Research Article

Preparation and Characterization of phenytoin Sodium-Controlled Release Solid Dosage Forms

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ABSTRACT

This research aimed to prepare and characterize phenytoin sodium-controlled release solid dosage forms. Phenytoin sodium and hydroxypropyl methylcellulose (HPMC) were mixed at the ratio of 1:0 - 1:3 using physical mixing (PM) and solid dispersion (SD) methods. Compared with the Fourier transform infrared (FTIR) spectrum of phenytoin sodium and HPMC, the spectrum of the obtained mixture using the PM method demonstrated that there were no significant interactions between phenytoin and HPMC. However, the presence of interactions between phenytoin sodium and HPMC was detected when using the SD method. Disintegration time (DT) of all prepared capsules using various ratios of HPMC was less than 15 min. For the *in vitro* release of capsules, phenytoin released from phenytoin incorporated with HPMC was more than that from non-incorporated phenytoin. Phenytoin released from the formulated capsule with HPMC was increased with increasing of the amount of HPMC. Two pre-formulations (phenytoin sodium and HPMC= 1:2 and 1:3) were used to formulate tablets. Both tablet formulations met the requirement criteria for thickness, hardness, and weight variation (USP41). For the *in vitro* release of tablets, phenytoin released from the formulated tablet was lower than 5%. This was due to the formulated tablet remaining a viscous white gel in the dissolution basket at the end of the experiment. In conclusion, incorporating phenytoin with HPMC might be suitable for sustained phenytoin release in oral administered tablets. However, DT will be increased and the appropriate ratio of phenytoin sodium and HPMC will be investigated in further studies.

Keywords: Phenytoin sodium, physical mixing, solid dispersion, capsules, tablets

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Introduction

Phenytoin is an antiepileptic drug with a narrow safety margin. Phenytoin sodium was developed to improve the solubility of phenytoin. However, phenytoin sodium will be recrystallized to the free acid form of phenytoin in the acidic pH of the gastric medium as shown in Figure 1A, resulting in poor absorption in the stomach after oral administration [1-2]. The chemical structure of phenytoin sodium is similar to that of barbiturates (Figure 1B), except it features a five-membered ring (Figure 1C). Therapy with recommended doses of 300 mg/day necessitates that the therapeutic concentration and the therapeutic dose must be maintained for at least 24 h [1]. While phenytoin sodium has a therapeutic concentration of 10-20 mg/mL, it is toxic at 20 mg/mL and it has a narrow therapeutic index as described above [2]. The conventional phenytoin dosage forms release the full drug in a matter of minutes, and therapeutic concentrations are only maintained for a short time, necessitating the administration of a second dose [2-3]. As a result, phenytoin sodium sustained release formulation that releases the medicine over a 24-h period would be advantageous. In addition, when the frequency of dose administration is reduced, the negative effects of phenytoin sodium were reduced. Controlled release solid dosage forms were selected to reduce the frequency of drug administration. The incorporation of the drug into the polymer matrices is usually prepared for prolonged drug release [4].

