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Dissolution properties and anticonvulsant activity of phenytoin-polyethylene glycol 6000 and -polyvinylpyrrolidone K-30 solid dispersions

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Abstract

Solid dispersions of phenytoin in polyethylene glycol 6000 and polyvinylpyrrolidone K-30 with different drug-to-carrier ratios were prepared by the solvent method with the aim of increasing dissolution rate and bioavailability of the drug. These new formulations were characterized in the solid state by FT-IR spectroscopy, X-ray powder diffraction, and differential scanning calorimetry. Drug solubility and dissolution rate are improved by these formulations, particularly with SDPEG 1/20 and SDPVP 1/20 systems. Storage was found to influence the stability of the solid dispersions. By maximal electroshock test, it was found that the intraperitoneal administration in mice of the SDPEG 1/20 and SDPVP 1/20 systems exhibited anticonvulsant activity similar to diphenylhydantoin sodium salt.

Keywords: Phenytoin; Solid dispersions; Polyethylene glycol 6000 and polyvinylpyrrolidone K-30; Dissolution properties; Anticonvulsant activity

1. Introduction

Phenytoin (diphenylhydantoin, DPH) is an antiepileptic agent extensively used for the treatment of generalized tonic clonic and grand mal epileptic seizures (Tunnicliff, 1996). Following oral administration, however, DPH exhibits slow rate of absorption and erratic bioavailability, these effects being probably due to its poor water solubility and insufficient dissolution rate (Arnold et al., 1970; Suzuki et al., 1970). To address these last issues, a number of methods have been attempted. In particular, solid dispersions of DPH with water-soluble carriers (i.e., polyethylene gly-

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col 6000 (PEG 6000) (Stavchansky and Gowan, 1984) polyvinylpyrrolidone–sodium deoxycholate (PVP-DC-Na) (Yakou et al., 1986)), complexation with natural cyclodextrins (Hsyu et al., 1984; Menard et al., 1988), and many water-soluble prodrugs (Varia and Stella, 1984; Varia et al., 1984; Scriba and Lambert, 1997) or lipid conjugates (Scriba et al., 1995) have been investigated. Among these various approaches, an attractive possibility is represented by the use of water-soluble polymers employing the solid dispersion technology (Chiou and Riegelman, 1971). This technique allows a particle size reduction of drug to nearly a molecular level. Once the system is exposed to aqueous media and the carrier is dissolved, the drug is released as very fine particles for quick dissolution and absorption (Serajuddin Abu, 1999). Solid dispersions of drugs are generally produced by two methods namely, the melting and the solvent methods, each of which had advantages and limitations (Serajuddin Abu, 1999; Leuner and Dressman, 2000).

It is worth noting that a solid dispersion of DPH with PEG 6000 at high drug-to-carrier ratio and employing the melting method has been previously studied (Stavchansky and Gowan, 1984). Similarly, solid dispersions of DPH with combinations of carriers (i.e., PVP-DC-Na) have already been prepared by the solvent method (Yakou et al., 1986), always employing a high drug-to-carrier ratio and high DC-Na content. Given that, (i) the higher the carrier level in solid dispersions, the higher the drug dissolution rate, (ii) DC-Na is a surface-active carrier which, as such influences greatly the corresponding solid dispersion behavior but presents drawbacks from in vivo safety profile (Yamamoto et al., 1996; Serajuddin Abu, 1999), (iii) manufacturing conditions might greatly influence the physicochemical properties of solid dispersions, it seemed of interest to study the behavior of solid dispersions characterized by the same carriers but at lower drug content and without the addition of any surface-active material. Thus, the aim of the present work was to investigate the solubility and dissolution rate of DPH-PEG 6000 and -polyvinylpyrrolidone (PVP) K-30 solid dispersions with a low drug level and prepared by the solvent method. Physicochemical characterization of these new formulations, based on FT-IR spectroscopy, X-ray powder diffraction, and differential scanning calorimetry was performed. Furthermore, since oral administration of DPH-PEG 6000 solid dispersion was previously demonstrated to be bioequivalent to a commercial prompt DPH sodium (NaDPH) formulation (Stavchansky and Gowan, 1984), an additional purpose of the present investigation was to evaluate the anticonvulsant activity of DPH-PEG 6000 or -PVP K-30 solid dispersions compared to that of NaDPH following a parenteral administration.

2. Materials and methods

2.1. Chemicals

DPH was purchased from Sigma Chemical Co. (USA). Tablets of Dintoina® containing NaDPH were purchased from a drugstore. Reagents used for the preparation of the buffers were of analytical grade. PEG 6000 and PVP K-30 were purchased from Fluka. Fresh deionized water from all glass apparatus was used in the preparation of all the solutions. High-performance liquid chromatography (HPLC) mobile phase was prepared from HPLC-grade methanol.

