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RESEARCH PAPER

Semisolid Matrix Filled Capsules: An Approach to Improve Dissolution Stability of Phenytoin Sodium Formulation

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ABSTRACT

Seven semisolid fill bases were selected for the formulation of 24 capsule formulations, each containing 100 mg of phenytoin sodium. The fill materials were selected based on the water absorption capacity of their mixtures with phenytoin sodium. The fill matrices included lipophilic bases (castor oil, soya oil, and Gelucire (G) 33/01), amphiphilic bases (G 44/14 and Suppocire BP), and water-soluble bases (PEG 4000 and PEG 6000). The drug:base ratio was 1:2. Excipients such as lecithin, docusate sodium, and poloxamer 188 were added to some formulations. The dissolution rate study indicated that formulations containing lipophilic and amphiphilic bases showed the best release profiles. These are F4 (castor oil–1% docusate sodium); F10 (castor oil–3% poloxamer 188); F14 (G33/01–10% lecithin); F17 (G33/01–1% docusate sodium), and F20 (Suppocire BP). Further, the dissolution stability of the five formulations above was assessed by an accelerated stability study at 30°C and 75% RH using standard Epanutin capsules for comparison. The study included the test and standard capsules either packed in the container of marketed Epanutin capsules (packed) or removed from their outer pack (unpacked). Release data indicated superior release rates of castor oil based formulations (F4 and F10) relative to standard capsules in both the unpacked and packed forms. For instance, the extent of drug release at 30 min after 1 month was 91% for F4 and F10 and 20% for standard capsules. Drug release from packed capsules after 6 months storage was 88% for both formulations F4 and F10 and 35% for standard capsules. In conclusion, the pharmaceutical quality of phenytoin sodium capsules can be improved by using a semisolid lipophilic matrix filled in hard gelatin capsules.

Key Words: Hard gelatin capsules; Semisolid matrix; Phenytoin sodium; Additives; Dissolution rate; Stability study.

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INTRODUCTION

Interest in liquid and semisolid matrix (SSM) filling of hard gelatin capsules was renewed in the late 1970s.[1] Recent decades have seen substantial advances in the use of new excipient mixtures for the filling of hard gelatin capsules and in the technology of their manufacture. Such advances have involved both the filling equipment and the design and sealing of the gelatin shells.[2,3]

SSM capsule formulations offer many advantages over conventional powder filled systems. These include excellent fill weight and content uniformity, the elimination of dust or cross contamination, easier formulation of oily drugs, improved drug stability and easy modification of drug release rate.[4–8]

This work discusses the use of the above technique in overcoming a dissolution stability problem related to phenytoin sodium capsules. Despite the relatively high water solubility of phenytoin sodium, variations in the dissolution rate of solid dosage forms and hence, bioavailability has been reported.[9,10] This was recognized by the USP and accordingly, dissolution specifications were set up. Reports on the failure of some phenytoin sodium capsules, produced by different manufacturers worldwide, to comply with the USP dissolution requirements and to affect bioavailability, have been published on various occasions.[11–14] In an earlier postmarketing assessment of the quality of phenytoin sodium solid dosage forms marketed in Egypt, marked interbrand and intrabatch variations in dissolution properties were observed.[14] The percentage dissolution in 30 min of fast-release capsules ranged from 5 to 96%. This presents a serious practical problem, in view of the narrow therapeutic index (10–20 μg/mL) of phenytoin, its dose-dependent metabolism, and the large number of patients depending on the drug for the control of seizures.

Fluctuation in the quality of phenytoin sodium solid dosage forms appears to be a complex process involving many factors including physicochemical properties of the drug, formulation factors, manufacturing method, packaging, and storage conditions of the raw material and the finished product.[15–19] Phenytoin sodium is a hygroscopic crystalline powder, which upon exposure to air gradually absorbs carbon dioxide with the liberation of the practically insoluble phenytoin acid. Conversion to the insoluble acid form occurs at the surface or inside solid dosage forms of phenytoin sodium, suppressing the drug release.[16] Formulation factors were shown to be widely implicated in the dissolution variability of phenytoin sodium capsules. For example, formulation of phenytoin sodium capsules with cornstarch or lactose increased dissolution rate while drug release was reduced by using calcium sulfate or sodium sulfate as excipients.[17] The effect of formulation excipients was also found to vary with the drug:excipient ratio.[18] The detrimental effect of improper storage on the clinical efficacy of phenytoin sodium capsules in controlling epilepsy was also reported.[19] These capsules showed discoloration without losing potency. However, dissolution studies revealed only 6% of the labeled drug being in solution at 90 min due to poor disintegration of the capsules. These data underscore the need for proper storage conditions, such as the use of well-protected airtight containers.

Incorporation of a drug in SSM could significantly reduce the access of oxygen and moisture into the dosage form. This technology has been successfully used to overcome a stability related formulation problem of drugs liable to oxidation or hydrolysis such as vitamin A[20] or vancomycin hydrochloride,[6] respectively.

Therefore, the aim of this work was to improve the pharmaceutical quality and dissolution stability of phenytoin sodium products by incorporating the drug in semisolid matrix capsule formulations.

