใจที่ใกล้เคียงกันคือ 0.13 และ 0.20 นาทีตามลำดับ และให้ลักษณะการละลายของยาที่คล้ายคลึงกันและเข้าตามข้อกำหนดของ USP การเติม menthol ลงในยาเม็ดชนิดแตกตัวในปากที่เตรียมจากโซลิดดิสเพอร์ชันของ PS-mannitol เพิ่มรสชาติของยาเม็ดเนื่องจากก่อให้เกิดรสเย็น และให้การละลายของยาเข้าตามข้อกำหนดของ USP แต่สังเกตพบอัตราการละลายของยาที่ลดลงในช่วงแรกของการละลาย

คำสำคัญ : ยาเม็ดแตกตัวในปาก เฟนิโทอินโซเดียม โซลิดดิสเพอร์ชัน

INTRODUCTION

Orally disintegrating tablets (ODT) are solid single-dosage forms that are designed to be placed in the mouth, allowed to disperse or dissolve in the saliva, and then swallowed without the aid of additional water. For a tablet to be classified as ODT the disintegration time should be sufficient rapid for the patient to not feel the need or compulsion to chew (Halm, 2008). By the definition given by The United States Food and Drug Administration's Guidance for Industry: Orally Disintegrating Tablets, the 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). By disintegrating rapidly in the oral cavity, this dosage form 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. However, the challenge in developing this dosage form consisted of the drug of unpleasant taste is how to mask the taste of the drug in order to improve the patient compliance. Solid dispersion technique has been investigated to mask the bitter taste of drotoverine ODT by using mannitol as carrier (Anusha *et al*., 2013),

The ODT can be prepared as lyophilized tablets, compressed tablets and other (including molded tablets, spray-dried powders, and sugar floss) (Hirani *et al*., 2009). However, the compressed ODT prepared by direct compression method is attractive since this method is a routinely practice in tableting process. The commonly utilized superdisintegrants applied in preparation of ODT are sodium starch glycolate, crospovidone and croscarmellose sodium. Among these disintegrants, crospovidone has been investigated as the best one for preparing ODT tablet consisted of a water-soluble drug propranolol hydrochloride by direct compression using spray-dried lactose and microcrystalline cellulose (Avicel® PH 102) as direct compressible diluents (Dangprasirt, 2015). In this study a water-insoluble drug, phenytoin sodium, was formulated into ODT by direct compression using crospovidone as the tablet disintegrant. Spray-dried lactose and Avicel® PH 102 were employed as direct compressible diluents and their effects on tablet disintegration and dissolution were investigated in order to search for an optimum ODT. Since phenytoin sodium has unpleasant bitter taste; therefore the solid dispersion of the drug in the water-soluble carriers of sweet taste, sorbitol and mannitol, was applied to mask the bitter taste of the drug in the chosen optimum ODT formulation. The aim of the present paper is dealt with the application of solid dispersion technique to improve the taste of phenytoin sodium ODT. Two carriers, mannitol and sorbitol, were used to prepare solid dispersion by coprecipitation method.

MATERIALS AND METHODS

Phenytoin sodium was obtained from Sigma Aldrich corporation, USA. Spray-dried lactose, Avicel® PH 102, FMC BioPolymer, USA) and crospovidone (Polyplasdone® XL-10EP6, Nanhang Industrial Co. Ltd., China) were supplied by Onimax Co. Ltd, Thailand. Lactose, mannitol, sorbitol, magnesium stearate, talcum, silicon dioxide (Aerosil®), saccharin sodium and menthol were purchased from Pharmaceutical Science Ltd., Part., Thailand.

Preparation of phenytoin sodium solid dispersions

The solid dispersions of phenytoin sodium (PS) in the water-soluble carriers exhibiting sweet taste, sorbitol and mannitol, were prepared by coprecipitation method. The ratio of 1:0.5 PS:sorbitol or 1:0.5 PS: mannitol were utilized. Saccharin sodium was also incorporated into the solid dispersion systems in order to provide the sweetness to the

systems. Phenytoin sodium was dissolved in absolute ethanol while sorbitol or mannitol and saccharin sodium were dissolved in the small amount of distilled water. The aqueous solution of sorbitol or mannitol and saccharin was added into the ethanolic phenytoin sodium solution. The solution was mixed thoroughly and allowed to evaporate. The obtained coprecipitate was stored in an incubator at 40^{o} C for 48 hours to eliminate the remaining solvent. The dry coprecipitate was then pulverized and screened through a 40 mesh sieve.