2.2. Apparatus

HPLC analyzes were performed using a Water Associates Model 600 pump equipped with a Water 990 variable wavelength UV detector, a Waters 712 WISP autosampler, and a 20 μl loop injection valve (U6K). For analysis, a reversed phase Simmetry (25 cm × 4.6 mm; 5 μm particles) column in conjunction with a precolumn module was eluted by using mixtures of methanol and deionized water 65:35. The flow rate of 0.8 ml min^{-1} was maintained. The column effluent was monitored continuously at 225 nm. Quantification of the compounds was carried out by measuring the peak areas in relation to those of standards chromatographed under the same conditions.

2.3. Preparation of solid dispersions of DPH/PEG 6000 and DPH/PVP K-30

Solid dispersions of DPH in PEG 6000 or PVP K-30 containing three different weight ratios (1:5, 1:10, 1:20) and denoted as SDPEG 1/5, 1/10, 1/20, SDPVP 1/5, 1/10, 1/20, respectively were prepared by the solvent method as follows. To a solution of DPH (10 mg) in ethanol 80° (25 ml) the appropriate amount of PEG 6000 or PVP K-30 was added. Next, the solvent was evaporated under reduced pressure at ~ 40 °C and the resulting residue, dried under vacuum for 3 h, was stored for at least overnight in a desiccator. No trace of ethanol was by ^{1}H-NMR spectroscopy in the case of SDPEG based formulations while the residual ethanol level was $\leqslant 1\%$ for SDPVP K-30 systems. The samples prior to be used for the subsequent analysis were pulverized using a mortar and pestle and the powders were passed through a 280 μm sieve.

Physical mixtures having the same weight ratios were prepared by thoroughly mixing in a mortar the appropriate amounts of DPH and PEG 6000 or PVP K-30. The resulting mixtures were sieved through a 280 μm sieve and denoted as PMPVP or PMPEG, respectively.

2.4. Fourier transform infrared spectroscopy

Fourier transform IR spectra were obtained on a Perkin–Elmer 1600 FT-IR spectrometer. Samples were prepared in KBr disks (2 mg sample in 200 mg KBr). The scanning range was 450–4000 cm^{-1} and the resolution was 1 cm^{-1}.

2.5. X-ray analysis

Powder X-ray diffraction patterns were recorded on a Philips PW 1800 powder X-ray diffractometer using Ni-filtered, CuKa radiation, a voltage of 45 kV and a current of 25 mA.

2.6. Differential scanning calorimetry

DSC curves were obtained by a Perkin–Elmer DSC 7, equipped with a thermal analysis automatic program.

Aliquots of about 5 mg of each sample were placed in an aluminium pan of 50 μl capacity and 0.1 mm thickness, press-sealed with a not perforated aluminium cover of 0.1 mm thickness. An empty pan sealed in the same way was used as reference. Thermograms were measured by heating the sample from 30 and 330 °C at a rate of 10 °C min^{-1}, under a nitrogen flow of 20 cm^3 min^{-1}. Indium was used as standard for calibrating the temperature. Reproducibility was checked running the sample in triplicate.

2.7. Determination of solubility

Solubility studies were carried out by adding an excess of DPH to 2 ml of solutions of PEG 6000 or PVP K-30 (0–30% w/v) in 0.05 M potassium phosphate buffer pH 6.0 in screw-capped test tubes. The mixtures were vortexed for 10 min and kept in a bath at appropriate temperature under magnetic stirring for 36 h. Then, an aliquot of each mixture was transferred to a 10 ml glass syringe preheated at the appropriate temperature and filtered through a 0.22 μm membrane filter (Millipore®, cellulose acetate) in thermostated test tubes. About 0.5 ml of the clear filtrate after appropriate dilution, were allowed to stand in bath at appropriate temperature until analyzed by HPLC. The injection volume was 20 μl. All of the manipulations were made without the removal of the test tubes from the water bath, using thermostated pipettes, syringes.

2.8. Dissolution studies

Dissolution experiments were carried out in triplicate with an Erweka DT dissolution test in 0.05 M potassium phosphate buffer pH 6 at 37 °C using the paddle method at a rotation speed of 60 rpm. Powdered samples of each preparation equivalent to 10 mg of DPH were added to the dissolution medium (400 ml of 0.05 M potassium phosphate buffer pH 6 at 37 °C). At appropriate time intervals, 2 ml of the mixture were withdrawn, filtered through a 0.22 μm membrane filter (Millipore®, cellulose acetate) in

thermostated test tubes. Samples were withdrawn from a zone roughly midway between the surface of dissolution medium and the top of the rotating blade. The initial volume was maintained by adding 2 ml of dissolution medium. About 1 ml of the clear filtrate after appropriate dilution was allowed to stand in bath at 37 °C until analyzed by HPLC. Samples were analyzed directly or diluted when needed with mobile phase. The injection volume was 20 μl. The results were computed with a standard calibration curve of the drug.