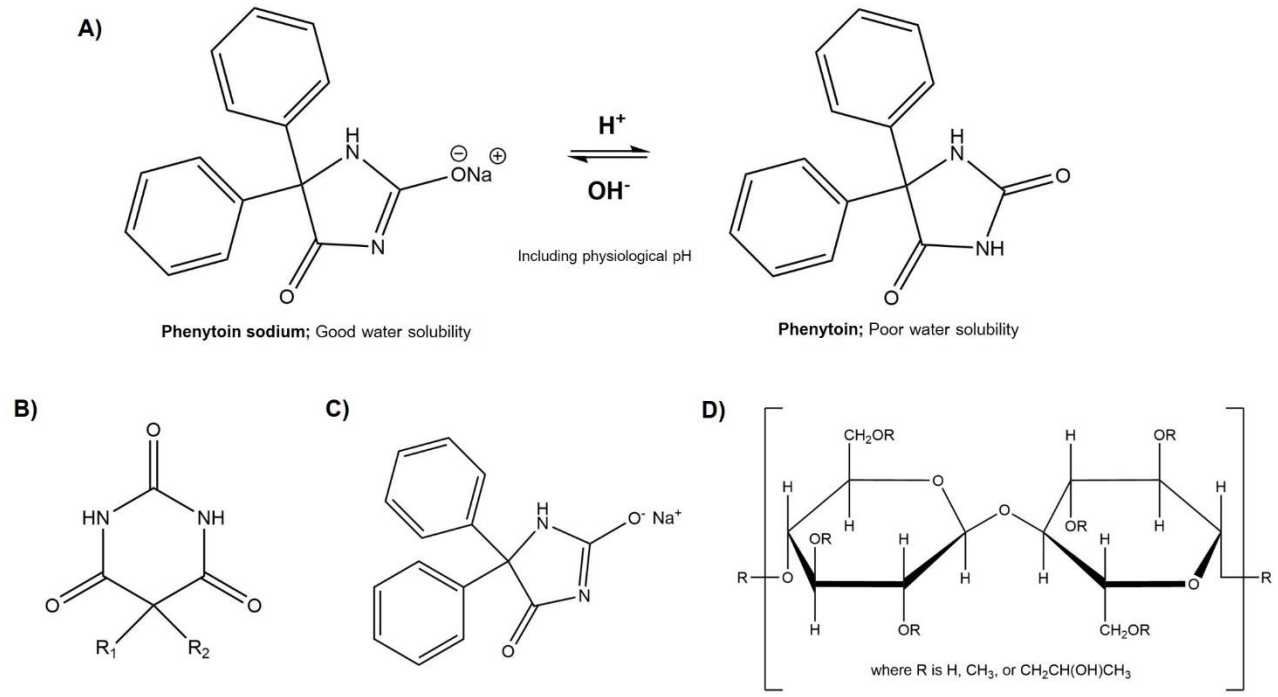

Figure 1 Chemical structure of phenytoin sodium in an acidic and alkaline medium (A), barbiturates (B), phenytoin sodium (C), and hydroxypropyl methylcellulose (D).

Hydroxypropyl methylcellulose (HPMC) is a partly O-methylated and O-(2-hydroxypropylated) cellulose ether derivative as shown in Figure 1D. HPMC is generally incorporated with drugs having poor aqueous solubility to improve their solubility [5]. Moreover, it had been reported that HPMC

incorporated with curcumin could significantly increase the oral curcumin bioavailability when compared to non-formulated curcumin [6]. Besides the improvement of drug solubility, HPMC is a common matrix material in oral controlled delivery systems, and HPMC matrices have a sustained release pattern due to two mechanisms: diffusion and gel layer erosion [6-7]. Roohullah *et al.* [8] reported that HPMC could be sustained phenytoin release from the tablet formulation up to 12 h. Based on these findings, HPMC could be used as an effective carrier material for phenytoin sodium-controlled release solid dosage forms. However, there are only a limited number of published comparative studies that have evaluated the effect of the incorporation method of phenytoin sodium into HPMC on drug release profiles. Therefore, this study was aimed to prepare and characterize phenytoin sodium-controlled release solid dosage forms by incorporating phenytoin sodium into HPMC via physical mixing and solid dispersion methods.

Materials and Methods

Phenytoin sodium was obtained as a gift from Atlantic Laboratory, Thailand. Corn starch, hydroxypropyl methylcellulose (HPMC), lactose, magnesium stearate, polyvinylpyrrolidone (PVP-K90), and talcum were obtained from Union Science Co. Ltd. (Chiang Mai, Thailand). All other reagents were of analytical grade and used without further purification.

Preparation of a mixture of phenytoin sodium and HPMC

Phenytoin sodium was mixed with HPMC using two methods; physical mixing (PM) and solid dispersion (SD).

Preparation of phenytoin sodium physical mixtures

Phenytoin sodium physical mixtures were prepared by mixing different ratios of phenytoin sodium and HPMC (1:0, 1:1, 1:2, and 1:3) thoroughly in a dried glass mortar and pestle for about 10 minutes until a homogeneous mixture was obtained and then stored in a desiccated environment until use. The obtained mixtures were designated as PM1, PM2, PM3, and PM4, respectively.

