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Crystal modification of phenytoin using different solvents and crystallization conditions

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Abstract

Phenytoin crystals having different types of habits, were prepared by recrystallization from ethanol and acetone solutions under different conditions (cooling rate or crystallization temperature, solvent evaporation and watering-out techniques). Scanning electron microscopy, X-ray powder diffractometry, FT-IR spectrometry and differential scanning calorimetry were used to investigate the physical characteristics of the crystals. The dissolution behavior and compaction properties of various batches of crystals were also studied. It was found that using watering-out technique as a crystallization method, produced thin plate crystals, while the crystals obtained by other methods were needle shape for alcoholic solutions and rhombic for acetone solutions. X-ray diffraction spectra and differential scanning calorimetry studies, did not show any polymorphic change. The dissolution rate of different crystals was lower than that of untreated samples. The compacts of phenytoin crystals produced from alcohol or acetone (especially those made by watering-out method) had higher crushing strengths than untreated phenytoin compacts due to the lower porosity and the lower elastic recovery.

Keywords: Phenytoin; Crystallization; Crystal habit; Crystal shape; Dissolution rate; Compaction

1. Introduction

The crystal habit is an important variable in pharmaceutical manufacturing which is affected during crystallization by some factors such as the presence of impurities in the solvent (Chow et al., 1985; Gordon and Chow, 1992; Kaul et al., 1992; Femi-Oyewo and Spring, 1994; Kachrimanis et al., 1998; Garekani et al., 2000a) and the polarity of crystallization solvent (Marshall and York, 1989; Garekani et al., 1999). A number of physical properties such as dissolution rate, (Burt and Mitchell, 1980; Watanabe et al., 1982; Chow et al., 1995) compaction behavior (Di Martino et al., 2000; Garekani et al., 2000b) depend on the habit modification of a particular drug. Solvent has

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strong influence on the habit of crystalline materials; however the role played by solvent–solvent interactions in enhancing or inhibiting crystal growth is still not completely resolved (Lahva and Leiserowitz, 2001). It has been shown that favorable interactions between solute and solvent on specific faces leads to reduce interfacial tension, causing a transition from a smooth to a rough interface and a concomitant faster surface growth.

Phenytoin (5,5-diphenylhydantoin) is an anti-epileptic agent used to control tonic–clonic (grand-mal) and partial seizures (Parfitt, 1999). Phenytoin, in the form of free acid or sodium salt, exhibits poor and/or erratic absorption in various dosage forms. This problem is related to its low water solubility and low dissolution rate (Chow and Hsia, 1991).

In the present work, phenytoin crystals in the form of free acid were modified using different crystallization conditions and techniques. The effects of some factors such as solvent type and crystallization temperature on the crystal habit were investigated. The solid state characteristics and compaction properties of the resulting were also evaluated.

2. Materials and methods

2.1. Materials

Phenytoin obtained as a gift from Alhavi (Iran), ethanol and acetone (Merck, Germany).

2.2. Preparation of phenytoin crystals

Two different solvents of ethanol and acetone were used to study the effect of solvent on the crystal growth as follows:

a) ethanol solutions were prepared by dissolving 3 g of phenytoin in 105 ml ethanol at 65 °C to form a clear solution.
b) acetone solutions were prepared by dissolving 3 g of phenytoin in 90 ml of acetone at 55 °C to form a clear solution.

In order to investigate the effect of cooling rate the following methods were used to crystallize phenytoin from the both ethanol and acetone solutions.

Method I: The solution was immediately transferred to freezer (−10 °C) and was left for a period of 48 h.

Method II: The solution was left to reach room temperature 25 °C (cooling rate of 1.5 ± 0.3 °C) and then transferred to fridge (6–8 °C) and was left for a period of 48 h. The precipitated crystals from the above two methods were collected by filtration through a sintered glass funnel vacuum.

Method III: The solution was left at room temperature until the solvent was completely evaporated.

Method IV: The solution (55–60 °C) was rapidly added to 200 ml cold water (10 °C) and under agitation by means of a glass rod and then left for 2 at 10–15 °C. The crystals were collected by filtration using a sintered glass funnel vacuum.

2.3. Scanning electron microscopy

Electron micrographs of crystals were obtained using a scanning electron microscope (Leica Cambridge S360, UK) operating at 12 kV. The specimens were mounted on a metal stub with double-sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to observation.

2.4. X-ray powder diffraction

The cavity of the metal sample holder of X-ray difractometer was filled with the ground sample powder and then smoothed with a spatula. X-ray diffraction patterns of phenytoin samples were obtained using the X-ray diffractometer (Seimens, Model D5000, Germany) at 40 kV, 30 mA and a scanning rate of 6°/min over a range of 5–70 2θ, using CuK_a radiation of wavelength 1.5406 Å.

2.5. Fourier transform infrared spectroscopy

The spectra were collected on a FT-IR spectrophotometer (Magna-IR, 550 Nicolet, USA), at 4 cm^{-1} resolution for scans. Samples (about 1% w/w) were mixed with KBr powder and compressed

to a 12 mm disc by a hydraulic press at 10 tons compression force for 30 s.

2.6. Thermal analysis

Differential scanning calorimetry (DSC) thermograms of the samples (3–6 mg) were recorded using a thermal analysis system (Polymer Laboratories, UK). After calibration with indium and lead standards, samples were heated at 10 °C/min, in an aluminum pan under a nitrogen atmosphere. A similar empty pan was used as the reference. Onsets, melting points and enthalpies of fusion were automatically calculated by the instrument.