2.9. Pharmacological studies

Male CD-1 mice with body masses of 30 g (Charles Rives, Como Italy) were used. Animals were housed in groups of 15–20 and kept in a temperature (23 ± 2 °C), humidity (65%) in a controlled room on 12 h light/dark cycle (light on from 8:00 to 20:00). Food and water were freely available, and the animals were acclimatized for > 7 days before use. Animal care and handling throughout the experimental procedure were in accordance with the European Community Council Directive of 24 November 1986 (86/609/EEC).

SDPEG 1/20 and SDPVP 1/20 were suspended in distilled water with 0.5% (w/v) of Tween 80, while powdered tablets of NaDPH were used in water solution containing, for a sake of homogeneous comparison, the same amount of surfactant. Drugs were administered intraperitoneally at the equivalent dose of 12 mg Kg^{-1} in a volume of 0.1 ml per 10 g of body mass. Drugs were administered to groups of six animals 30 min before induction of maximal electroshock (MES). Control mice received an equivalent volume of vehicle or vehicle and carrier (PEG 6000, PVP K-30). Mice received an electroshock of 55 mA for 0.2 s with a frequency pulse/s of 50 Hz having a pulse-width duration of 0.4 ms, through intraaureal clip electrodes, sufficient to produce a hindlimb tonic extensor response in at least 67% of control animals. The complete suppression of the hindlimb extensor component of seizures was taken as evidence of anticonvulsant activity.

3. Results and discussion

To gain information on the physicochemical characteristics of the prepared solid dispersions, FT-IR spectroscopic, X-ray powder diffraction, and thermoanalytical (DSC) measurements were conducted. The purpose of these studies was to evaluate possible interaction between DPH and carriers in the solid state as well as to estimate the physical stability of these solid dispersions after storage of 2 years at room temperature in dessicator. The FT-IR spectra of DPH and its solid dispersions SDPEG 1/20 and SDPVP 1/20 are shown in Fig. 1. The spectrum of DPH is characterized by the presence of three strong absorption bands at 1716, 1738, and 1772 cm^{-1}. Furthermore, in the spectra of PEG-based solid dispersions two strong absorption bands at about 1739 and 1777 cm^{-1} are present, whereas in the spectra of PVP-based solid dispersions there is a large absorption band at 1655 cm^{-1}. These spectral features may suggest a chemical interaction between DPH and carriers. Furthermore, significant differences of absorptions were observed between the FT-IR spectra of freshly prepared SDPEG 1/20 and SDPVP 1/20 and those of the corresponding solid dispersions after 2 years of storage showed some differences of absorptions.

Fig. 2 shows the X-ray diffraction patterns of DPH, SDPEG 1/20 and SDPVP 1/20 and corresponding physical mixtures. In the X-ray diffractogram of DPH powder, sharp peaks at a diffraction angle of 2ϑ 8.51, 11.27, 12.89, 16.49, 17.19, 18.10, 20.28, 22.31, 22.78 and 25.76° are present, and it suggests that the examined powder is a crystalline material. PEG 6000 produced peaks at 2ϑ 19.08, 23.26, 25.98 and 26.85°. Peaks characteristic of the drug were observed in the X-ray diffractograms of SDPEG 1/20 and PM-PEG 1/20 systems. These results indicate that SDPEG 1/20 is roughly crystalline as the corresponding physical mixture. As for the PVP based systems, peaks characteristic of DPH are detectable in the X-ray diffractogram of the corresponding 1/20 physical mixture, whereas none of these characteristic peaks occurs in the diffractogram of SDPVP 1/20 which appears similar to that of pure PVP. Therefore, this