MATERIALS AND METHODS

Materials

The following materials were used as received: phenytoin sodium (the Nile Company for pharmaceuticals, Cairo, Egypt. Fractions of particle size range less than 160 μm were used throughout this study), castor oil BP, soya bean oil USP, soya lecithin USNF, hydrogenated and partially hydrogenated soya bean oil USP, white beeswax, polyethylene glycol (PEG) 400 (gifts from Scherer, Egypt), G44/14 (a mixture of mono-, di-, and triglycerides and mono- and difatty acid esters of polyethylene), G33/01 (hemisynthetic glycerides consisting of saturated fatty acids from C8 to C18 triglycerides), and Suppocire BP (saturated polyglycolyzed glycerides) (gifts from Gattefossé Etablissement, France), polyethylene glycol 1500, 4000, 6000 (Pharco Pharmaceuticals, Alexandria, Egypt), docusate sodium (dioctyl sodium sulfosuccinate, El Amreya Phamaceuticals, Alexandria, Egypt), and poloxamer 188 (nonionic polyoxyethylene polyoxypropylene copolymer, BASF-Ludwigshahen, Germany). A commercial

brand of Epanutin capsules 100 mg (Parke Davis, England, batch No 2206119, expiry date 10/2000) was also used in this study as a standard reference product. Epanutin capsules are size 3 hard gelatin capsules each containing white powder composed of phenytoin sodium as active ingredient and lactose and magnesium stearate as excipients. The gelatin capsule shell also contains E127 (erythrosine), E104 (quinoline yellow), and E171 (titanium dioxide) as coloring agents.

Moisture Uptake and Base Selection

A preliminary study was performed on the suitability of a range of bases for use as semisolid fills for phenytoin sodium capsules, in terms of moisture uptake. The study involved nine bases. These included lipophilic bases (soya oil, castor oil, and G33/01), amphiphilic bases (G44/14 and Suppocire BP), and water-soluble bases (PEG 400, 1500, 4000, and 6000). Mixtures (300 mg each) containing one part of phenytoin sodium (100 mg) to two parts of the base (200 mg) were prepared by incorporating the drug in the molten base, with stirring, in vials of constant dimensions (10-mL capacity and a body cross diameter of 2 cm). The uncovered vials containing the mixtures (300 mg each) or the corresponding bases alone (200 mg each) were exposed to a high humidity challenge by storage at 90% RH at ambient temperature (25°C) for 5 days. Phenytoin sodium drug substance (100 mg) was included in the study, for comparison. The percentage moisture uptake by the different samples was assessed gravimetrically.

Formulation of the SSM Capsule Fills

Based on the results of the moisture uptake study, all bases tested except PEG 400 and PEG 1500 proved provisionally suitable for subsequent formulation studies. Twenty-four capsule formulations (Table 1) were prepared using a drug-to-base ratio of 1:2 except for formulae F23 (1:4) and F24 (1:5). The drug content in all formulations was 100 mg. A wax mixture was added to thicken soya oil

Table 1. Semisolid matrix prepared formulations containing 100 mg of phenytoin sodium.

	Formulation ingredients (mg/capsule)									
Formula	Soya oil	Castor oil	Gelucire 33/01	Lecithin	Docusate sodium	Poloxamer 188	Gelucire 44/14	Suppocire BP	PEG 4000	PEG 6000
F1	170									
F2		200.0								
F3		198.5			1.5 (0.5%)					
F4		197			3 (1%)					
F5		195.5			4.5 (1.5%)					
F6		191			9 (3%)					
F7		185			15 (5%)					
F8		197				3 (1%)				
F9		194				6 (2%)				
F10		191				9 (3%)				
F11		188				12 (4%)				
F12			200							
F13			191	9 (3%)						
F14			170	30 (10%)						
F15			125	75 (25%)						
F16			80	120 (40%)						
F17			197		3 (1%)					
F18			191		9 (3%)					
F19							200.0			
F20								200.0		
F21					3 (1%)			197		
F22		75 (25%)						125		
F23									400.0	
F24										500.0

formulation (F1). This consists of four parts partially hydrogenated soya oil, one part hydrogenated soya oil, and one part white beeswax. The excipients in each formulation were weighed in a glass beaker and heated to 5–10°C above the melting point. Phenytoin sodium was added to the molten base with continuous stirring. The mixture was filled manually into size 3 transparent hard gelatin capsules to a weight of 300 ± 3 mg. The capsules were kept upright until the fill solidified at room temperature.

Assessment of Drug Release Characteristics of SSM Formulations Under Study

In vitro release of phenytoin sodium from the freshly prepared formulations was determined according to the dissolution procedure for prompt phenytoin sodium capsules specified in USP 24. The dissolution medium was 900 mL distilled water kept at 37°C and stirred at 50 rpm using USP apparatus I. Samples were withdrawn at intervals of 10, 20, 30, 45, and 60 min, filtered through 0.45-μm cellulose nitrate membrane filters, and assayed spectrophotometrically at 258 nm. The results presented are the means of three determinations.

Gel Strength Measurements

The gel strength of SSM formulations based on castor oil containing 1–4% poloxamer 188 or 0.5–5% docusate sodium was tested using a penetrometer (Eijkelkamp Agrisearch, Equipment Gisbeek, The Netherlands). The tested formulations (25 g) were prepared by the same method of capsule fill preparation mentioned above. The formulations were stored for 24 hr at room temperature. Before testing, the formula surface was leveled to be at 90° angles to the penetrating cone. The cone was held in place at the surface of the gel and the instrument zeroed. The cone was then allowed to penetrate into the sample for 20 sec. Penetration depth was then read. This was taken as a parameter to assess the consistency of the matrix.

Differential Thermal Analysis (DTA)

Shimadzu DTA-50 was used to record the thermograms of the samples. The instrument was calibrated with indium standard after adjustment of the base. The heating rate was 5°C/min over a temperature range from 25 to 400°C. Samples under study were phenytoin sodium powder, Gelucire 44/14, and mixture of drug: Gelucire 44/14 (1:2).

Stability Studies

Based on the release data obtained, five formulations, namely F4, F10, F14, F17, and F20, were selected to assess the in vitro performance of the capsules upon storage. Standard phenytoin sodium capsules (Epanutin) were used for comparison.