2.7. Dissolution studies

The dissolution rate of 25 mg of phenytoin crystals with specific size range (90–250 μm), was determined in a USP no. 1 dissolution test apparatus at 37 °C, with basket (100 mesh) stirred at 200 rpm. The dissolution medium was 1000 ml water containing 10% ethanol. Triplicate samples (5 ml) were withdrawn from the dissolution vessels at selected time intervals and analyzed for phenytoin content at 232 nm on an UV spectrophotometer (Shimadzu, Japan). The results are the mean and standard deviations of three determinations

2.8. Determination of porosity

Twenty four hours after ejection, the thicknesses and diameters of tablets were measured to ±10 μm using a micrometer and the weight measured to ±0.1 mg. The percentage porosity, ε, was calculated from the following equation:

$$\varepsilon = [(V - V_0)/V] \times 100$$

where V is the tablet volume and V_0 the volume of material at zero porosity. The results are the means of six tablets.

2.9. Preparation of compacts

Crystals were ground using a mortar and pestle to achieve a similar particle size distribution (90–250 μm) for each batch. Compacts were prepared directly from the ground crystals using 8 mm flat-faced punches on a hydraulic press (Riken Seiki Co, Japan). The material for each tablet was weighed (120 mg), introduced into the die and compacted at increasing compression pressures of 12.5, 25 and 37.5 MPa. The compaction surfaces were lubricated with 2% w/w magnesium stearate in acetone before compaction. The compacts were held under load for 30 s, ejected and stored in screw-capped bottles for 24 h before testing, to allow for possible hardening and elastic recovery.

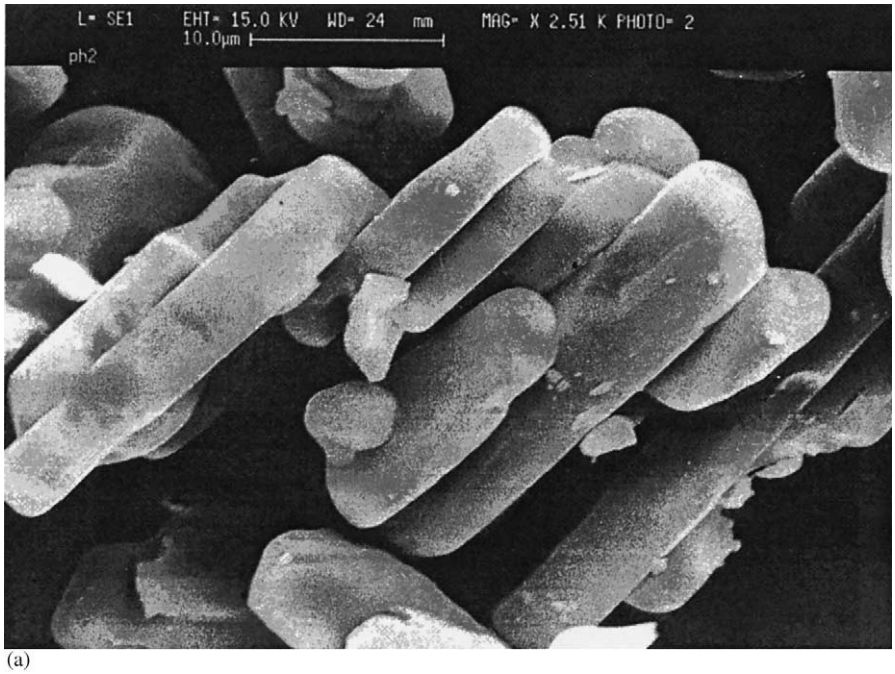
2.10. Crushing strength of compacts

Crushing strengths were determined from the force required to fracture the compacts by diametral compression on a motorized tablet hardness tester (Erweka, Germany). Since it was not possible to obtain the idealized diametrical breaking because of the fragile nature of the compacts, the crushing strength was employed instead of the tensile strength. The results are the mean and standard deviations of at least five determinations.