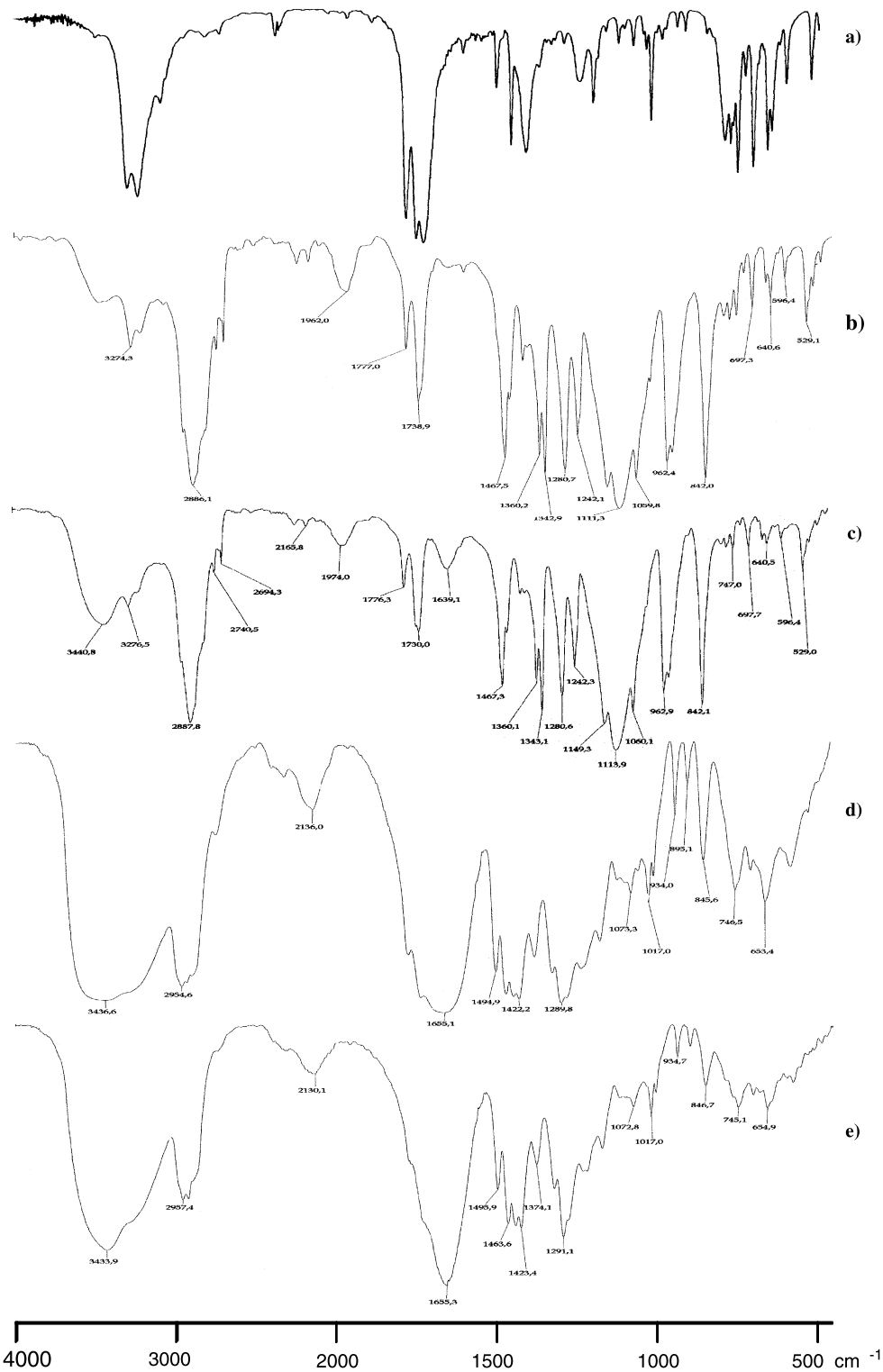

Fig. 1. (a) FT-IR spectra of DPH; (b) SDPEG 1/20 freshly prepared; (c) SDPEG 1/20 after 2 years of storage; (d) SDPVP 1/20 freshly prepared and (e) SDPVP 1/20 after 2 years of storage.

solid dispersion is an amorphous material. Furthermore, X-ray diffractograms of the 2 years aged SDPEG 1/20 and SDPVP 1/20 solid dispersions showed the presence of diffraction peaks characteristic of DPH. It may be due to crystallization of the drug on aging (Serajuddin Abu, 1999).

The thermograms of DPH and SDPEG 1/20, SDPVP 1/20 solid dispersions over the temperature range from 100–310 °C are shown in Fig. 3. The DSC curve of pure DPH showed a single endothermic peak at about 296 °C corresponding to the melting of the drug. In the DSC curve of SDPEG 1/20, the peak intensity at 296 °C nota-