Preparation of phenytoin sodium tablets

PS tablet formulations, F1 to F11 (Table 1), were used for preparing 100 tablets per formulation by direct compression. The drug and carriers (sorbitol and mannitol), PS solid dispersion powder, direct compressible diluents, crospovidone, lactose, saccharin sodium and menthol were passed through a 40 mesh sieve while magnesium stearate, talcum and Aerosil® 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 2 to 5 kg.

Test for tablet properties

Each tablet formulation was tested for hardness, friability, weight variation and disintegration time. Six 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, 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).

Table 1. Formulations of the prepared phenytoin sodium tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Phenytoin sodium	50	50	50	50	50	50	-	50	50	-	-
1:0.5 PS:sorbitol SD	-	-	-	-	-	-	75	-	-	-	-
1:0.5 PS:mannitol SD	-	-	-	-	-	-	-	-	-	75	75
Lactose	25	25	25	-	-	-	-	-	-	-	-
Sorbitol	25	25	25	25	25	25	-	25	-	-	-
Mannitol	-	-	-	-	-	-	-	-	25	-	-
Avicel® PH 102	100	100	150	150	150	150	150	125	150	150	150
Sprayed dried lactose	50	50	50	50	50	50	50	75	50	50	50
Crospovidone	15	15	15	20.6	27.5	20.6	20.6	20.6	20.6	20.6	20.6
Magnesium stearate	3.8	3.8	4.5	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1
Talcum	12.5	12.5	15	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8
Aerosil®	-	0.5	1.5	1.4	2.8	1.4	1.4	1.4	1.4	1.4	1.4
Saccharin sodium	1.3	1.3	1.3	1.3	1.4	1.4	1.4*	1.4	1.4	1.4*	1.4*
Menthol	-	-	-	-	-	-	-	-	-	-	1.1

*Add into the solid dispersion system

Evaluation of taste masking

Five volunteers performed taste masking by placing the ODT tablets in their mouths for 10 seconds and bitterness recorded against pure drug using a numerical scale. The bitterness levels were recorded from the scale of 1 to 5.

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^{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

The results obtained from the tablet hardness, friability, uniformity of weight, disintegration time and dissolution tests of the prepared phenytoin sodium orally disintegrating tablets are shown in Table 2. In order to mask the bitter taste of PS, the water-soluble carrier possessing the sweet taste, sorbitol, was selected to prepare the PS solid dispersion by coprecipitation method. However, sorbitol was hygroscopic substance and the use of sorbitol as single carrier might result in hygroscopic mass of solid dispersion and hence resulting in tableting problem. The usage of sorbitol and a nonhygrocopic diluent, lactose, as combined-carriers in preparing the 1:0.5:0.5 PS:sorbitol:lactose solid dispersion was considered. The tablet containing the physical mixture of PS, sorbitol and lactose was prepared according to F1. However, the tableting process was unsuccessful due to poor flowability of the powder during the tableting process. Inclusion of a glidant, Aerosil®, as indicating in F2 was found to solve the problem but the percentage of tablet friability of this formulation was 1.33% (Table 2) which did not meet the USP requirement of 1% (The United States Pharmacopeia, 2014).

In order to improve the tablet friability, the ratio of Avicel® PH 102:spray-dried lactose was changed from 2:1 (F2) to 3:1 (F3) since Avicel® PH 102 provided more compressibility to the tablet than did the spray-dried lactose (Carlin Brain, 2008). F3 provided the PS tablet of required physical properties and met the requirements for tablet friability (The United States Pharmacopeia, 2014) and uniformity of weight (The Department of Health, Great Britain, 2015). Disintegration time of this formulation was 1.93 minute (116 seconds). The 1:0.5:0.5 PS:sorbitol:lactose solid dispersion was prepared in order to incorporate into tablet using F3 as its physical mixture tablet formulation. However, the prepared solid dispersion was found to be yellow solid mass indication the occurrence of incompatibility between the solid dispersion compositions. Lactose was omitted and the 1:0.5 PS:solrbitol solid dispersion was prepared successfully without color change.