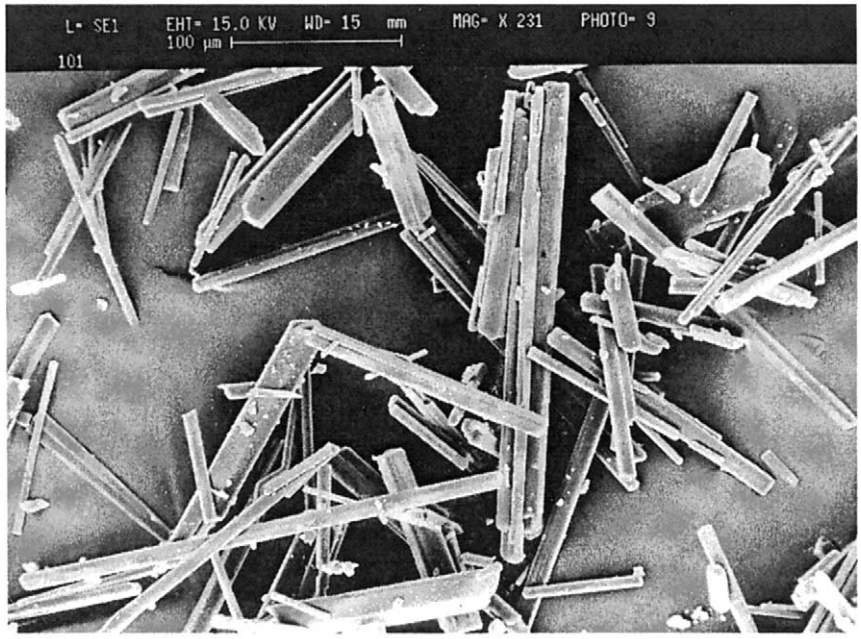
3. Result and discussion

3.1. Morphology of crystals

Fig. 1 shows the scanning electron micrographs (SEM) of untreated and recrystallized phenytoin from alcohol under different conditions. It is clear from the figure that the untreated phenytoin crystals is rod like or columnar (Fig. 1a), whereas the crystals obtained from alcohol using different conditions (I, II and III) are needle shape (Fig. 1b–d). While using method IV, the shape of crystals changes to thin plates or leaflets (Fig. 1e). Recrystallization of phenytoin from acetone solutions with the same method as from alcoholic solutions, produced different shapes of crystals (Fig. 2). Similar to the crystals obtained from alcohol, the crystals shape made from acetone solution using method IV, is thin plate (Fig. 2d). This is because in both cases the solvent is water. However, the shape of crystals obtained from method I, II and III in acetone solution is rhombic (Fig. 2a–c).

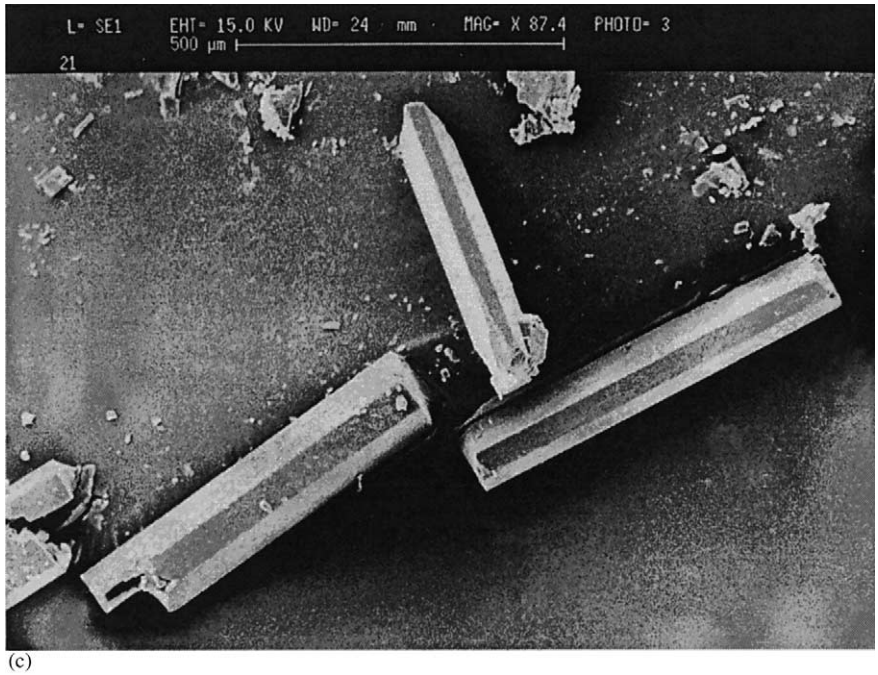


(a)

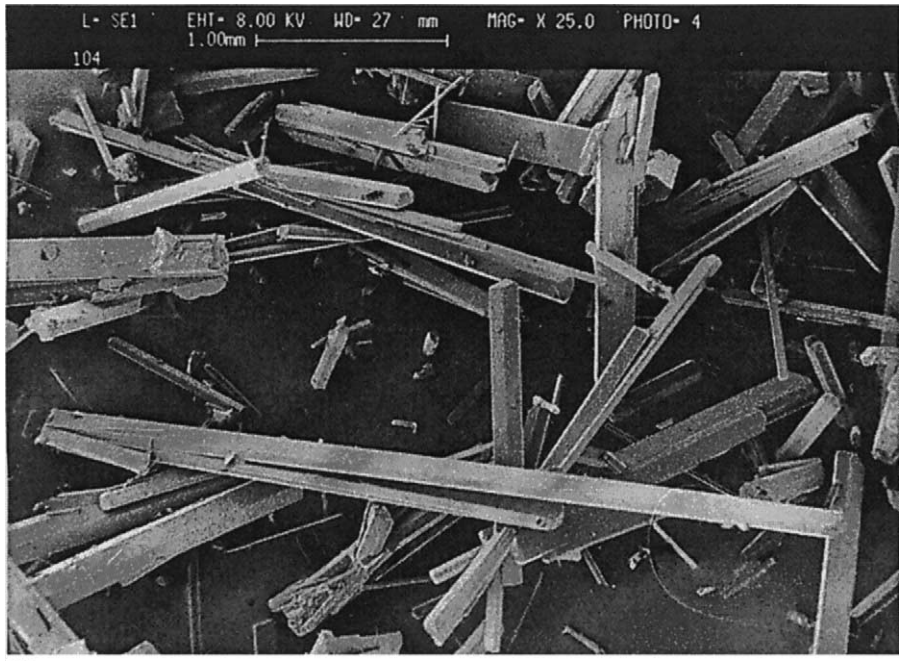


(b)

Fig. 1. Scanning electron micrographs of: (a) untreated phenytoin, phenytoin crystallized from alcohol by: (b) method I; (c) method II; (d) method III; (e) method IV.