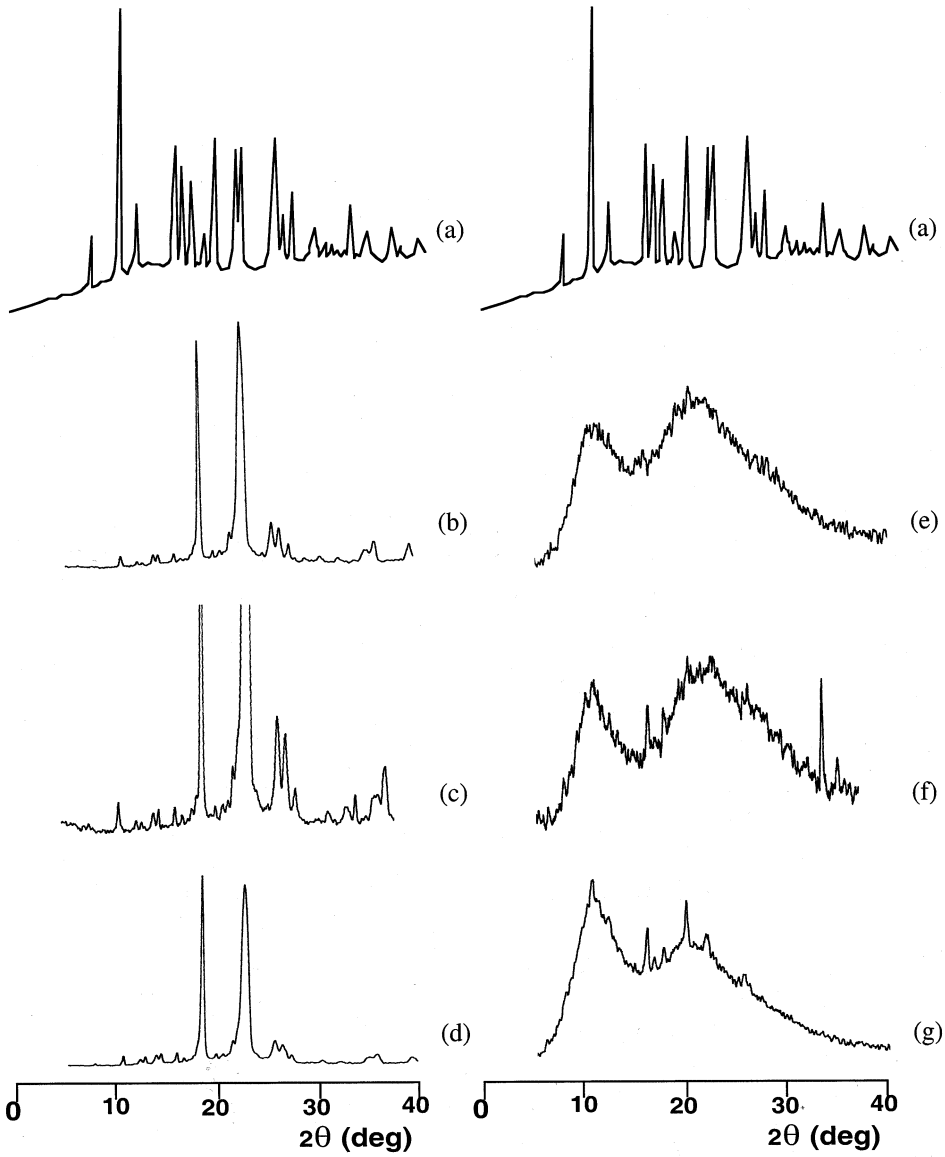

Fig. 2. (a) X-ray diffraction patterns of DPH; (b) SDPEG 1/20 freshly prepared; (c) SDPEG 1/20 after 2 years of storage; (d) PMPEG 1/20 freshly prepared; (e) SDPVP 1/20 freshly prepared; (f) SDPVP 1/20 after 2 years of storage and (g) PMPVP 1/20 freshly prepared.

