International Journal of Pharmaceutics, 35 (1987) 7–12
Elsevier

IJP 01131

Dissolution rates of partially water-soluble drugs from solid dispersion systems. II. Phenytoin

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(Received 8 April 1986)
(Accepted 23 June 1986)

Key words: Phenytoin; Dissolution; Solid dispersion system

Summary

The dissolution behaviour in water of phenytoin in solid dispersions with urea, PEG and PVP have been studied in comparison with the corresponding physical mixtures and pure phenytoin. The results revealed a marked increase of dissolution rate and solubility of phenytoin contained in solid dispersion. An X-ray diffraction technique was employed to investigate the nature of the studied forms. Phenytoin was stable and did not decompose during preparation of the dispersion systems or during direct compression of the tablets. Dissolution rate was generally unchanged with age for most studied tablets.

Introduction

Phenytoin is the drug of choice for epileptic grand mal therapy. The main disadvantage of phenytoin administration to patients results from marked differences in biological half-lives among individuals as well as incomplete and irregular absorption after oral administration (Yamamoto et al., 1976) although therapeutic levels can be maintained after intramuscular infection (Perier et al., 1976). Attempts have therefore been made to modify the physical properties of phenytoin, and success has been achieved by the formation of solid dispersion systems (Bogdanova et al., 1981; Chiou, 1971: Ford and Rubinstein, 1978; Stavchansky and Gowan, 1984).

The aim of this present study was to evaluate the pharmaceutical availability of phenytoin in solid dispersion systems with selected carriers.

Experimental

Materials

Materials used: phenytoin [1], urea [2], polyethylenglycol (PEG) 6000 [3], polyvinylpyrrolidone (PVP) [4].

Procedure

Preparation of the solid dispersions. The studied samples included the solid dispersion or the physical mixture of 10% phenytoin and 90% carrier.

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The solid dispersions with PEG and urea were prepared by the fusion method, with PVP by the solvent method.

Tablet manufacture. Three kinds of tablets were prepared: formulation A containing drug alone; formulation B containing a physical mixture with the carrier; and formulation C containing a solid dispersion.

The composition of formulation B and C for 100 tablets was the following:

Drug	1.0 g
Carrier	9.0 g
Starch	0.7 g
Lactose	0.3 g

In formulation A, sodium chloride was used as the carrier. All tablets were prepared using direct-compression method. Each tablet was of 6 mm diameter and weight 0.110 g. The drug content and disintegration time was determined (Table 1).

Solubility studies. An excess amount of phenytoin (3–500 mg) was placed in 20 ml ampoules containing 15 ml of water. The content of each ampoule was equilibrated by shaking for 24 h at 37°C in a thermostatically controlled water bath. The suspensions were then filtered and the filtrate was analyzed for amount of dissolved drug (Figs. 1, 2).

Dissolution studies. The dissolution rate at 37°C phenytoin from the powdered samples and tablets was determined using the flow-through method (see Jachowicz 1986a). An equivalent of 100 mg of phenytoin or 10 tablets was placed in the vessel with two glass sinters. The flow rate of the solution was 40 ml per min. Samples were taken at different time intervals, suitably diluted and assayed for phenytoin content (Figs. 3, 4).

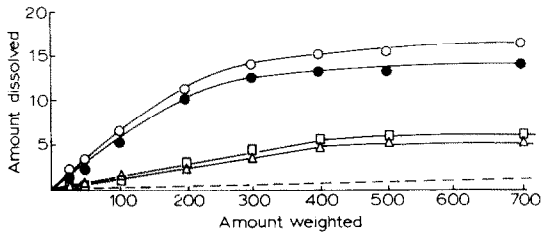

Fig. 1. Solubility of phenytoin from solid dispersions in water at 37°C. – – –, pure phenytoin; △———△, PEG 6000; □———□, urea; ●———●, PVP 160000; ○———○, PVP 25000.

Assay procedure. A spectrophotometrical method of assay for phenytoin was chosen (Johansen and Wiese, 1970); it was measured at $\lambda = 232$ nm using a Unicam SP 500 spectrophotometer.

Stability studies. A TLC method was used to study the chemical stability of phenytoin in solid dispersions. The solvent systems were: (1) chloro-

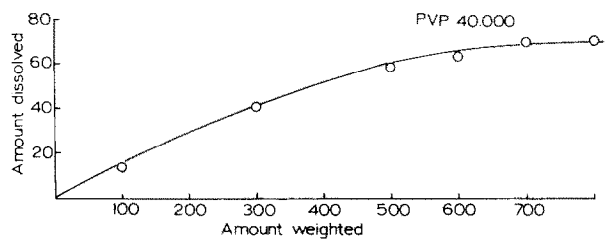

Fig. 2. Solubility of phenytoin from solid dispersion in water at 37°C.