Preparation of phenytoin sodium solid dispersions

Phenytoin sodium solid dispersions were prepared by mixing different ratios of phenytoin sodium and HPMC (1:0, 1:1, 1:2, and 1:3) as followed. Phenytoin sodium (50 mg) was dissolved in isopropyl alcohol using a magnetic stirrer, while 0-150 mg HPMC was dissolved in distilled water to produce a clear solution. Then, the phenytoin sodium solution was added into the HPMC solution with continuous stirring. All solvent was completely evaporated at 40°C using a hot-air oven (Memmert, Schwabach, Germany). The phenytoin sodium solid dispersions obtained were designated as SD1, SD2, SD3, and SD4, respectively.

Characterization of a mixture of phenytoin sodium and HPMC

Mixtures of phenytoin sodium and HPMC were characterized by using Fourier transform infrared (FTIR) spectroscopy analysis (IRAffinity-1S, Shimadzu, Japan). The dried mixture obtained was ground into powder and then placed on the FTIR sample holder. Scans were obtained at a resolution of 4/cm from 4000 to 400/cm.

Pre-formulations composition of the granule

Phenytoin sodium was mixed with HPMC using two methods including PM and SD as described above. Eight pre-formulations were prepared using a wet granulation method as followed. The composition of the pre-formulations consisted of mixtures of phenytoin sodium and HPMC including PM1-PM4 and SD1-SD4 (phenytoin sodium acts as an active drug while HPMC as a diluent), 10% (w/w) PVP-K90 starch paste as a binder, magnesium stearate (3% w/w) and talcum (1% w/w) acted as lubricants and glidants. The composition of pre-formulation granules is shown in Table 1.

Table 1 The composition of the pre-formulation granule

Compositions	Amount (g)							
	PM1	**PM2**	**PM3**	**PM4**	**SD1**	**SD2**	**SD3**	**SD4**
Phenytoin sodium	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
HPMC	-	5.0	10.0	15.0	-	5.0	10.0	15.0
10% PVP-K90	3.4	8.9	7.7	10.1	-	-	-	3.0
Magnesium stearate	1% w/w of dried granule weight							
Talcum	3% w/w of dried granule weight							
Lactose add to	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0

Pre-formulation evaluation of granule

PM4 was selected to evaluate granule properties based on it contained the highest amount of HPMC in the pre-formulation. Pre-formulation granules were evaluated as follows.

Bulk density

Bulk density of the granule was determined as follows. In brief, granules (20 g) were placed into a measuring cylinder. Then, the granules were tapped three-times and the bulk volume of the granule was measured. The bulk density of the granule was calculated using the following equation:

$$\text{Bulk density } (\rho_B) = \frac{\text{weight of the granules}}{\text{bulk volume of granules}}$$

Tapped density

Tapped density of the granule was determined by mechanically tapping a measuring cylinder containing the granules until little further volume or mass change is visually observed. The tapped density of the granule was calculated using the following equation:

$$\text{Tapped density } (\rho_T) = \frac{\text{weight of the granules}}{\text{tapped volume of granules}}$$

Compressibility index

Compressibility index (%) was determined by comparing the difference value of the tapped density (ρ_T) and the bulk density (ρ_B), to the tapped density (ρ_T) using the following equation:

$$\text{Compressibility index } (\%) = \left(\frac{\rho_T - \rho_B}{\rho_T} \right) \text{x } 100$$

Hausner's ratio

Hausner's ratio of the granule was determined by comparing the tapped density (ρ_T) to the bulk density (ρ_B) as follows:

$$\text{Hausner's ratio} = \frac{\rho_T}{\rho_B}$$

Angle of repose

The angle repose of granules was measured using the funnel method. In brief, 20 g of pre-formulation granule were taken in the funnel which was fixed to the clamp stand 5 cm height from the base. Then, the granules were allowed to flow through the funnel freely to the base. The angle repose of granule was calculated using the following equation:

$$\tan \theta = \frac{h}{r}$$

where θ is the angle of repose, h is the height of the granule pile (cm) and r is the radius of the granule pile (cm).