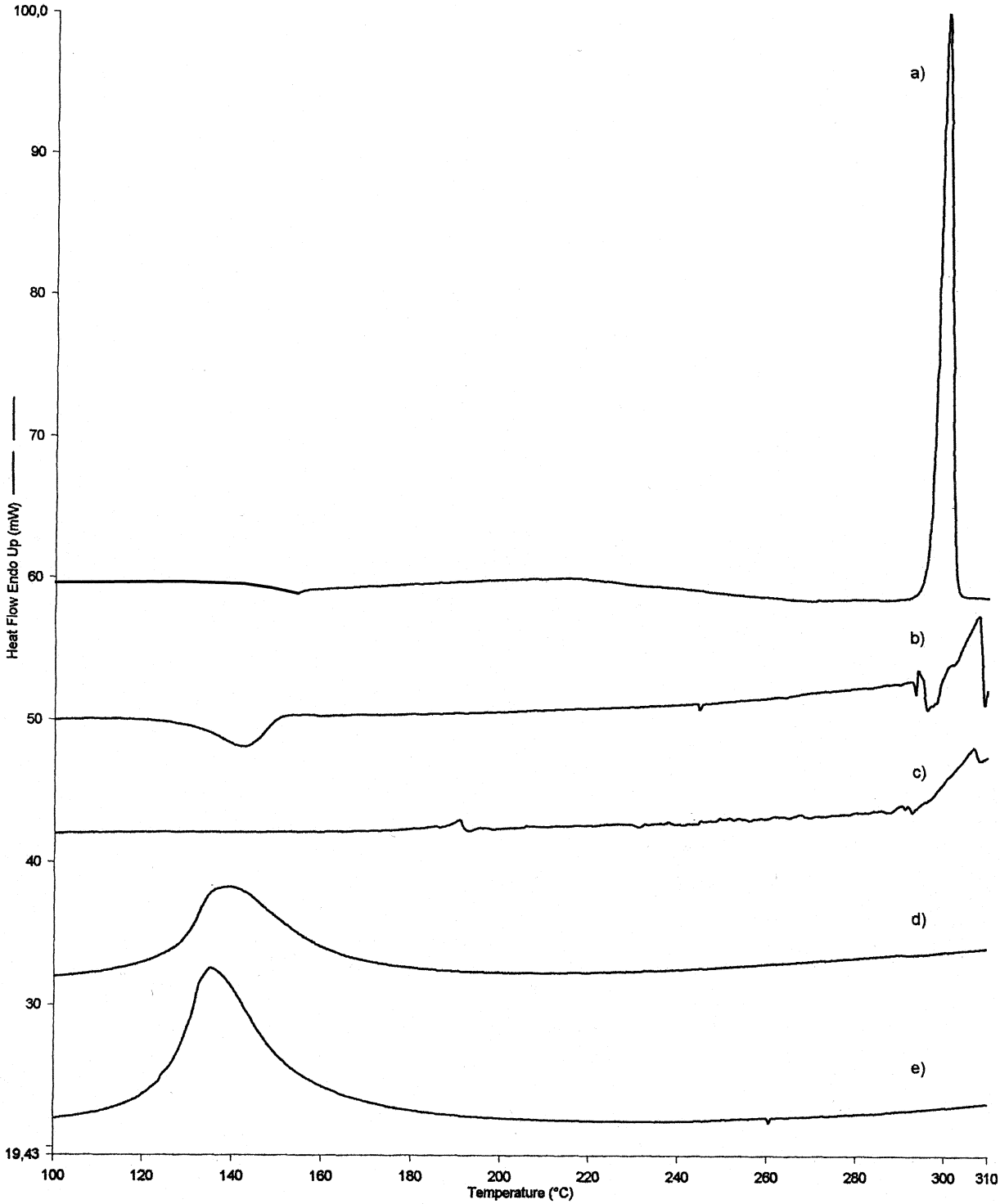

Fig. 3. (a) DSC spectra of DPH; (b) SDPEG 1/20 freshly prepared (c) SDPEG 1/20 after 2 years of storage; (d) SDPVP 1/20 freshly prepared and (e) SDPVP 1/20 after 2 years of storage.

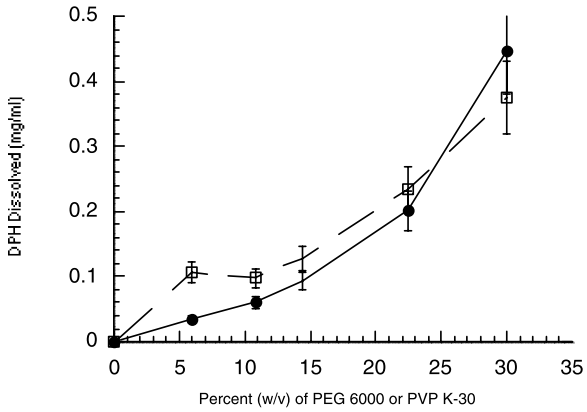

Fig. 4. Phase-solubility diagram of DPH in the presence of PEG 6000 (●) or PVP K-30 (□). Data are the mean of three determinations.

bly decreased. Whereas in the DSC thermogram of SDPVP 1/20 the melting endotherm peak of DPH disappeared, and a single endothermic peak at about 140 °C is present. The DSC curve of the 2 years aged SDPVP 1/20 showed no significant changes, whereas marked differences were observed for the similarly storaged SDPEG 1/20 system. Results from FT-IR spectroscopy, X-ray analysis and DSC taken together led to conclusion that SDPEG 1/20, SDPVP 1/20 solid dispersions are not stable on aging.

