CHAPTER 3

P H E N Y T O I N

Experimental

Materials : Phenytoin (Pheny, Courtesy Cadila Laboratories Pvt. Ltd., Ahmedabad, India), Polyethylene glycol 6000 (sd - Fine Chemicals, Boisar, India), Urea (Sarabhai M. Chemicals, Baroda, India), Polyoxyl-40-stearate (POS, SG Chemicals, Baroda, India) Poloxamer 188 and Poloxamer 407 (BASF Wyandotte Corp., U.S.A.), were used as received. All other reagents were either pharmacoepoeial or reagent grade.

Methods :

Particle size and size distribution - Particle size (average diameter) and particle size distribution were measured using optical microscopy.

Preparation of calibration curve - About 0.02g of Phenytoin was dissolved in sufficient 0.1N NaoH to make 100 ml. Aliquots were withdrawn from this and diluted appropriately to get a range of concentrations (0 - 20 μg/ml), the absorbance of which were measured at 235 nm on a uv spectrophotometer (vsv-2P, cz-Jena, G.D.R). The Beer's plot is shown in Fig. 2.

Preparation of dispersion systems - Physical mixtures and solid dispersions were prepared in a similar manner as mentioned in the first section dealing with Nifedipine but in physical mixtures, Phenytoin was used as received.
The composition of systems prepared and evaluated are shown in Table : 1.

The solid dispersions were stored in a desiccator at room temperature for 24 hr before dissolution studies were undertaken. The particle size fraction used in dissolution experiments was # 35/60 (250-500 µm) except in case of Pheny-Polyoxyl-40 stearate solid dispersion and physical mixture where, size of the fraction used, was #16/35(500 -1190 µm) as it was extremely difficult to pass the material through # 35 screen because of the waxy nature of polyoxyl-40-stearate. Phenytoin was also crystallized from its solution in methanol : dichloromethane (1:1) to get the crystal size of # 35/60 (250-500 µm) to be used in comparative dissolution studies.

IR Spectral Studies - IR spectra of pure drug, excipients, physical mixtures and solid dispersions were taken in nujol on Shimadzu recording IR spectrophotometer (Shimadzu Corporation, Japan).

Solubility determinations - Aqueous solubility studies were performed in order to check for any possible interaction between drug and excipients. The method was same as used in case of ketoprofen except that shaking time in this study was 24 hr. followed by equilibration time for another 24 hr. The measurements were made at 235 nm. after aliquot s were first neutralised with an equal volume of 0.IN NaOH followed by dilution to an appropriate volume with 0.01N NaOH.

Dissolution Studies - The dissolution rate studies were performed by USP method II. Dissolution studies with tape method yielded very low and inconsistent results with respect to variation in drug content, particularly in case of its solid dispersion with urea, thus they are not included in this study.

Dissolution study using USP method II - The method used was same as that used for ketoprofen except aliquots withdrawn and filtered were first neutralised with 0.1N NaOH followed by its dilution to appropriate volume with 0.01N NaOH. The measurements were made at 235 mm by uv spectrophotometry. The amount of test preparation, added to the dissolution media was equal to the quantity representing 200 mg. of Phenytoin.

Solid solid interaction - Phase diagrams of two selected systems were constructed with aim to look into possible mechanism of enhanced dissolution. The phase diagrams were obtained using Differential Thermal Analysis.

Differential thermal analysis - Twenty five milligrams of sample was heated at 10°C/min. in a thermal analyser (DTA Me B system, VEB Laborelektronik Halle, G.D.R.). Alumina was used as a reference material, and static air was the gas phase. The instrument was calibrated using benzoic acid.

X-ray diffraction studies - The method and instrument used were same as that for Nifedipine and Ketoprofen.

Photomicrographic studies - Photomicrographs of various samples were taken on a polarising microscope (Leitz Laborlux, W. Germany).

Stability studies - The chemical stability of two test preparations was conducted on samples stored under ambient conditions for a period of two years.