Capsule preparation

Pre-formulation granules with a mass of 370 mg were weighted and then manually filled into capsule no. 000. Physical properties of formulated capsules were followed by weight variation using a Mettler Toledo analytical balance and capsule disintegration time using the Erweka ZT-322 disintegration tester.

Tablet compression

The tablet compression method was performed using a hydraulic press (PerkinElmer, IL, USA). The pre-formulation granule with an approximate weight of 300 mg was used to compress with the compression force of 2.0 kN using a flat-faced round punch with a diameter of 12.73 mm. Physical properties of formulated tablets were followed by weight variation using a Mettler Toledo analytical balances, thickness and hardness using a thickness hardness tester (Erweka, Germany), tablet disintegrating time using the Erweka ZT-322 disintegration tester.

***In vitro* drug release**

Phenytoin sodium release was determined using a Erweka dissolution tester USP apparatus type I, with 600 mL of 0.1 N HCl as a dissolution medium, temperature was maintained at 37±0.5 ^{o}C with a rotating basket rate at 50 revolutions per minute (rpm) [9]. Aliquots of 5 mL were sampled manually at 15, 30, 60, and 120 minutes with the replacement of 5 mL of the fresh medium. After two hours, the dissolution medium was adjusted to pH 6.8 with 2 N NaOH and maintained pH at 6.8 for 60 minutes. Aliquots of the sample with a volume of 5 mL were manually withdrawn at 15, 30, 45, and

60 minutes with the replacement of 5 mL of the fresh medium. All the samples were analyzed directly at a maximum wavelength of 229 nm using a JASCO V-630® UV-Vis spectrophotometer. The amount of phenytoin sodium released was calculated using an equation obtained from the standard curve. Thereafter, the percentage of cumulative drug release was reported.

Statistical analysis

The data values were expressed as mean ± SD. One-way Analysis of Variance (ANOVA) with post hoc LSD test was performed using Sigma Stat software version 3.5 (Systat Software Inc., San Jose, CA, USA). A *p*-value of less than 0.05 was considered to indicate a statistically significant difference.

Results and Discussion

Preparation of a mixture of phenytoin sodium and HPMC

Following preparation of the mixture of phenytoin sodium and HPMC using physical mixing and solid dispersion method, all PM formulations i.e. PM1-PM4 powder were obtained, while SD2-SD4 powder was obtained. This might be due to only phenytoin sodium could not be precipitated after isopropanol evaporation. In addition, with a higher amount of HPMC of SD3 and SD4, the obtained resin was too viscous. Therefore, SD2 was used for further investigation.

IR spectrum results

FTIR analysis was used to determine the physicochemical interaction possibilities between phenytoin and HPMC. The FTIR spectra of phenytoin sodium and HPMC are shown in Figure 2A and 2B. The FTIR spectra of the mixture of phenytoin sodium and HPMC by PM and the mixture of phenytoin sodium and HPMC by SD are shown in Figure 3A and 3B, respectively. The spectrum of phenytoin sodium shows stretching vibrations at 3300 cm^{-1} for the NH group and at 3068 cm^{-1} for the aromatic C-H [10]. The spectrum of HPMC shows strong bonded hydroxyl bands (n = 3200-3600 cm^{-1}) and stretching vibrations at 2850-3000 cm^{-1} for C–H alkyl group [11]. Compared with the FTIR of phenytoin sodium and HPMC, the spectrum of mixtures using the PM method demonstrated that there were no significant interactions between phenytoin and HPMC (Figure 3A). However, the spectrum of the mixture of phenytoin sodium and HPMC using the SD method showed stretching vibrations at 1725 cm^{-1} for the C=O group (Figure 3B). This implies the presence of interactions between phenytoin sodium and HPMC for material prepared using the SD method. These results agree with those published by Tran *et al.* [12], who reported that the interactions between the drug and the polymer might occur within the SD method.