Solubility experiments showed that the concentration of DPH in 0.05 M potassium phosphate buffer pH 6 at 37 °C increased as a function of PEG 6000 or PVP K-30 concentration. According to the phase-solubility diagram classification introduced by Higuchi and Connors (1965), the solubility diagrams of DPH and the hydrophilic polymers (i.e., PEG 6000 or PVP K-30) at 37 °C correspond to A_P-type profiles (Fig. 4). The obtained results indicate that 30% w/v SDPEG 1/20 and SDPVP 1/20 solutions provided for a 0.45 and 0.38 mg ml^{-1} content of DPH corresponding to a 22.5- and 19-fold solubility increase of DPH, respectively.

The results of dissolution studies of DPH solid dispersions and pure drug are shown in Figs. 5 and 6. Inspection of the reported data reveals that the dissolution rate of pure DPH is very slow, with about 30% of the drug being dissolved after

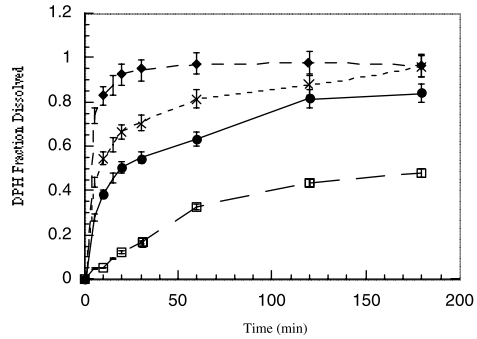

Fig. 5. Dissolution profiles of DPH alone (□) and SDPEG 1/5 (●), SDPEG 1/10 (×), and SDPEG 1/20 (◆). Data are the mean of three determinations.

1 h. The Q_{10}, Q_{30} and Q_{60} values (Anguiano-Igea et al., 1996) (i.e., percent of dissolved DPH at 10, 30 and 60 min) were 5.2, 16.6, and 32.3% for the pure drug. The dissolution rates of solid dispersions were remarkably enhanced compared to that of the drug alone. Moreover, the dissolution of solid dispersions with a drug-to-carrier ratio of 1:20 (i.e., SDPEG 1/20 and SDPVP 1/20) was the highest observed. The corresponding Q_{10}, Q_{30} and Q_{60} values, indeed, were 82.8, 94.4 and 97.2% for SDPEG 1/20 and 75.1, 79.3 and 78.6% for SDPVP 1/20, respectively (Anguiano-Igea et al., 1996). Such dissolution studies confirmed previous observations that the dissolution rate is dependent on drug concentration in the solid dispersion. The fraction dissolved of the SDPEG 1/20 system was somewhat higher than the corresponding SDPVP 1/20 which is an amorphous

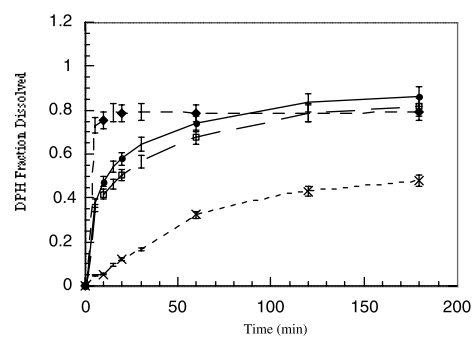

Fig. 6. Dissolution profiles of DPH alone (×) and SDPVP 1/5 (●), SDPVP 1/10 (□) and SDPVP 1/20 (◆). Data are the mean of three determinations.

Table 1
The β and τ parameters of Weibull

Sample	Weibull β	Weibull τ (min)
SDPEG 1/5	0.48 ($r^2 = 0.989$)	60
SDPEG 1/10	0.44 ($r^2 = 0.985$)	15
SDPEG 1/20	0.44 ($r^2 = 0.988$)	<15
SDPVP 1/5	0.40 ($r^2 = 0.997$)	>20
SDPVP 1/10	0.40 ($r^2 = 0.995$)	>30
SDPVP 1/20	[a]	<5
DPH	0.81 ($r^2 = 0.970$)	>180

[a] No satisfactory linearization was obtained.

material. This is not surprising, as it has been demonstrated in other studies that X-ray allows a rough estimation of amorphicity of solid dispersion but no conclusion can be drawn concerning the dissolution performance (Ohm, 2000).

Several mechanisms have been proposed to account for the increase in the dissolution kinetic of drugs from solid dispersions. These mechanisms include the carrier controlled dissolution (Corrigan et al., 1979; Dubois and Ford, 1985; Craig and Newton, 1992), the continuous drug layer formation (Dubois and Ford, 1985) and that involving the release of intact particles with dissolution occurring over a large surface area (Saers Sjökvist and Craig, 1992). The latter mechanism has been suggested to be important at low drug levels. It is also clear that a modification of the surface properties and hence a reduction of the contact angle value improves the wettability of the powder and it should lead to an increase of dissolution rate.