Storage Conditions

Sample capsules of the five selected formulations and Epanutin capsules were stored at 30°C/75% RH away from light. The capsules were both stored in unstoppered glass bottles (referred to in this work as unpacked capsules) and packed in the innovator container of phenytoin sodium capsules (referred to as packed capsules). The storage time was 1 month and 6 months for unpacked and packed capsules, respectively.

Assessment Parameters

The capsules under study were assessed for their appearance (visual inspection), moisture uptake (gravimetric analysis), and dissolution rate (same procedure described above).

RESULTS AND DISCUSSION

Moisture Uptake and Base Selection

Shafik et al.[15] have investigated the primary determinants of fluctuations in the in vitro performance of commercial phenytoin sodium capsules marketed in Egypt. They found that the problem of fluctuations of the pharmaceutical quality of these products is complex, the underlying cause being absorption of moisture. Moisture does affect the dissolution properties of the drug substance and enhances the color change, which is attributed to reaction or interaction of the main excipient, lactose. The results also indicate the inefficiency of the packaging in protecting the product from moisture, which further aggravates the problem. Thus, a preliminary

Table 2. Moisture uptake of free bases and mixtures of phenytoin sodium/semisolid capsule fill bases (1:2) in comparison to phenytoin sodium powder (25°C/90% RH).

	Moisture uptake (mg)					
	1 day		2 days		5 days	
Base	200 mg base	300 mg mixture	200 mg base	300 mg mixture	200 mg base	300 mg mixture
Soya oil	0	10.2	0	14.1	0	27.6
Castor oil	1	11.7	1	14.7	1	25.2
Gelucire 33/01	1	14.4	1	19.8	1	31.8
Gelucire 44/14	27.0	34.5	44.4	52.2	84.0	91.5
Suppocire BP	14.0	13.5	16.0	17.7	17.5	37.2
PEG 400	55.0	62.1	91.4	92.4	152.3	146.1
PEG 1500	35.5	45.0	61.2	72.6	124.1	126.9
PEG 4000	22.4	26.1	35.5	42.0	75.0	85.8
PEG 6000	17.4	26.7	28.5	43.2	62.0	88.8
Phenytoin sodium powder	26.8		32.7		51.0	

moisture uptake study was carried out for the semisolid fill bases under study and mixtures of phenytoin sodium with these bases. This study aimed at selecting the bases with low moisture uptake and/or good moisture protective characteristics. Data obtained are shown in Table 2. The results indicated that the moisture uptake by the bases under study was expectedly highest with the water-soluble polyethylene glycol bases, intermediate with the amphiphilic bases, and lowest with the lipophilic bases.

The group of lipophilic bases showed almost negligible moisture uptake even after 5 days storage. Soya oil and castor oil provided about 50% reduction in the moisture uptake, when compared to phenytoin sodium powder. For example, the moisture uptake by 300 mg soya oil and castor oil based formulations, after 5 days storage, was 27.6 and 25.2 mg, respectively, against 51 mg for phenytoin sodium powder. G33/01 exhibited lesser protection against humidity (31.8 mg) relative to soya oil and castor oil. This can be attributed to its weak surface-active properties (HLB = 1), which might facilitate moisture penetration. In general, the three lipophilic bases under study were considered provisionally suitable for the formulation of phenytoin sodium capsules.

Regarding amphiphilic bases, G44/14 exhibited a higher moisture uptake (91.5 mg), after 5 days, compared to Suppocire BP (37.2 mg) because of its more pronounced hydrophilic properties, conferred by the polyethylene glycol chain (HLB = 14; hydroxyl value = 36–56).[21]

Water-soluble polyethylene glycol bases, specially the lower molecular weight PEG 400 and PEG 1500, exhibited a relatively high moisture uptake (146.1 and 126.9 mg, respectively) after 5 days and hence were excluded from the study. PEG 4000 and 6000 were selected for further formulation studies.

Formulation Studies

Bases with a relatively low moisture absorption capacity were used either alone or with various additives to formulate 24 semisolid capsule fills as shown in Table 1. These were evaluated for drug release properties. Suitability of the bases was based on the fulfillment of the USP dissolution limit for prompt phenytoin sodium capsules (not less than 85% dissolved in 30 min).

Lipophilic Based Formulations

Figure 1 shows the dissolution profiles of phenytoin sodium from SSM capsules formulated with lipophilic bases. The G33/01-based formulation (F12) showed a higher initial dissolution rate compared to soya oil (F1)- and castor oil (F2)-based formulations. Further, both the rate and extent of drug release were higher from the castor oil-based relative to the soya oil-based formulation. This may be attributed to the less hydrophobic nature of castor oil because of its high content of free hydroxy fatty acid fraction. However, none of the formulations conformed to the USP dissolution limit.

Attempts were made to improve drug release from G33/01 and castor oil bases by incorporating

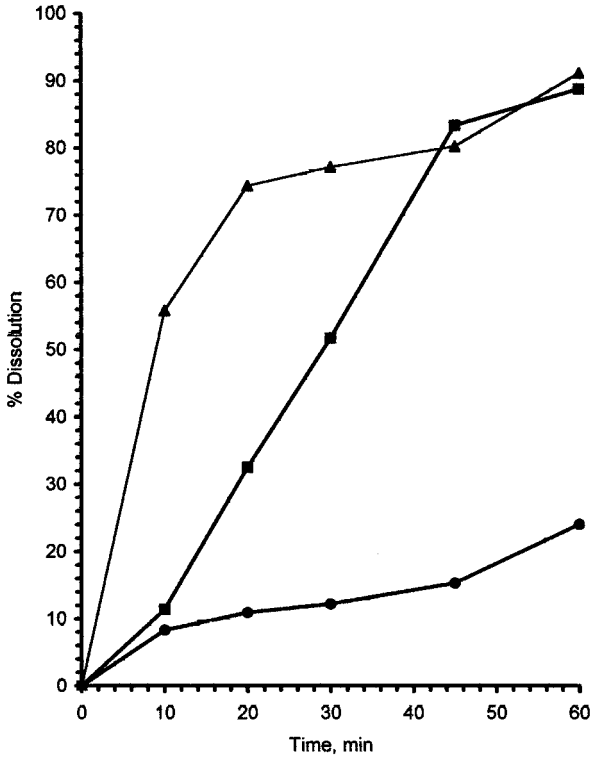

Figure 1. Dissolution profiles of phenytoin sodium from semisolid matrix capsules formulated with lipophilic bases. (●) soya oil, (■) castor oil, and (▲) Gelucire 33/01.