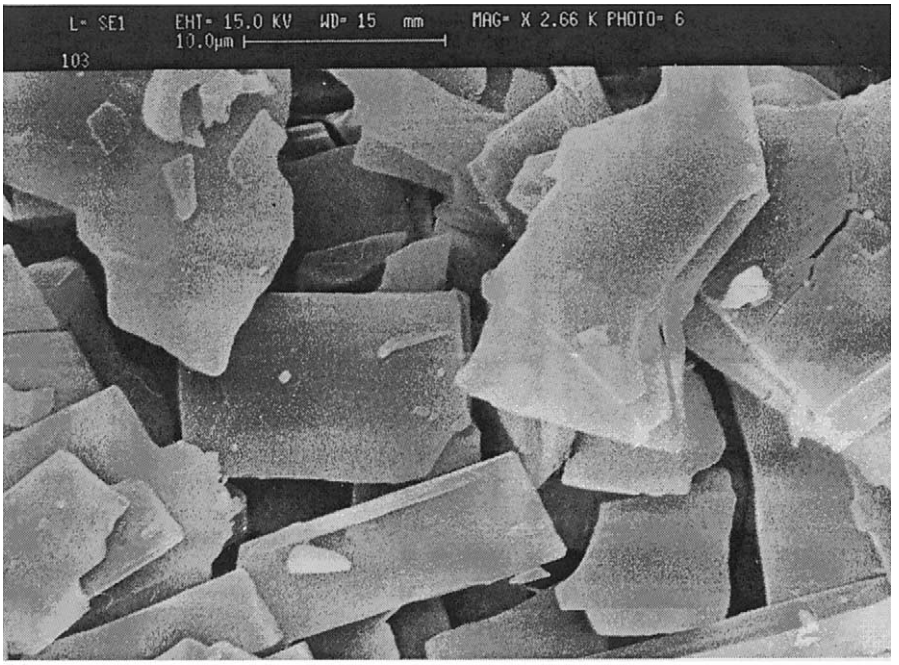


(c)



(d)

Fig. 1 (*Continued*)



(e)

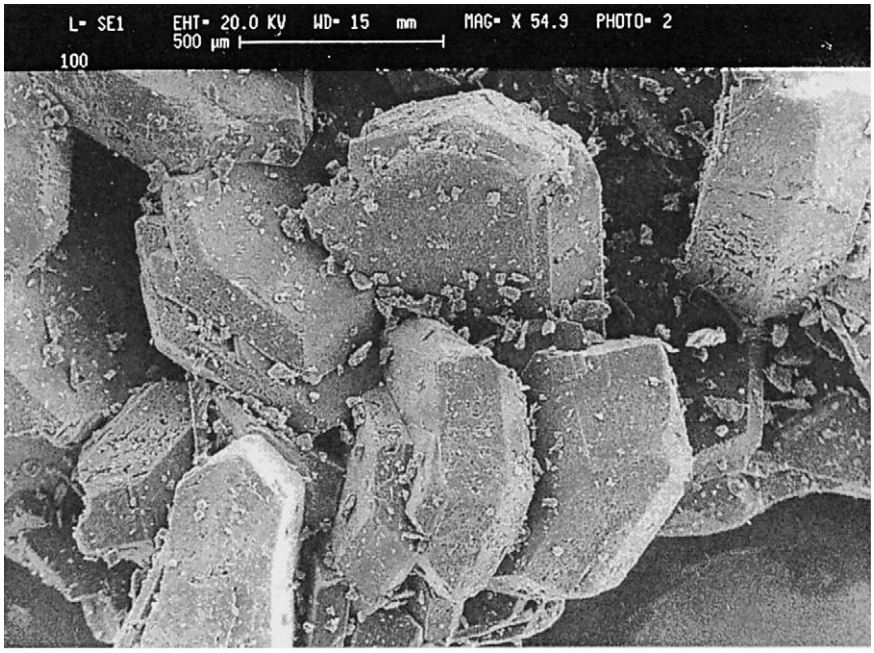
Fig. 1 (*Continued*)

The results also showed that the size of crystals produced from alcohol and acetone under various conditions, is significantly different from the size of untreated phenytoin and follows the order: method III > method II > method I (compare the magnification of the S.E.M. in Figs. 1 and 2). Therefore, it can be concluded that increasing the rate of cooling, decreased the crystal size, due to incomplete growth of a large number of small crystals. In other words, the lower temperature causes the higher supersaturation leading to the increased nucleation and many small crystals. Comparing SEM of crystals obtained from alcoholic and acetone solutions shows that the size and shape of crystals produced in these two solvents are significantly different. The variations in face dimensions or the appearance or disappearance of some faces could be the cause of the change in morphology of phenytoin crystals, obtained from different solvents (Khamskii, 1976).

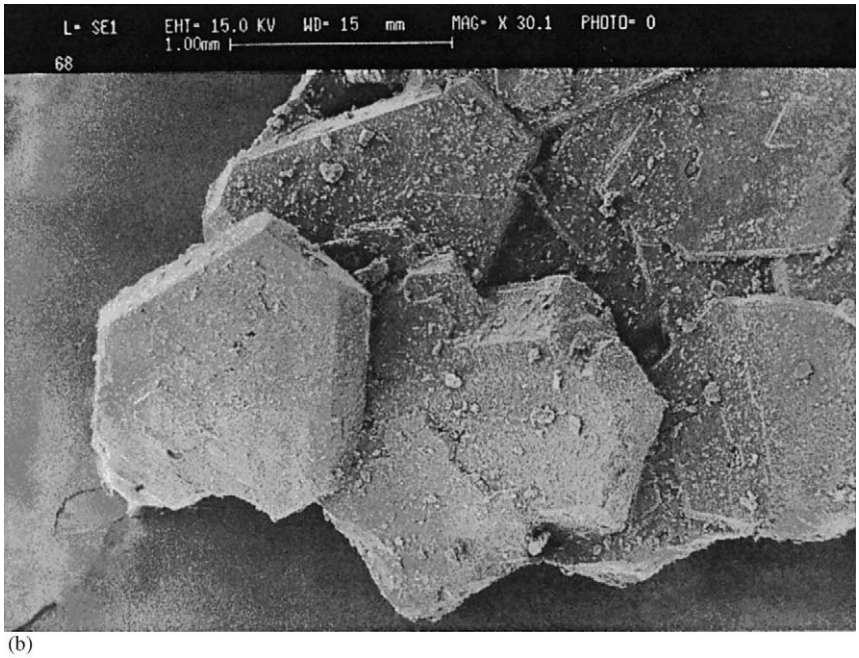
Under certain conditions of crystallization, the growth of one set of crystal faces may be retarded, or the other set of faces may be induced to grow faster. For instance, using different solvents as a crystallization medium with the same method (I, II or III) changes the pattern of crystal growth from rhombic (in acetone solution) to needle shape (in alcoholic solution). This can be explained by the interaction between the solvent molecules and different crystal faces which is believed to change the crystal morphology (Mullin, 1993). It is suggested that polar solvents were preferentially adsorbed by polar faces and non-polar solvents by non-polar faces (Berkovitch-Yellin, 1985). Both alcohol and acetone as crystallization medium interact through hydrogen bonds with phenytoin hydroxyl groups. Since the interaction of acetone is stronger than alcohol due to its relatively high polarizability, (π^* 0.71 for acetone and 0.54 for ethanol indicating the higher solubility of phenytoin in acetone rather than alcohol), the growth of crystals from that side is more inhibited and the crystal growth is continued from other sides