TABLE 1

Phenytoin content and disintegration time of tablets after preparation (1) and 2 years storage at 20°C (2)

Formulation	Carrier	The content of phenytoin (mg)		The disintegration time (min)	
		1	2	1	2
A	none	10.00	9.90	4.0	4.5
B	PEG 6000	10.05	9.85	5.5	6.0
C	PEG 6000	10.10	9.90	6.5	7.0
B	PVP 40000	9.90	9.70	7.0	7.5
C	PVP 40000	10.10	9.80	8.0	10.0
B	Urea	9.80	9.40	5.5	6.0
C	Urea	10.10	9.80	6.0	7.0

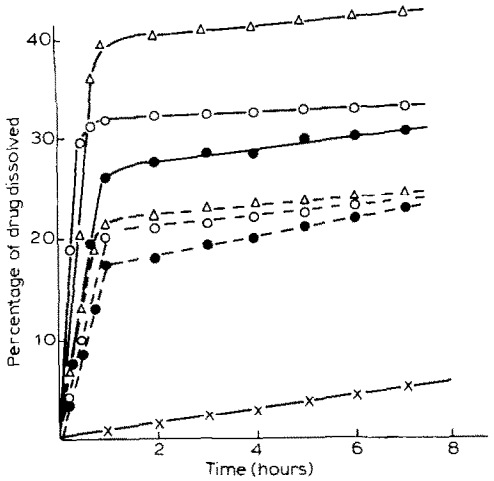

Fig. 3. Dissolution rates of phenytoin from physical mixtures (Ph.M.) and solid dispersions (S.D.). ●— — —●, phenytoin–PVP 160 000 (Ph.M.); ●———●, phenytoin–PVP 160000 (S.D.); ○— — —○, phenytoin–PVP 25000 (Ph.M.); ○——— ○, phenytoin–PVP 25 000 (S.D.); △— — —△, phenytoin –PVP 40000 (Ph.M.); △———△, phenytoin–PVP 40000 (S.D.); ×——— ×, pure phenytoin.

form–acetone (9 : 1); (2) benzene–ether (1 : 1); (3) acetone-butanol–25% solution of ammonia (45 : 45 : 10). Phenytoin was detected after spraying with 1% solution of mercuric nitrate.

X-Ray diffraction studies. X-Ray diffraction spectra were obtained using difractometer Dron-2 and Cu-Kα radiation. The rate of counting was 4000 pulses per second. All diffraction spectra were 2°/min in terms of a 2θ angle. The samples studied included the pure phenytoin, carriers and their physical mixtures and solid dispersions (Figs. 5–7).

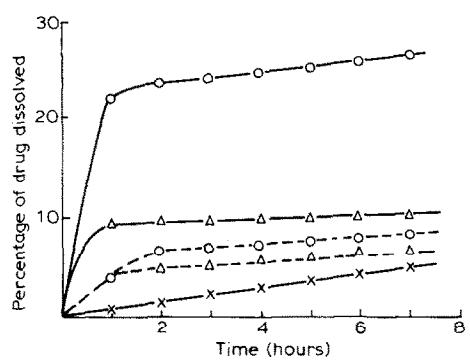

Fig. 4. Dissolution rates of phenytoin from physical mixtures (Ph.M.) and solid dispersions (S.D.). △— — —△, phenytoin–urea (Ph.M.); △———△, phenytoin–urea (S.D.); ○— — —○, phenytoin–PEG 6000 (Ph.M.); ○——— ○, phenytoin–PEG 6000 (S.D.); ×——— ×, pure phenytoin.

Results and Discussion

The results of the studies confirmed the assumption of higher solubility and dissolution rate of phenytoin from solid dispersions. In all cases the solid dispersion had a greater dissolution rate than that of the corresponding physical mixture. Results showed that differences in dissolution rates from solid dispersions containing 10% phenytoin resulted from the nature and the molecular weight of carriers. Among the studied carriers, PVP gave the best results; for example, after 7 h of dissolution, 42.46% phenytoin was dissolved from solid dispersion with PVP 40 000, and 33.1% and 30.5% with PVP 25 000 and PVP 160 000, respectively. PVP 25 000 solid dispersion showed the fastest dissolution rate at the initial time period while after 30 min this process was slower as compared to solid dispersion with PVP 40 000 (Fig. 3). There were no significant differences in the dissolution behaviour of phenytoin from physical mixtures with all types of PVP used as carriers.