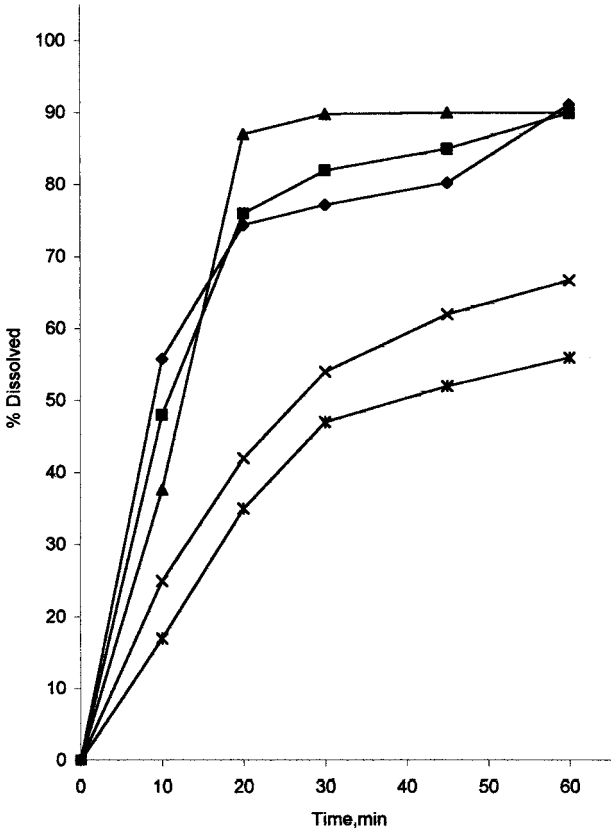

Figure 2. Dissolution profiles of phenytoin sodium from semisolid matrix capsules formulated with Gelucire 33/01 containing: (◆) 0%, (■) 3%, (▲) 10%, (×) 25%, and (*) 40% lecithin.

surface-active agents in the fill formulations. Surfactants are reported[22] to increase the rate and extent of drug release from lipophilic matrix systems and suppository bases via improvement of wetting and water absorption properties of the base. Addition of lecithin, at concentration levels of 3% (F13) and 10% (F14), to G33/01 SSM markedly increased the drug dissolution rate (Fig. 2). However, further increase of lethicin concentration to 25% (F15) and 40% (F16) resulted in a reduced dissolution rate of phenytoin sodium. This may be explained by the observed precipitate formed during the dissolution rate study of these formulations. The precipitate formation may be attributed to a concentration dependent ion pair formation between phenytoin sodium and lecithin. The interaction possibly involves electrostatic attraction of the negatively charged phenytoin ring and the positively charged choline head of lecithin. Ion pair interaction of phenytoin sodium with organic cations as procainamide has been previously reported.[22]

Incorporation of the surfactant docusate sodium in castor oil or G33/01 based formulations provided a pronounced drug dissolution enhancing effect. Figure 3 shows the dissolution profiles from castor oil formulations containing docusate sodium in concentrations ranging from 0.5 to 5% w/w (F3–F7). The dissolution enhancement observed was concentration dependent, the effect being maximal at 1–1.5% docusate sodium. A higher surfactant concentration (3 and 5%) resulted in a less dissolution enhancing effect with a slower initial dissolution rate. This may be attributed to an increased consistency of the SSM formulated with high surfactant concentration, as was shown from the results of gel strength measurements. As the concentration of docusate sodium increased from 0.5 to 5%, the penetration depth through the matrices decreased from 34.2 to 6.5 mm/20 sec. Formulations F3 to F6 containing 0.5 to 3% docusate sodium, respectively, conformed to the USP dissolution requirement. Addition of 1 and 3% docusate sodium to G33/01 based formulations resulted in 92.5 and 84.7% drug release, respectively, at 30 min.

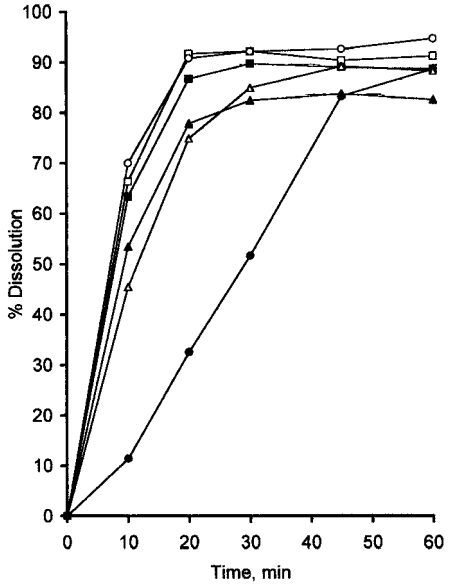

Figure 3. Dissolution profiles of phenytoin sodium from semisolid matrix capsules formulated with castor oil containing: (●) 0%, (■) 0.5%, (□) 1%, (○) 1.5%, (△) 3%, and (▲) 5% docusate sodium.