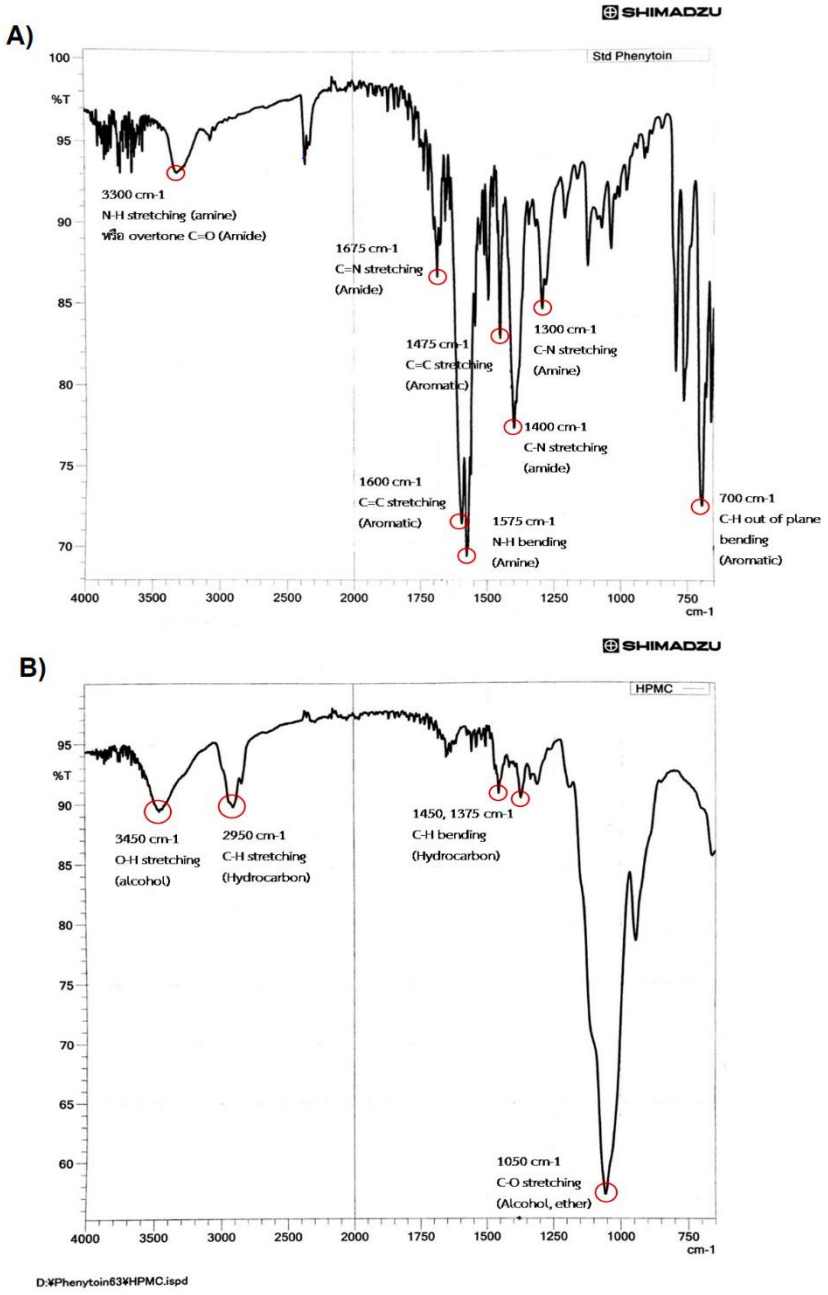

Figure 2 IR spectrum of phenytoin sodium (A) and hydroxypropyl methylcellulose (B).