Similar studies with PEG 6000 indicated that after 7 h 28% of phenytoin dissolved from the solid dispersion and 8.30% from the physical mixture. The results for urea were 10.60% and 6.90%, respectively (Fig. 4). It was also seen that solid dispersions exhibited a higher dissolution rate than the drug alone independent of the solubilizing effect of the carrier.

Phenytoin is practically insoluble in water. Therefore it seemed interesting to investigate the solubility of phenytoin after formulation into solid dispersion systems. Results indicated that solubility of phenytoin in water was approximately 1 : 3000 from solid dispersions with PEG 6000. 1 : 2500 with urea, 1 : 1100 with PVP 160 000, 1 : 930 with PVP 25 000 and 1 : 200 with PVP 40 000, while the solubility of phenytoin alone was 1 : 31 000 (Figs. 1, 2). It is evident that the solubility of phenytoin increases when solid dispersion are formed. These results varied surprisingly and

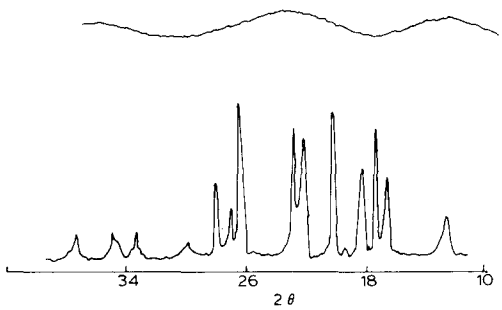

Fig. 5. X-Ray diffraction spectra of pure phenytoin (bottom) and solid dispersion phenytoin-PVP 40000 (top).

there were big differences in solubility of phenytoin according to the molecular mass of PVP.

The diffraction method was helpful in explaining this problem. The absence of major phenytoin and PVP diffraction peaks indicated that an amorphous form existed only in solid dispersion with PVP 40000. A halo was observed on the spectrum (Fig. 5).

In the phenytoin–PVP 25000 solid dispersion only diffraction peaks of PVP 25000 were estimated (Fig. 6). Chiou (1977) showed that the absence of diffraction peaks characterized for drug was possible, particularly in samples containing smaller fraction of drug. Based on results with griseofulvin he explained it as colloidal or ultrafine crystallization.

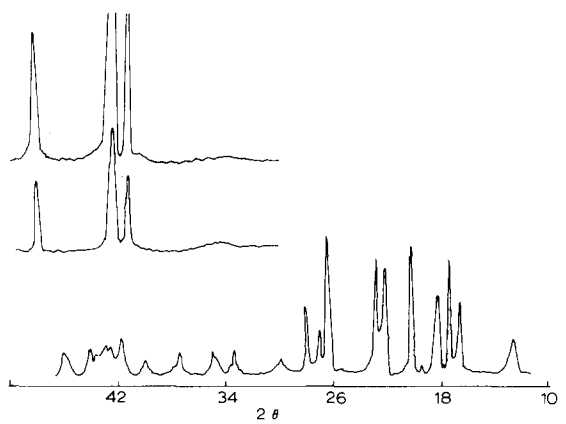

Fig. 6. X-Ray diffraction spectra of pure phenytoin (bottom), solid dispersion phenytoin–PVP 25000 (middle), pure PVP 25000 (top).

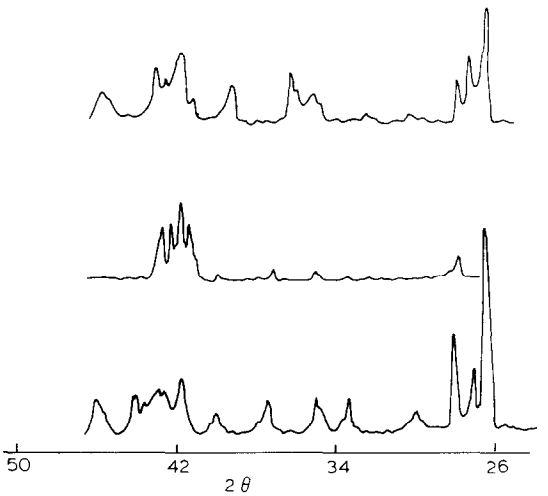

Fig. 7. X-Ray diffraction spectra of pure phenytoin (bottom), solid dispersion phenytoin–PVP 160000 (middle), solid dispersion phenytoin–PEG 6000 (top).