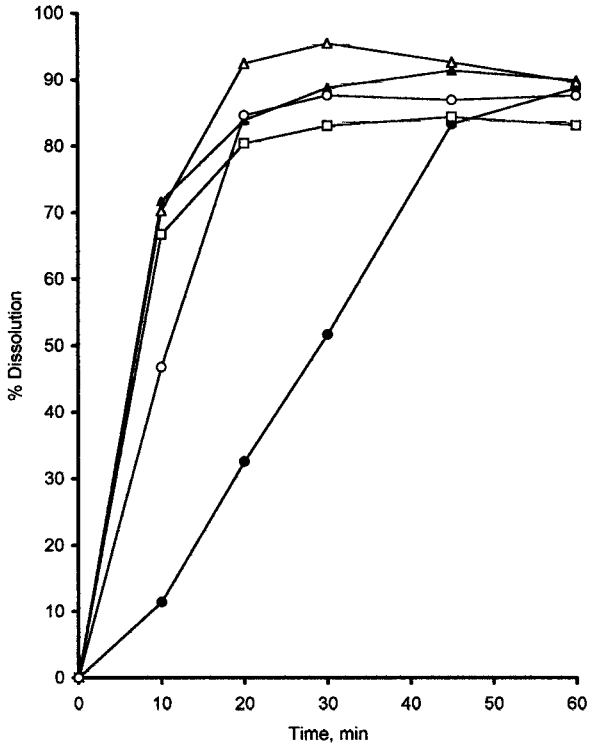

Figure 4. Dissolution profiles of phenytoin sodium from semisolid matrix capsules formulated with Castor oil containing (●) 0%, (□) 1%, (▲) 2%, (△) 3%, and (○) 4% poloxamer 188.

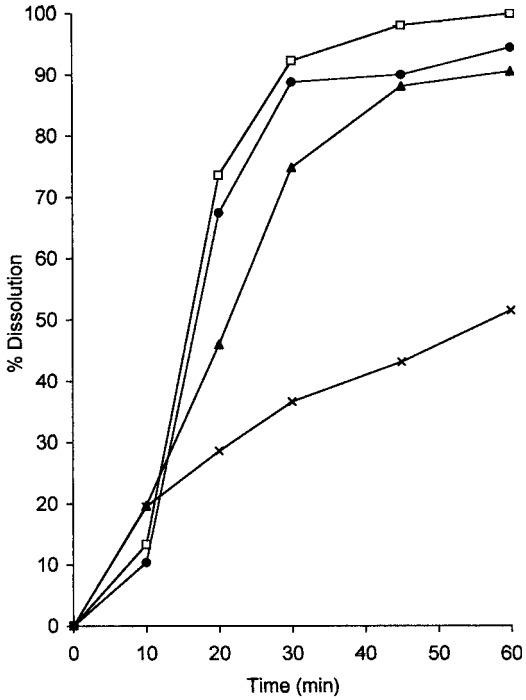

Figure 5. Dissolution profiles of phenytoin sodium from semisolid matrix capsules formulated with amphiphilic bases: (●) Suppocire BP, (□) Suppocire BP/1% docusate sodium, (▲) Suppocire BP/25% castor oil, and (×) Gelucire 44/14.

Phenytoin sodium release profiles from castor oil-based formulations containing 1–4% poloxamer 188 (F8–F11) are shown in Fig. 4. The percentage dissolved at 30 min ranged from 87 to 95% with maximal dissolution enhancement at 3% poloxamer 188 concentrations. The formulation containing 4% poloxamer 188 (F11) showed a less dissolution enhancing effect, probably due to an increase in matrix gel strength. Matrices with increasing poloxamer 188 concentration from 1 to 4% exhibited a penetration depth ranging from 30.5 to 12.2 mm/20 sec, respectively.

Amphiphilic Based Formulations

The use of suppocire BP as a base resulted in 90% drug release in 30 min (Fig. 5). Addition of 1% docusate sodium slightly improved the release pattern. Trials to decrease the melting point and viscosity of the molten base by addition of castor oil resulted in an unexpected decrease in release rate (Fig. 5). This may be the effect of decreased melting

point and viscosity as release enhancing factors on one hand, and increased hydrophobicity as a dissolution-suppressing factor on the other hand.

Addition of phenytoin sodium to Gelucire 44/14 unexpectedly resulted in a nondisintegrating slowly soluble matrix associated with a slow release, 36% of the drug was released at 30 min (Fig. 5). This is probably due to a physicochemical interaction as indicated by the results of DTA (Fig. 6). The thermogram of phenytoin sodium (Fig. 6(a)) showed a melting peak of the drug at about 375°C. The thermogram of Gelucire 44/14 (Fig. 6(b)) exhibited a melting peak at about 45°C and a decomposition peak at about 170°C. Figure 6(c) illustrates that phenytoin sodium/Gelucire 44/14 mixture showed almost disappearance of the melting peak of Gelucire 44/14, with addition of some endothermic peaks between 240 and 367°C. The presence of these endotherms indicates beakdown of an interaction product, rapid melting of the liberated Gelucire, and partial melting of the undissociated product. The formation of water-insoluble product is probably due to hydrogen bonding between the unsubstituted hydrogen of phenytoin sodium and polyoxyethylene chain of the PEG chain of G44/14.

Water-Soluble Based Formulations

Formulations with PEG 4000 and 6000 (F23 and F24) produced highly viscous capsule fills even at temperature up to 70°C. Therefore, they were considered unsuitable for liquid filling of hard gelatin capsules.[6] The observed high viscosity may be attributed to the previously discussed interaction.