3.2. X-ray powder diffraction

To gain information on the physicochemical characteristics of the prepared crystals, X-ray

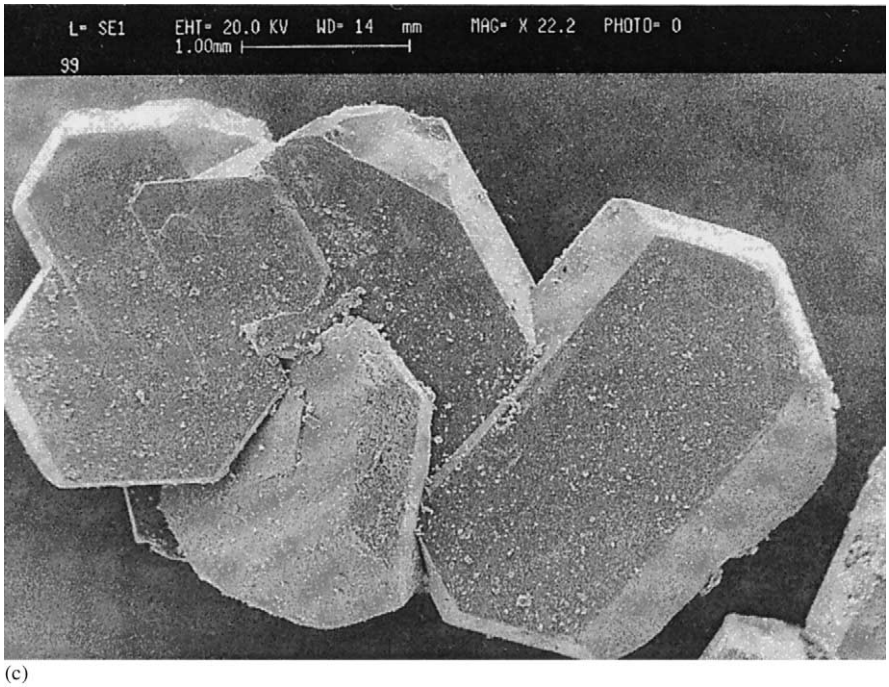


(a)

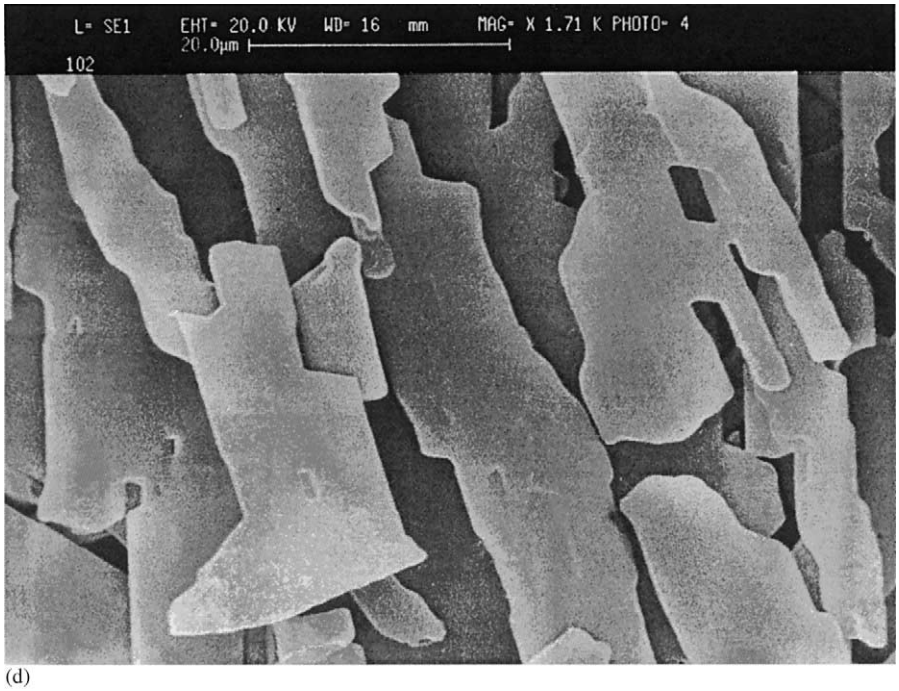


(b)

Fig. 2. Scanning electron micrographs of phenytoin crystallized from acetone by: (f) method I; (g) method II; (h) method III; (i) method IV.