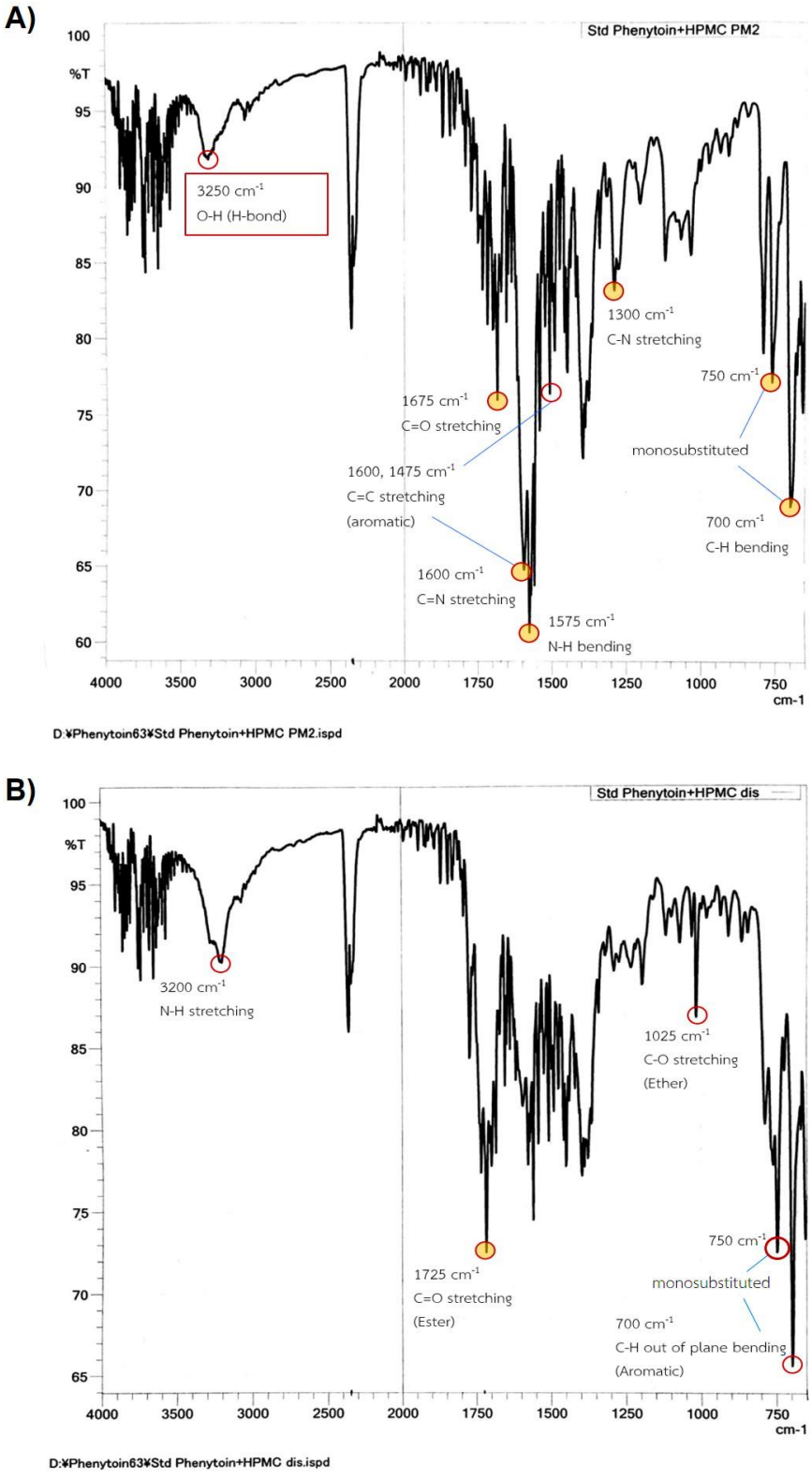

Figure 3 IR spectrum of physical mixture of phenytoin sodium and HPMC (A) and solid dispersion of phenytoin sodium and HPMC (B).

Pre-formulation evaluation of granule

The PM4 granule formulation showed bulk density of 0.29, tapped density of 0.35, % compressibility index of 17.14, Hausner's ratio of 1.22, and the angle of repose within 29. These results indicated that the PM4 granule formulation showed good flowability properties with Hausner's ratio value less than 1.25 and angle of repose value less than 30 [9].