The physical mixture tablet containing 1:0.5 PS:sorbitol, F4, was developed by omitting lactose and increasing the content of the disintegrant, crospovidone (Polyplasdone® XL) from 5% (15 mg) to 7.5% (20.6 mg), in order to improve the tablet disintegration time. F4 was successfully prepared without tableting problem. F4 provided the percentage of tablet friability of 0.17% and the disintegration time of less than 0.5 minute (0.39 ± 0.14 minute) which met the requirement of ODT (U.S. Department of Health and Human Services. Food and Drug Administration, 2008).

Table 2. The properties of the prepared PS tablet formulations

	Drug and carrier(s)	Preparation method	Hardness (mean±SD) (kg)	Weight (mean±SD) (mg)	Friability (%)	Disintegration Time minute±S.D. (seconds±SD)	Q_{30} (mean±SD) (%)
F1*	1:0.5:0.5 PS:lactose:sorbitol	Physical mixture	-	-	-	-	-
F2**	1:0.5:0.5 PS:lactose:sorbitol	Physical mixture	-	-	1.33	-	-
F3***	1:0.5:0.5 PS:lactose:sorbitol	Physical mixture	4.5±0.80	333.2±5.73	0.30	1.94±1.07 (116.3+64.0)	-
F4***	1:0.5 PS:sorbitol	Physical mixture	3.95±0.39	319.3±4.03	0.17	0.39±0.14 (23.7+8.36)	-
F5***	1:0.5 PS:sorbitol	Physical mixture	2.17±0.41	322.8±6.36	1.53	0.37±0.04 (22.4±2.3)	-
F6	1:0.5 PS:sorbitol	Physical mixture	2.20±0.57	319.5±6.92	0.11	0.16±0.03 (9.7±1.9)	86.45±1.33
F7	1:0.5 PS:sorbitol	Solid dispersion	3.30±0.46	318.3±3.79	0.04	0.14±0.01 (8.2±0.6)	78.61±7.14
F8	1:0.5 PS:sorbitol	Physical mixture	3.00±0.18	319.5±6.87	0.12	0.16±0.02 (9.7±1.5)	80.36±1.77
F9	1:0.5 PS:mannitol	Physical mixture	3.10±0.26	314.2±5.84	0.42	0.13±0.01 (7.7+0.6)	89.49±0.68
F10	1:0.5 PS:mannitol	Solid dispersion	3.20±0.46	319.5±5.08	0.40	0.15±0.02 (9.2±1.0)	87.20±1.36
F11	1:0.5 PS:mannitol (menthol)	Solid dispersion	3.00±0.30	320.4±5.27	0.21	0.20±0.01 (11.8±0.7)	86.54±1.32

*Fail for tableting.
**Unsatisfied tablet friability, no further tests on tablet properties were performed due to low tableting yield.
***Not being tested for dissolution due to unsatisfied tablet friability or disintegration.

In an attempt to obtain further improvement in disintegration time, F5 was formulated by increasing the amounts of crospovidone from 7.5% (20.6 mg) to 10% (27.5 mg). Aerosil® and saccharin sodium were also increased from 0.5% to 1.0% and 0.45% to 0.50% in order to provide better flowability and additional sweetness to the ODT. The disintegration time of F5 was 0.37±0.04 minute which was similar to F4 (0.39±0.14 minute) while the high percentage of tablet friability of 1.53% was observed. Therefore, F5 was not the satisfied tablet formulation and F4 was recognized as the suitable formulation. F4 provided the tablet hardness of 3.95 kg and the percentage of tablet friability was 0.17%. Although the mean disintegration time of F4 (0.39 minute±0.14 minute) was less than 0.50 minute but the high value of the standard deviation was observed. To improve the tablet disintegration time of F4, this formulation was prepared by reducing the tablet hardness to 2-3 kg (2.20±0.57 kg) and increasing saccharin sodium from 0.45% to 0.50% as represented by F6. F6 provided the percentage of tablet friability of 0.11% and the disintegration time of 0.16±0.03 minute which was faster than that of F4. Therefore, F6 was chosen as the optimum formulation of ODT.