Stability Testing

According to the drug release data obtained (Figs. 1 to 5), formulations F4 (castor oil–1% docusate sodium), F10 (castor oil–3% poloxamer), F14 (G33/01–10% lecithin), F17 (G33/01–1% docusate sodium), and F20 (Suppocire BP), which fulfilled the USP dissolution requirement, were selected for the stability study. Epanutin capsules were used as reference product for comparison.

According to the I.C.H. and W.H.O.[23] guidelines for stability testing of drug products, 6-month storage at $40 \pm 2^{\circ}C/75 \pm 5\%$ RH is required for accelerated stability testing of drug products intended for global marketing. However, when significant changes occur during the course of accelerated studies, testing at intermediate conditions should be conducted, e.g., $30 \pm 2^{\circ}C/60 \pm 5\%$ RH. Significant changes include failure of the product to meet specifications for appearance and physical properties. Since the formulations under study either soften (F4, F10) or melt (F14, F17, and F20) at 40°C, accelerated studies were carried out at 30°C/75% RH.

Further, hard gelatin capsules may undergo cross-linking upon exposure to stress conditions of humidity and temperature.[24] This may cause considerable changes in the in vitro dissolution profiles of drugs. For instance, dissolution retardation has been reported for capsules containing chloramphenicol,[25] nitrofurantoin,[26] and other water-insoluble or relatively water-soluble agents[27] upon exposure to high relative humidity. Incorporation of enzymes as pepsin (at pH 1.2) and pancreatin (at pH 7.2) in the dissolution media for hard gelatin capsules has been shown recently to negate the adverse effects of storage on the in vitro dissolution performance of capsules.[28] Dey et al.[29] have reported that the dissolution of stressed etodolac capsules in the presence of enzymes nearly simulated that of fresh capsules and was a better reflection of the in vivo behavior of the product. In the present study, enzymes could not be used because of precipitation of phenytoin sodium at either pH 1.2 or 7.2 required for the action of pepsin and pancreatin, respectively. In order to exclude the possibility of dissolution retardation by cross-linked shells, the contents of stressed capsules were refilled into fresh hard gelatin shells at the time of dissolution testing. Refilling of the contents of stressed capsules in fresh shells has been reported.[24]

Figure 7 shows the change in percentage dissolution at 30 min of unpacked capsules of the standard product (Epanutin) and castor oil based formulations F4 and F10 over the 4-week study period. The test formulations showed high stability during the test period. The decrease in the amount of drug released at 30 min from these formulations did not exceed 3%. However, the standard capsules failed to pass the USP limit after 1 week of storage. A dramatic decrease in the extent of drug release from the standard Epanutin capsules was observed after 4 weeks (the % dissolution at 30 min was $\approx$ 20%). This was accompanied by yellow discoloration of the capsules.

The dissolution stability of formulations F4 and F10 points to the protective effect of the lipophilic semisolid fill base, minimizing moisture absorption and subsequent conversion of phenytoin sodium to the insoluble acid form. This view is supported by the moisture uptake results of unpacked capsules of the standard product and test formulations.