Evaluation of capsule properties

PM1-PM4 and SD2 were used to prepare phenytoin sodium capsules. Pre-formulation granules with a mass of 370 mg were weighted and then were manually filled into capsules as previously described. Granule weight in the capsule was in the range of 359.05 - 370.59 mg. DT of all capsules was less than 15 minutes. Hence, the formulated capsules using PM1- PM4 and SD2 were found to be meet the requirement of the BP standard [13].

Evaluation of tablet properties

PM3 and PM4 were used to prepare phenytoin sodium tablets using wet granulation method. As shown in Table 1, the composition of the tablet formulations consisted of PM3 and PM4 (phenytoin sodium acts as an active drug while HPMC as a diluent). PVP-K90 paste (10% w/w) as a binder, magnesium stearate, and talcum acted as lubricants. The formulated tablets with a flat surface were obtained as shown in Figure 4. Based on the color of HPMC, the formulated tablet using PM4 was a light yellow in color (Figure 4B), whereas the formulated tablet using PM3 was a white in color (Figure 4A). The diameter of the formulated tablets using PM3 and PM4 was in a range between 12.72 -12.76 mm. The thickness of the formulated tablets was approximately 2.20 mm. The hardness of the formulated tablet using PM3 and PM4 was 7.37 $\pm$ 0.73 KP and 5.86 $\pm$ 0.49 KP, respectively. The results indicated that two formulated tablets could be strong enough to avoid friability during packaging and transportation. Using a greater amount of HPMC, the tablet hardness decreased. Moreover, the tablet hardness of the two formulations was significantly different. The tablet weight was in a range between 319.10 - 327.50 mg, which was not more than 5% of the target weight of 325 mg. The formulated tablets showed a narrow weight variation range with a percentage weight variation of less than 2%. Thus, the formulated tablets using PM3 and PM4 were found to meet the requirement of the USP41 standard [9].

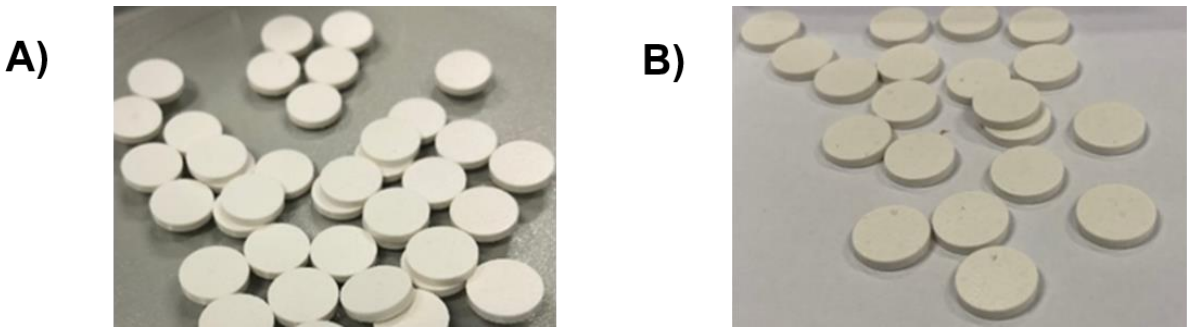

Figure 4 The physical appearance of the formulated tablets using PM3 (A) and PM4 (B).

***In vitro* studies**

The *in vitro* release of phenytoin from the formulated capsule is shown in Figure 5A. The results showed that phenytoin released from formulated capsules using PM1, PM2, PM3, PM4, and SD2 in an acidic medium were approximately 30%, 30%, 29%, 49%, and 24%, respectively. Phenytoin released from the formulated capsule using PM4 showed significantly higher drug release when compared to non-incorporated phenytoin with HPMC (PM1). While, in an alkaline medium, phenytoin released from the formulated capsules using PM3 and PM4 showed significantly more drug released when compared to that from the formulated capsule using PM1 (Figure 5A). Using the same amount of HPMC, there was no significant different drug released from the formulated tablet using the PM (PM2) and SD (SD2) methods. For *in vitro* release of phenytoin from formulated tablets, phenytoin released from formulated tablets is lower than that from the formulated capsules. This was due to the effect of compaction force from the tablet compression process. As shown in Figure 5B, phenytoin released from the formulated tablets using PM3 and PM4 were approximately 5% and 4% at the end of the experiment. These results differed from those published by Madhavi *et al*. [14], who reported that phenytoin, released from the formulated tablets by incorporating phenytoin sodium into HPMC via PM, was approximately 50% at the end of 6 h. Also, the results differed from those published by Roohullah *et al.* [8], who reported that phenytoin released from the formulated tablets by incorporating phenytoin sodium into HPMC via SD was approximately 60%. This was due to the formulated tablets using PM3 and PM4 remaining a viscous white gel in the dissolution basket at the end of the experimental (data not shown). Future work will seek to increase dissolution time for evaluation time of 100% phenytoin released from the formulated tablets.