As sugar alcohol, sorbitol was used as water-soluble carrier in preparing PS solid dispersion to mask the bitter taste of PS. Saccharin sodium was also incorporated into the solid dispersion to provide sweetness to the 1:0.5 PS:sorbitol solid dispersion. The low content of the carrier was employed in order to avoid overfilling of the 9 mm diameter die utilized in the tableting process. The prepared PS solid dispersion was formulated as ODT tablet (F7) by using F6 as its physical mixture formulation thus the 1:0.5 PS:sorbitol solid dispersion was used instead of the 1:0.5 PS:sorbitol physical mixture. Better taste was recognized for the ODT prepared from the 1:0.5 PS:sorbitol solid dispersion.

The ODT tablets consisted of 1:0.5 PS:sorbitol physical mixture (F6) and solid dispersion (F7) were compared for their physical properties, disintegration times and dissolution. Similar disintegration time was obtained from F7 (0.14±0.01 minute) and F6

(0.16±0.03 minute). Dissolution profiles of F6 and F7 are illustrated in Figure 1. The slower dissolution profile was observed from F7 and the drug dissolution did not meet the USP requirement for prompt release PS dissolution that stated that the percentage of drug dissolved at the 30th minute time interval (Q_{30}) must equal or exceed 85% (The United States Pharmacopeia, 2014). The Q_{30} of the prepared ODT tablets are presented in Table 2. The Q_{30} of F6 and F7 were 86% and 78%, respectively. Therefore, the application of sorbitol as carrier in preparing PS solid dispersion improved the taste of the ODT tablet. However, the reduction in drug dissolution was observed. This dissolution retardation might due to more viscous environment resulting from dissolving of sorbitol around the poorly water-soluble drug, PS, in the solid dispersion system which caused slow diffusion of the drug in the initial period. In order to improve the tablet dissolution, the ratio of Avicel® PH 102 to spray-dried lactose in the 1:0.5 PS:sorbitol physical mixture was reduced from 3:1 (150 mg: 50 mg) to 5:3 (125 mg:75 mg) in F8 since high content of the insoluble direct compressible diluent, Avicel® PH 102 might retard drug dissolution. F8 provided disintegration time of 0.16±0.02 minute while the percentage of tablet friability was 0.12%. Comparing to F6, the slightly improvement of dissolution profile was observed from F8 in the initial period. F8 provided Q_{30} of 80% which was less than 85%, therefore the incorporation of the 1:0.5 PS:sorbitol solid dispersion into this formulation was not performed.

Unlike sorbitol which exhibits hygroscopic property, mannitol has been reported as non-hygroscopic (Rowe *et al.*, 2009). Therefore, mannitol was utilized in preparing the 1:0.5 PS:mannitol solid dispersion. Saccharin sodium was also incorporated into the solid dispersion to provide more sweetness to the 1:0.5 PS:mannitol solid dispersion. The tablets containing the 1:0.5 PS:mannitol physical mixture (F9) and solid dispersion (F10) instead of the 1:0.5 PS:sorbitol physical mixture and solid dispersion were prepared and compared for their physical properties and disintegration times.