(c)



(d)

Fig. 2 (*Continued*)

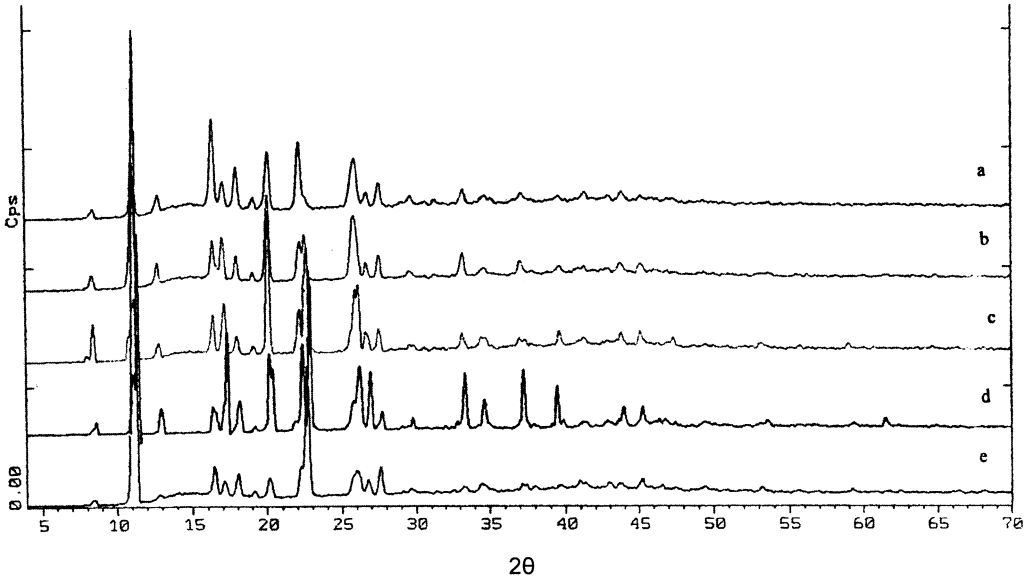


Fig. 3. X-ray powder diffraction patterns of untreated phenytoin and phenytoin crystallized from alcohol (legends are the same as mentioned in Fig. 1).

powder diffraction, FT-IR spectroscopic and thermoanalytical (DSC) measurements were conducted. The purpose of these studies was to evaluate possible polymorphic modification of phenytoin crystals.

XRD spectra for all phenytoin crystals are presented in Figs. 3 and 4. In the X-ray diffractogram of phenytoin powder, sharp peaks at a diffraction angle of 2θ 8.51, 11.27, 16.49, 17.19, 20.28, 22.78 are present which is in agreement with the literature (Franco et al., 2001). These sharp peaks are given in the diffragtograms of all the samples indicating no polymorphic modifications. In this study, there is not any significant differ-

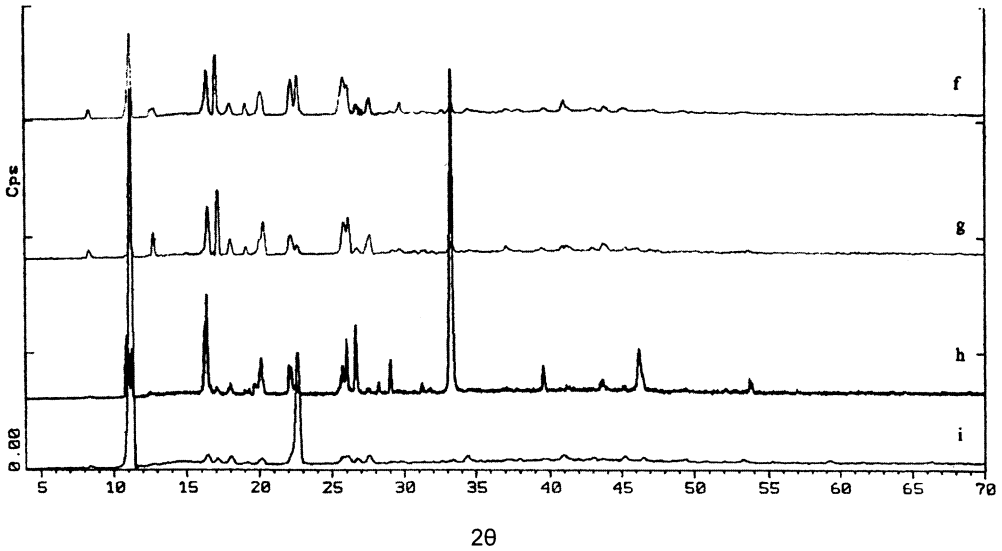


Fig. 4. X-ray powder diffraction patterns of phenytoin crystallized from acetone: (f) method I; (g) method II; (h) method III; (i) method IV.

ences in either the diffraction pattern or *d*-spacing values between XRD spectra of untreated and treated phenytoin samples, referring to the habit modification. On the other hand the intensity of peaks in all treated samples specially crystals made using methods III and IV, are higher than that of untreated phenytoin. This is probably due to the higher crystal perfection or different preferred orientations of the crystals in the sample holder because of their different crystal habits. Therefore the abundance of the planes exposed to the X-ray source would have been altered, producing the radiation in the relative intensities of the peak (Marshall and York, 1989).

3.3. Fourier transform infrared spectroscopy

The spectra of all samples were identical and the main absorption bands of phenytoin appeared in all of the spectra. This indicated that there were no differences between the internal structure and conformation of these samples and that the altered XRD spectra for these samples were not associated with changes at the molecular level.