Aging studies - The aim and method for this study were same as that in case of Nifedipine.

Bioavailability study - Urinary excretion study was undertaken to evaluate the bioavailability of the selected test preparations.

a) Formulation and dose - Phenytoin powder (dose : 300 mg./ body) and Phenytoin - Polyoxyl-40-stearate solid dispersion (Pheny-POS (1:3), dose; 200 mg. in two capsules/ body), were administered orally to healthy male volunteers.

b) Subjects - A two way cross over study was carried out in five healthy male volunteers aged between 24 and 28 yrs (mean 25.5 yrs) and weighing between 54-72 kg (mean 60.3 kg.). The volunteers gave their written consent after the object and the procedure of the trial had been fully explained to them. No abnormalities were detected on clinical examination.

c) Trial design - A preparation was administered to each subject with 200 ml. of water following an overnight fast. The volunteers continued fasting for 4 hr. after the dose was given however water was allowed adlibitum.

Results & Discussion

Phenytoin (average dia 2.45 µm, Fig. 1) did not show any degradation during preparation, checked by monitoring the drug content in solid dispersion which were within compendial limit (93.0 - 107.0 % w/w); and by measuring the λ max in alkaline solution which did not show any shift (shoulder at 235 nm).

Most of the solid dispersions did show an improvement in the dissolution of drug (Table : 2-6 & Fig. 3-7). The minimum relative dissolution rate of drug from these solid dispersions was 0.83 times and the maximum being about 2.00 times the dissolution rate of micronised Phenytoin at 60 min. The recrystallized Phenytoin of same particle size as of solid dispersion (except Pheny-POS solid dispersion where the particle size is 500-1190 µm), gave still lower dissolution rate i.e. 0.68 times that of micronised drug, at the end of sixty min.

The rating of excipients in terms of their drug releasing efficiency at 60 min. was found to be Urea > POS > PEG 6000 > Poloxamer 407 > Poloxamer 188.

The minimum relative dissolution rate of drug from these solid dispersion systems, was 0.81 times and the maximum being about 2.00 times the rate of dissolution of Phenytoin (micronised) at 120 min. The ranking of excipients based on their drug releasing efficiency was same as at 60 min.

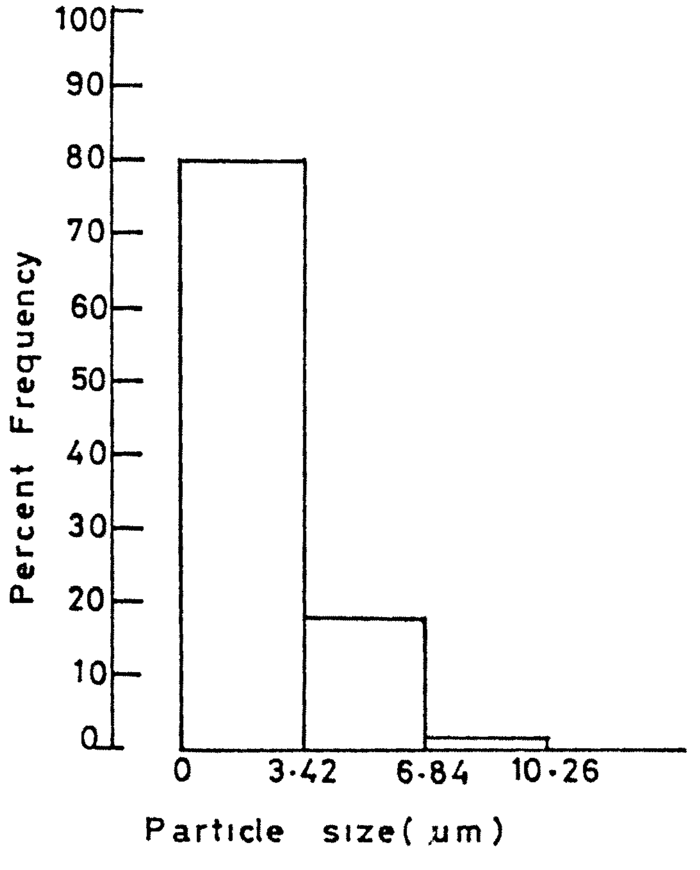

Fig.1 PARTICLE SIZE DISTRIBUTION OF PHENYTOIN.