By comparing the spectra of phenytoin–PVP 160000 solid dispersion with the diffraction spectrum of pure phenytoin it was found that the solid dispersion contains separated phenytoin crystals. The aforementioned diffraction peaks of phenytoin were also presented in solid dispersion with PEG 6000 and urea (Fig. 7).

It is interesting that, in spite of identical methods of preparation of solid dispersion and the same proportions between drug and carriers, different spectra were obtained which appeared to be dependent on the molecular mass of PVP.

TABLE 2

R_f values of phenytoin from physical mixture (Ph.M.) and solid dispersion (S.D.)

Preparations	Solvent system		
	I	II	III
Phenytoin	0.36	0.53	0.83
Ph.M.-PEG	0.36	0.53	0.83
S.D.-PEG	0.36	0.53	0.83
Ph.M.-PVP	0.36	0.53	0.84
S.D.-PVP	0.37	0.53	0.83
Ph.M.-Urea	0.36	0.54	0.83
S.D.-Urea	0.37	0.54	0.84
Deteriorated drug	0.45	0.28	0.30
	0.60	0.50	0.92

TABLE 3

Phenytoin release in % from different tablet formulations: (1) freshly prepared; (2) after 2 years storage at temperature 20°C

Time (h)	Formulation A		PVP 40000			
			Formulation B		Formulation C	
	1	2	1	2	1	2
0.25	0.86	0.75	5.02	4.50	12.30	10.90
0.50	1.23	1.15	9.06	8.70	16.50	16.00
1.00	1.52	1.46	16.95	10.50	24.87	26.90
2.00	2.15	2.08	17.80	17.50	28.37	28.05
3.00	2.77	2.60	18.39	18.00	30.05	29.10
4.00	3.53	3.40	18.98	18.45	31.98	30.30
5.00	4.13	4.00	19.50	19.02	33.12	31.00
6.00	4.67	4.10	19.94	19.30	34.23	31.45
7.00	4.79	4.20	20.32	19.50	35.85	31.80

The stability of drugs formulated in solid dispersion is very important; no additional new spots were detected by TLC-method. Phenytoin dispersed in carriers showed the same R_f value (single spot only) as pure compound (Table 2). These data indicated that phenytoin was not decomposed by the technological process.

The results obtained from release studies of phenytoin from tablets confirmed the results from powdered samples. As shown in Table 3, the release of phenytoin from tablets containing solid dispersion in PVP 40000 was extremely fast. The amount of phenytoin released from these tablets was 35.8%; this was 3–7 times greater than of either the tablets formulated with PEG 6000 and urea or tablets of pure drug respectively (Table 4). The release profile of phenytoin from the tablet formulations B and C had two phases. A fast initial release phase up to 2 h was followed by a slower release in the second phase. The faster release rate of phenytoin from the tablets containing solid dispersion can be explained by a reduction in the particle size of the drug, and enhanced dispersion. Negligible differences in release rate were noted between freshly prepared and stored tablets for all formulations.

In the case of tablet formulations A and C with PVP, the amount of dissolved drug insignificantly

TABLE 4

Phenytoin release in % from different tablet formulations: (1) freshly prepared; (2) after 2 years storage at temperature 20°C

Time (h)	Urea				PEG 6000			
	Formulation B		Formulation C		Formulation B		Formulation C	
	1	2	1	2	1	2	1	2
0.25	1.05	1.10	5.65	4.30	1.10	1.00	7.05	6.90
0.50	2.10	2.00	6.90	7.10	1.76	1.50	10.20	11.00
1.00	3.55	3.50	8.33	8.13	3.20	3.10	11.30	11.20
2.00	4.06	3.90	8.63	8.40	4.78	4.20	11.50	11.40
3.00	4.70	4.48	8.97	8.75	5.52	5.50	11.75	11.60
4.00	5.30	5.00	9.10	8.90	6.32	6.20	11.93	11.80
5.00	5.80	5.50	9.15	9.00	7.17	6.85	12.10	11.90
6.00	6.00	5.70	9.25	9.05	7.45	6.95	12.15	12.00
7.00	6.20	5.80	9.55	9.10	7.63	7.05	12.60	12.20

exceeded 10%. According to Schou's (1959) assumption the studied solid dispersions in tablets could be recognized as the stable preparations.

Although the parameters of prepared tablets with solid dispersions were satisfactory, some difficulties were experienced in formulating the tablets with PEG 6000. The necessity of increasing the tablet mass ten-fold and difficulties experienced during compression limited practical application of this type of solid dispersion.

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