3.4. Thermal analysis

DSC data for untreated and treated phenytoin crystals are shown in Table 1. It should be noted that the DSC thermograms of all treated samples were identical with that of untreated phenytoin. The DSC curve of untreated and recrystallized sample showed a single endothermic peak at about 296 °C corresponding to the melting of the drug. This is in good agreement with those data reported by Franco et al. (2001). Results from FT-IR spectroscopy, X-ray analysis and DSC taken together led to conclusion that only habit modifications were observed during recrystallization of phenytoin under various conditions of crystallization. The melting endotherms occurred in the range of 297.10–298.62 °C. According to the results, increasing the crystallization temperature from method I to method III, slightly altered the melting point, T_m, of the crystals, but reduced the enthalpy of fusion of the crystals. The stastistical ANOVA test showed that there was no difference between the melting points or enthalpies for different phenytoin crystals ($P > 0.05$). These little changes in DSC data may be an effect of crystal size.

3.5. Dissolution studies

The dissolution profiles of phenytoin recrystallized from alcohol and acetone solutions, are shown in Figs. 5 and 6, respectively. The dissolution profiles were also analyzed according to four release models namely Peppas, Hixon-Crowel, Higuchi and first order release kinetic model. It was found that the first order kinetic model produced the highest correlation coefficient among the other models. The slope and correlation coefficient of the models are listed in Table 2. According to the results, the dissolution rate of untreated sample is significantly faster than the

Table 1
DSC data of phenytoin crystals ($n = 3$)

Type of crystals		Fusion temperature (°C)	Onset temperature (°C)	Enthalpy of fusion (cal/g)
Untreated sample		297.10 ± 1.11	295.81 ± 1.23	40.57 ± 1.93
Treated samples using				
Method I:	Alcohol	297.59 ± 1.25	295.44 ± 1.39	44.39 ± 2.72
	Acetone	297.99 ± 1.08	295.97 ± 1.41	44.59 ± 2.02
Method II:	Alcohol	297.89 ± 1.42	296.05 ± 1.89	42.65 ± 2.34
	Acetone	298.56 ± 1.36	295.83 ± 2.05	44.22 ± 1.83
Method III:	Alcohol	298.23 ± 1.43	296.14 ± 1.62	41.80 ± 3.15
	Acetone	298.62 ± 1.17	296.27 ± 1.97	42.11 ± 1.79
Method IV:	Alcohol	297.91 ± 1.02	295.89 ± 1.24	41.28 ± 2.56
	Acetone	297.38 ± 1.49	296.29 ± 1.87	41.65 ± 2.58

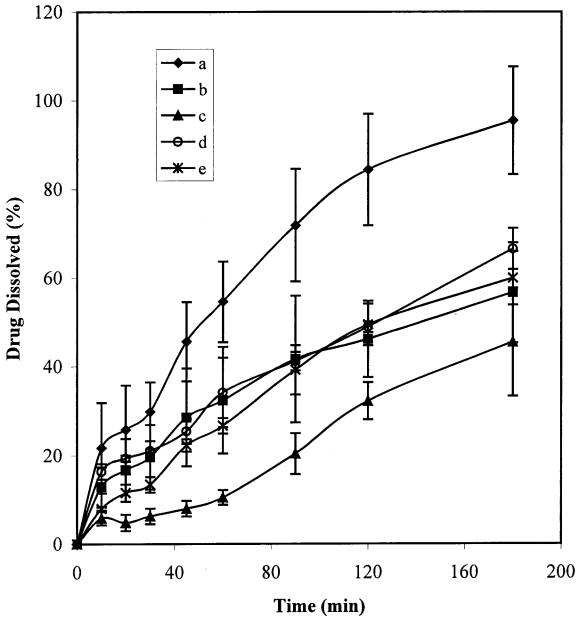


Fig. 5. The dissolution profiles of untreated phenytoin and phenytoin crystals obtained from alcohol (legends are the same as mentioned in Fig. 1).

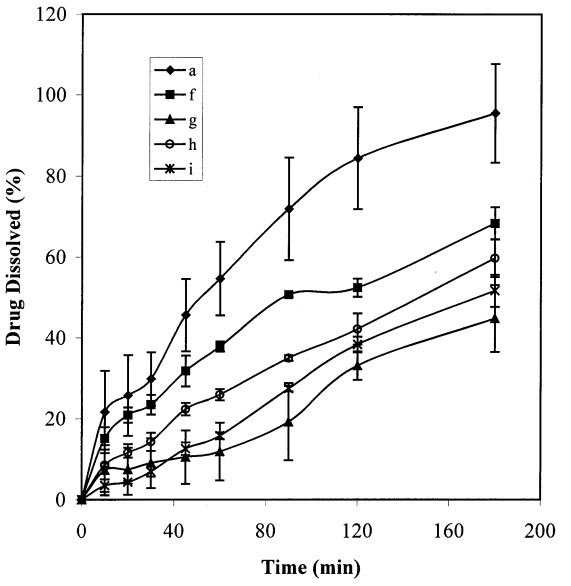


Fig. 6. The dissolution profiles of phenytoin crystals obtained from acetone: (f) method I; (g) method II; (h) method III; (i) method IV.

treated samples ($P < 0.05$). The dissolution rate of crystals obtained from both solvents using method I or II is identical and the rate of the latter is lower than others. It seems that the nature of recrystallization solvent does not affect the dissolution profiles ($P > 0.05$). The results also show that changes in cooling rate have significant effect on the dissolution rate of phenytoin samples. The difference in dissolution rate is often related to the surface area of various crystals with different shapes, however, the surface area of phenytoin crystals was not measured in this study.