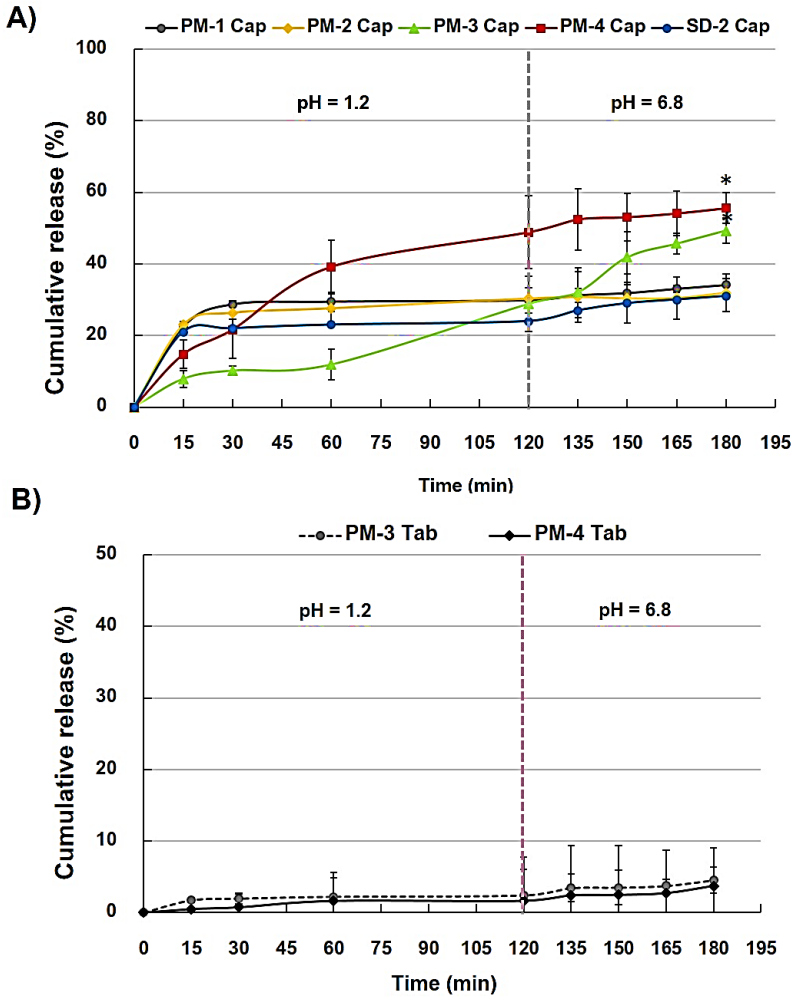

Figure 5 *In vitro* release patterns of phenytoin released from the formulated capsules using (A) and that from the formulated tablets (B); * $p < 0.05$ when compared with non-incorporated phenytoin with HPMC (PM1).

Conclusions

This study concluded that phenytoin incorporated with HPMC at a ratio of 1: 4 (PM4) could be increased phenytoin released from the formulated capsules in the acidic medium. Also, it might be prolonged phenytoin released from the formulated capsules in the dissolution medium. For tablet formulation, incorporation of phenytoin with HPMC might be suitable for sustained phenytoin release in tablet dosage forms after oral administration. However, DT will be increased and the appropriate ratio of phenytoin sodium and HPMC will be investigated for further studies.

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