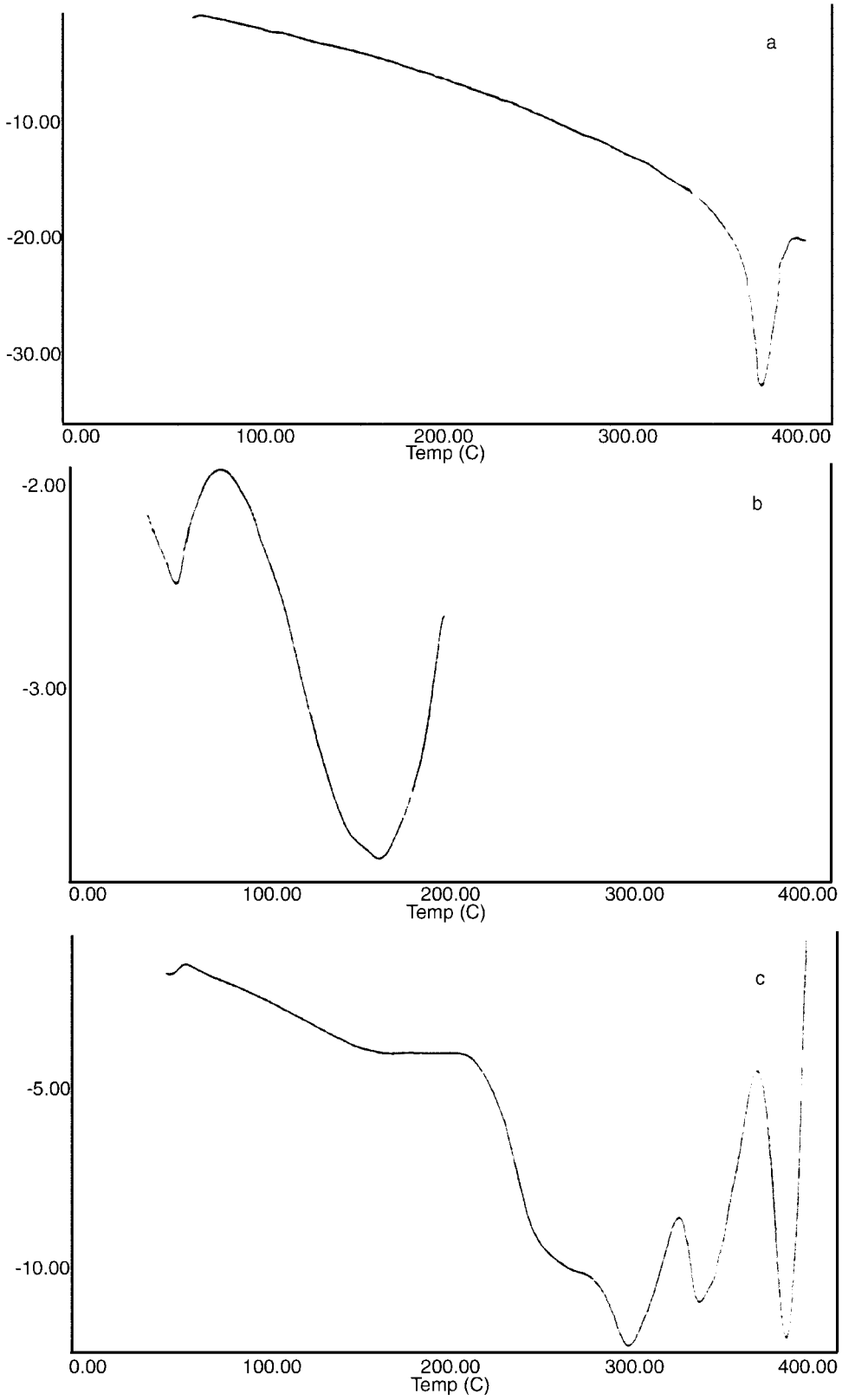

Figure 6. DTA curves of a. phenytoin sodium; b. Gelucire 44/14, and c. mixture of phenytoin sodium/Gelucire 44/14 (1:2).

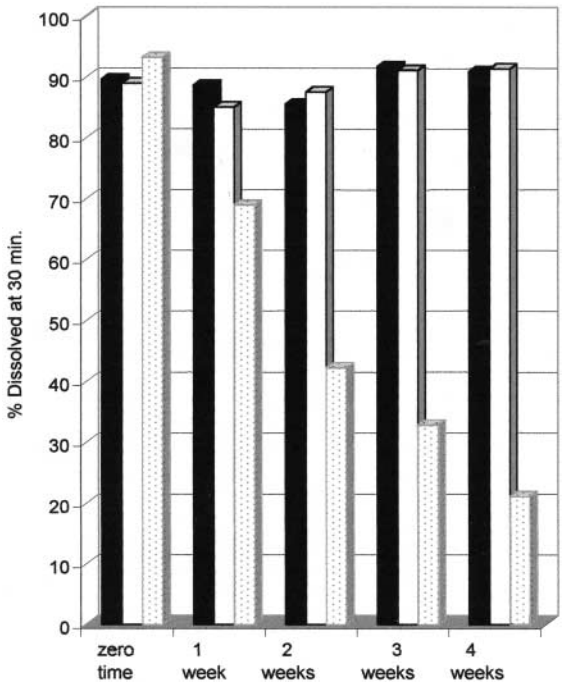

Figure 7. Percentage dissolution at 30 min of phenytoin sodium from unpacked capsules: (⬚) Epanutin, (□) F4 (castor oil/1% docusate sodium), and (■) F10 (castor oil/3% poloxamer 188) after storage at 30°C/75% RH.

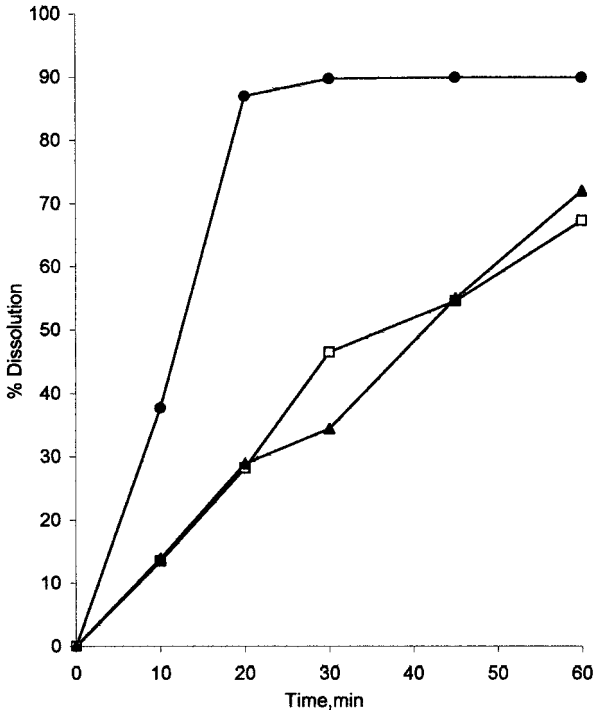

Figure 9. Dissolution profiles of phenytoin sodium from unpacked and packed F14 capsules (Gelucire 33/01–10% lecithin) stored for 1 week at 30°C/75% RH. (●) Zero time, (□) unpacked, and (▲) packed.

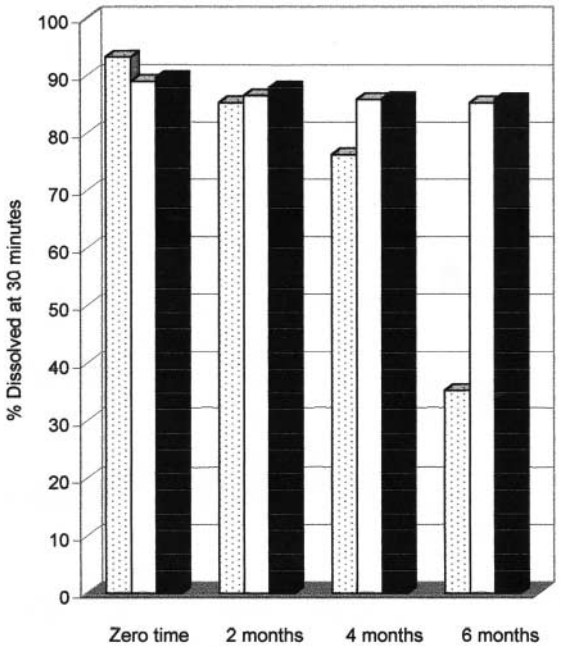

Figure 8. Percentage dissolution at 30 min of phenytoin sodium from packed capsules: (⬚) Epanutin, (□) F4 (castor oil/1% docusate sodium), and (■) F10 (castor oil/3% poloxamer 188) stored at 30°C/75% RH.