Table 2
The values of slope (k) and correlation coefficient (r) of the first order kinetic model ($n = 3$)

Type of crystals		k (min^{-1})	r
Untreated sample		-0.0221 ± 0.0002	0.987
Treated samples using			
Method I:	Alcohol	-0.0049 ± 0.0010	0.979
	Acetone	-0.0048 ± 0.0013	0.975
Method II:	Alcohol	-0.0053 ± 0.0013	0.988
	Acetone	-0.0058 ± 0.0004	0.996
Method III:	Alcohol	-0.0064 ± 0.0007	0.992
	Acetone	-0.0039 ± 0.0014	0.983
Method IV:	Alcohol	-0.0052 ± 0.0001	0.995
	Acetone	-0.0046 ± 0.0001	0.994

3.6. Compaction studies

Table 3 shows the crushing strengths of tablets compressed at different compression pressures. Compression of untreated phenytoin crystals at all compaction pressures, produced weak compacts with low crushing strength. Thin plate like crystals, which were obtained using method IV, (watering-out technique), showed considerable improvement in the compactibility of the phenytoin crystals. This could be attributed to the lower tablet porosity or lower elastic recovery of the compacts made with phenytoin crystals obtained by method IV (Table 3). Tablets made from particles produced using method I, II and III also exhibited a slight improvement in their compaction properties.

It has been shown that the shape of a crystal is a complex characteristic, and its importance in relationship to powder properties is therefore difficult to assess. There are a limited number of studies in the pharmaceutical literature which have

Table 3
The effect compression pressure (MPa) on the hardness, porosity and elastic recovery of compacts obtained with various phenytoin crystals (the results are the mean and S.D. of six determinations)

Type of crystal	Hardness (N)			Porosity (%)			Elastic recovery (%)		
	12.5	25	37.5	12.5	25	37.5	12.5	25	37.5
Untreated phenytoin	8.2±1.0	11.2±3.2	15.9±2.5	21.9±1.5	18.1±0.90	15.6±2.2	7.1±0.5	6.9±0.4	6.0±0.9
Treated with alcohol:									
I	12.3±2.2	14.9±2.3	24.0±1.8	17.3±1.4	15.4±0.80	11.4±1.6	5.1±0.4	4.1±0.3	3.5±0.7
II	16.8±2.8	17.9±3.1	18.9±2.8	13.8±1.4	13.6±1.1	10.6±1.2	5.2±0.5	6.9±0.7	6.4±0.7
II	12.2±2.3	14.9±1.5	19.7±2.5	17.6±1.9	14.4±1.2	12.0±1.2	5.0±0.4	5.2±0.7	5.2±0.6
IV	17.3±2.4	28.2±3.1	34.3±2.2	11.5±0.8	5.5±0.7	5.0±1.1	1.5±0.3	1.0±0.3	0.9±0.5
Treated with acetone:									
I	13.6±2.5	16.1±2.1	17.3±2.1	17.4±1.9	14.2±1.4	14.1±2.0	6.8±0.7	6.4±0.6	5.9±0.9
II	14.3±2.6	15.0±2.4	16.3±1.8	18.1±2.0	13.1±0.9	13.4±1.5	7.0±0.9	4.5±0.5	5.2±0.8
II	14.3±1.9	16.1±2.8	16.3±2.5	18.3±1.7	13.0±1.6	12.1±0.9	5.5±0.5	4.5±1.0	4.9±0.5
IV	14.4±2.4	19.9±2.8	32.6±1.8	18.1±1.6	6.0±1.1	4.2±0.8	2.5±0.7	1.3±0.5	1.1±0.4

specifically discussed the relationship between particle shape and compact strength for a specific material. It has been previously shown that various phenytoin crystals undergo plastic deformation (low fragmentation) during compression (Bolourtchian, 2001). Compaction of the powders into tablets showed that for the materials which fragmented to a limited degree during compression, the particle shape affected the compact strength; i.e. a more irregular particle improved the compactibility (Alderborn and Nystrom, 1982a,b; Alderborn et al., 1988; Wong and Pilpel, 1990). However, for materials which fragments markedly during compression, the shape of the particles before compaction did not affect compact strength. Hence, the effect of particle shape on the compact bonding characteristics and, thus, the compact strength is dependent on the volume reduction properties of the material. For materials which fragments to a large extent, the physical structure of the formed compact is to a limited extent affected by variations in particle shape before compaction, provided that the particles can be described as the same particle size.

It is reasonable that with an increased particle irregularity, the number of possible interparticulate attraction zones in a compact, and consequently the compact strength, will increase, although the packing properties of the particles are similar. It is also possible that during the compression process, the particles can undergo an increased degree of deformation due to an increased particle irregularity, especially at edges and corners of the crystals. The consequence of the increased local particle deformation will be an increased bonding force of the attraction zones between compact particles and this in turn will reduce the porosity of the compacts (Table 3). These are the reasons for an increase in crushing strength of the compacts made from the phenytoin crystals obtained from method IV.

The compression studies showed that the crushing strength of tablets made from the crystals obtained by watering-out technique were sensitive to compression pressures. In other words, the crushing strengths of those tablets markedly increased as the compression pressure was increased from 12.5 to 37.5 MPa.

4. Conclusion

In conclusion, the crystallization medium has a major effect on phenytoin crystal habit modification. Crystallization of phenytoin in alcohol resulted in needle shape crystals whereas the crystals made in acetone solutions were rhombic. Using watering-out technique, produced thin plate crys-

tals, with higher compactibility, compared to untreated and other treated samples. Changing the crystallization temperature only altered the size of crystals.

Acknowledgements

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