The dissolution profiles were also analyzed according to non-linear models using the MSFIT computer program (Lu et al., 1996). Five release models are implemented in the program: Baker-Lonsdale, Peppas, Hixon-Crowell, Higuchi, and first order release kinetic models. It was found that all models failed to fit each individual dissolution profile, both drug alone and solid dispersions. Conversely, with the exception of SDPVP 1/20, the release profiles were satisfactory linearized by using the Weibull function (Langenbucher, 1976). The Weibull shape parameter β, whose value characterizes exponential ($\beta = 1$, first order kinetic), sigmoid ($\beta > 1$) or parabolic ($\beta <$ 1) curves, resulted ~ 0.40 (Table 1). Furthermore, the Weibull parameter τ indicating the time required to dissolve 63.2% of the material resulted shorter than 15 or 5 min for SDPEG 1/20 and SDPVP 1/20, respectively, indicating high release rates. For the free drug, the β and τ values were 0.81 and > 180 min, respectively.

In an attempt to account for the good dissolution performance of the PEG- and PVP-based formulations, we used Hildebrand solubility parameters to estimate the miscibility/compatibility between drug and carrier. These parameters have recently been proposed as predictors of drug-carrier miscibility/compatibility (Suzuki and Sunada, 1998; Greenhalgh et al., 1999). Table 2 shows the solubility parameters of both DPH and polymers estimated by the group contribution methods of Fedors (1974) and Van Krevelen/Hoftyzer (Breitkreutz, 1998). According to literature suggestions (Greenhalgh et al., 1999), it may be argued that a good miscibility/compatibility between DPH and the carriers occurs because the calculated differences in drug/carrier solubility parameters ($\Delta\delta$) are below 7. It could account for the good performance showed by the prepared formulations.

Finally, to evaluate the pharmacological efficacy after parenteral (intraperitoneal) administration of the formulations characterized by better dissolution profiles (i.e., SDPEG 1/20 and SDPVP 1/20), we investigated their activity in protecting mice against seizures induced by MES test. The anticonvulsant activities of these solid dispersions were compared with those of NaDPH, PEG 6000 and PVP K-30. Number of animals protected vs

Table 2
Calculated Hildebrand solubility parameters for DPH and carriers

Substance	δ (MPa$^{1/2}$)	$\Delta\delta$
DPH	24.99[a]	–
PEG 6000	19.8[b]	5.19
PVP K-30	25[c] or 22.5[b]	0.1 or 2.49

[a] Breitkreutz (1998).
[b] Greenhalgh et al. (1999).
[c] Suzuki and Sunada (1998).

Table 3
Evaluation of the anticonvulsant effect in mice of DPH/PEG 6000 and DPH/PVP K-30 solid dispersions

DPH formulations	Number of animals protected vs total number of animals tested (% protection)
Controls	0/6 (0)
PEG 6000	0/6 (0)
PVP	0/6 (0)
DPH sodium	6/6 (100)
SDPEG 1/20	5/6 (83)
SDPVP 1/20	6/6 (100)

total number of animals tested as well as percent of protection were recorded and the results are summarized in Table 3. Data indicate that PEG 6000 and PVP K-30, as such did not protect the animals from convulsions, whereas SDPEG 1/20 resulted roughly active as SDPVP 1/20 and NaDPH. Therefore, these intraperitoneally administered solid dispersions appear to be advantageous for obtaining a formulation potent as NaDPH. In this regard, it may be of interest to note that the NaDPH formulation currently used for parenteral use exhibits a serious risk of DPH precipitation at the injection site, because formation of the corresponding insoluble free acid in physiological media ($pH \leqslant 8$) occurs (Varia et al., 1984; Scriba and Lambert, 1997). It should not occur when DPH-PEG 6000 and DPH-PVP K-30 systems are used.

In conclusion, solid dispersions of DPH with PEG 6000 and PVP K-30 prepared by the solvent method at low drug level and without the addition of any surface-active material were found to be more effective than that at high drug/carrier ratio, providing a remarkable increase in the apparent solubility and dissolution rate of DPH as free acid. Results from FT-IR spectroscopy, X-ray analysis and DSC led to conclusion that SDPEG 1/20, SDPVP 1/20 solid dispersions are not stable on aging. The SDPEG 1/20 and SDPVP 1/20 systems intraperitoneally administered to mice exhibit anticonvulsant activity in the MES test practically equal to NaDPH. Therefore, these systems appear to be advantageous for obtaining a formulation of DPH potent as NaDPH.

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