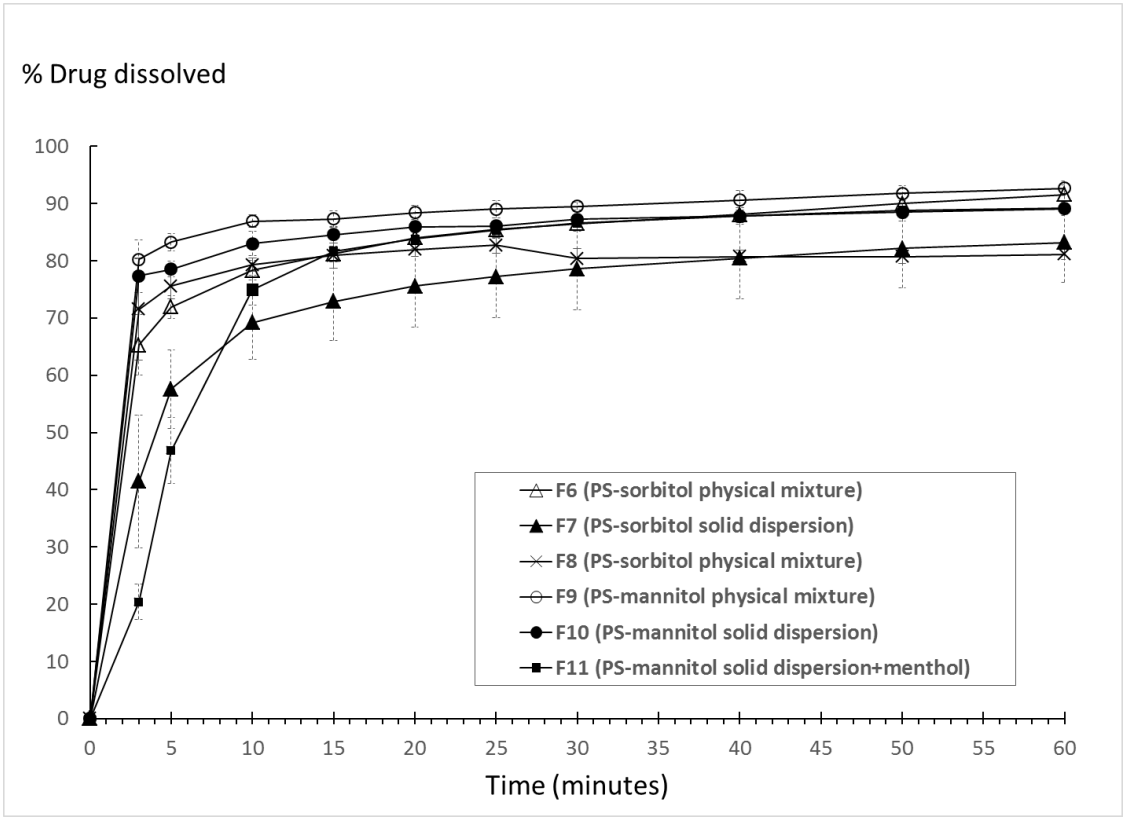

Figure 1. Dissolution profiles of the prepared ODT

F9 and F10 provided the tablets of satisfied physical properties as shown in Table 2. The tablet disintegration times were 0.13±0.01 and 0.15±0.02 minutes for F9 and F10, respectively. Dissolution profile of F9 was slightly faster than that of F10. F9 and F10 yielded the comparable Q_{30} of 89% and 87%, respectively. However, the better taste was recognized in F10. Menthol was added to F10 resulting in F11 as a mean to provide cooling sensation to the ODT during disintegration in the oral cavity. But the decreased tablet dissolution was observed in the initial period of dissolution profile as shown in Figure 1. Disintegration times of F10 (0.15±0.02 minute) and F11 (0.20±0.01 minute) were comparable. Comparing to F10, F11 yielded the better taste due to the presence of menthol which gave a cooling effect in the mouth due to its interaction with the mouth's coldness receptor (Rowe *et al*., 2009). F11 also provided the Q_{30} of 86% which met the USP requirement for the prompt PS dissolution test. In the ideal situation the faster onset of PS dissolution was required in order to obtain the fast absorption of the drug since PS was classified as Class 2 in BCS system (WHO Technical Report Series, No 937, 2006) thus the drug absorption depended on dissolution rate. Therefore, F10 was the optimum formulation of phenytoin sodium orally disintegrating tablet if only the therapeutic aspect was considered. However, in commercial point of view when the taste of the ODT was the main consideration, F11 was the suitable ODT formulation although its initial dissolution rate was slower than that of F10. However, the drug dissolution from F11 was proven to meet the USP dissolution requirement.

CONCLUSION

The PS orally disintegrating tablets consisted of sorbitol or mannitol as sweetening agent having the required disintegration times of less than 0.5 minutes and satisfied dissolution profiles were successfully prepared by direct compression using the optimum ratio of Avicel® PH 102:spray-dried lactose. The formulation provided the fast disintegration time and required drug dissolution was chosen to prepare the ODT by using the PS-sorbitol or PS-mannitol solid dispersion powder in order to mask the bitter taste of the drug. The solid dispersion ODT provided better taste than those of the physical mixture ODT. The ODT consisted of PS-mannitol solid dispersion was found to be the optimum formulation regarding to its fast disintegration time and drug dissolution. Inclusion of menthol into the PS-mannitol solid dispersion ODT caused more improvement in the taste of the tablet.

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