While the percentage moisture uptake by the test formulations F4 and F10 attained a maximum of about 5% after 2 weeks, moisture uptake by Epanutin capsules increased progressively, attaining about 13.5% after 4 weeks.

The same stability patterns were obtained for packed capsules. Figure 8 illustrates the change in percentage dissolution at 30 min of packed Epanutin, F4 and F10 capsules over the 6-month storage period. Formulations F4 and F10 exhibited higher stability during the test period in comparison to the standard product. Standard capsules failed the USP test after storage for 4 months with 76% drug release at 30 min. Results for formulations F4 and F10 showed a limited decrease in the rate and extent of drug release upon storage. This could be explained also by the moisture uptake results of the packed capsules under study. The percentage of moisture absorbed by the packed Epanutin capsules (2.93%) was more than double that taken up by packed F4 and F10 capsules (1.3 and 1.2%, respectively) after 4 months of storage.

Dissolution data for G33/01 based formulations F14 and F17 (Figs. 9 and 10, respectively) and

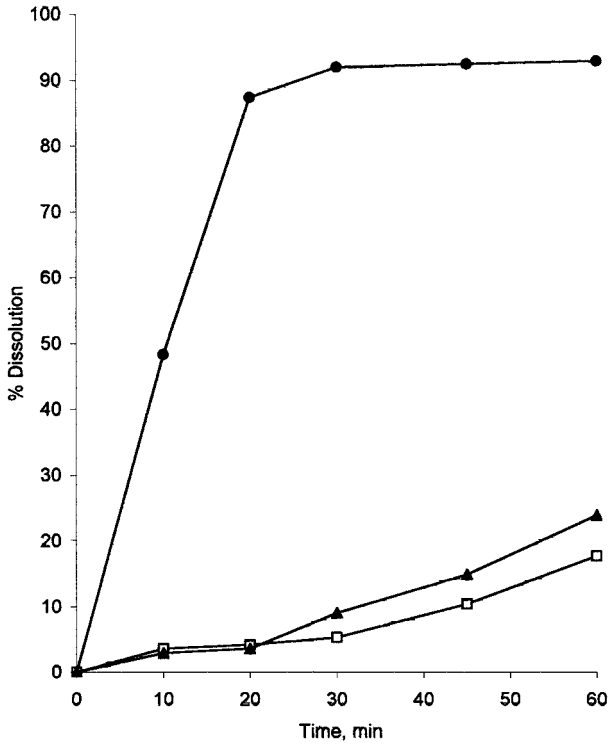

Figure 10. Dissolution profiles of phenytoin sodium from unpacked and packed F17 capsules (Gelucire 33/01–1% docusate sodium) stored for 1 week at 30°C/75% RH. (●) Zero time, (□) unpacked, and (▲) packed.

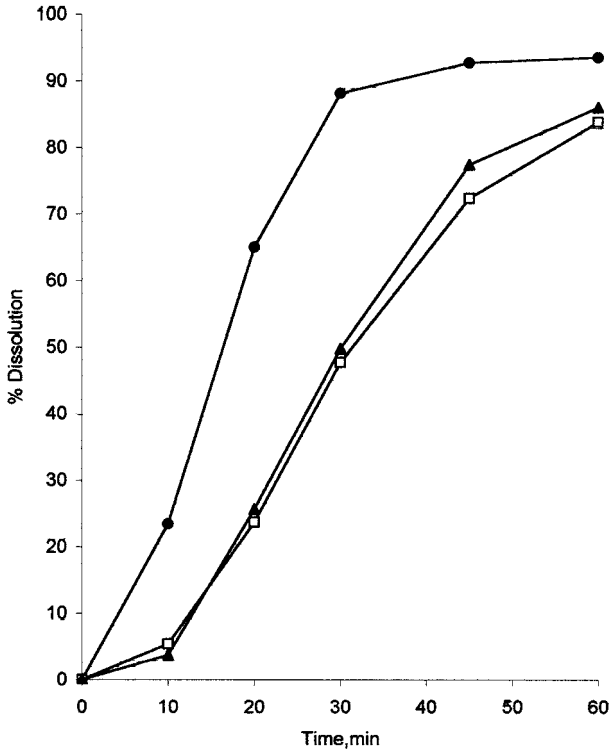

Figure 11. Dissolution profiles of phenytoin sodium from unpacked and packed F20 capsules (Suppocire BP) stored for 1 week at 30°C/75% RH. (●) Zero time, (□) unpacked, and (▲) packed.

Suppocire based formulation F20 (Fig. 11) indicate failure of both packed and unpacked capsules to comply with the dissolution requirement after only 1 week of storage at 30°C/75% RH. The moisture uptake of unpacked formulations, during this period, did not exceed 0.6%. It is well established that glyceride based products may exhibit aging effects. The melting point, softening point, and dissolution rate of glyceride suppository bases may change on storage of the base. The mechanism involved may include the conversion of the base into a more stable polymorphic form,[30] the conversion of the amorphous form to the crystalline state of the fat form,[31] and/or the formation of network structure. Therefore, the observed lower release rates could be attributed to such physical changes of the SSM rather than drug precipitation due to moisture uptake.

CONCLUSION

Based on the above data, it can be concluded that formulation of stable phenytoin sodium capsules can be achieved by the use of semisolid matrices of fatty nature filled into hard gelatin capsules. Castor oil based formulations containing 1% docusate sodium or 3% poloxamer 188 seemed promising and exhibited superior stability to standard Epanutin capsules.

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