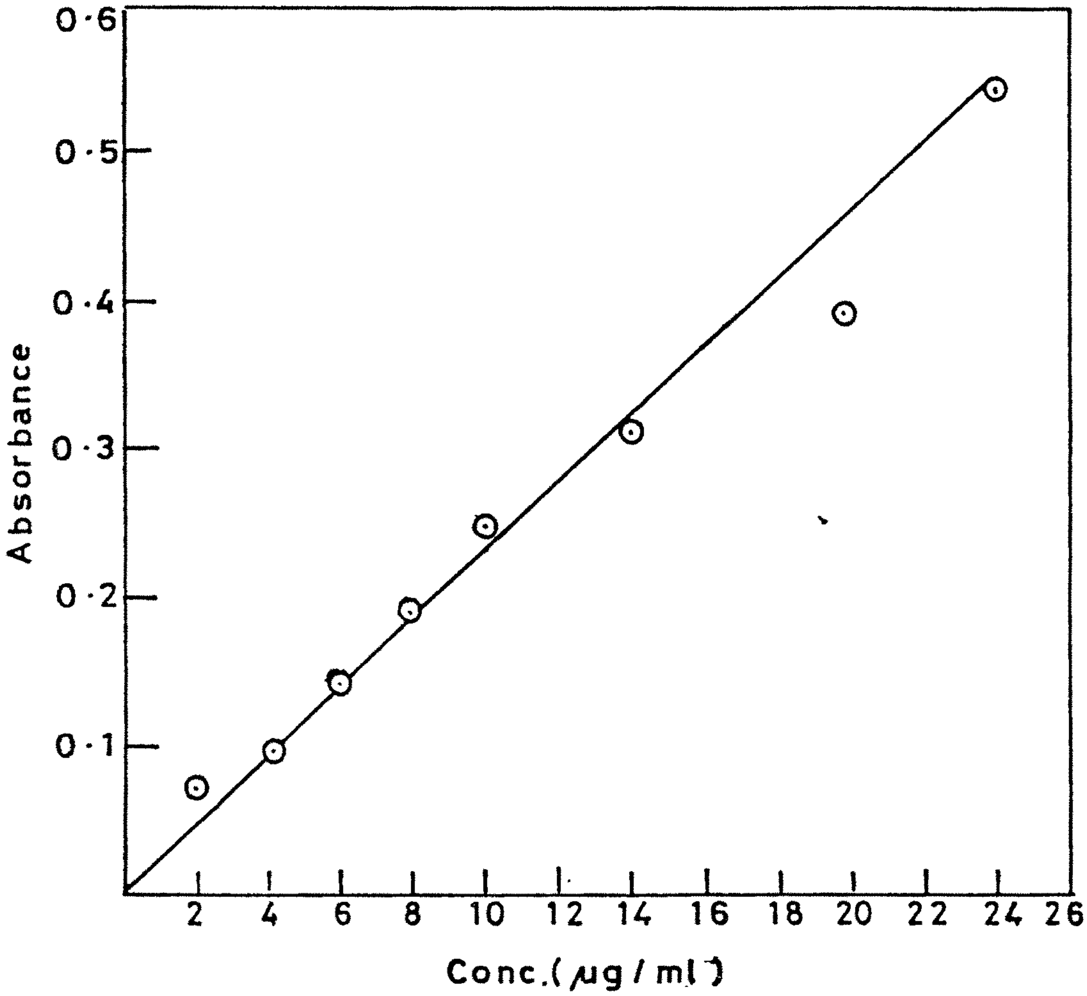

Fig 2   CALIBRATION CURVE OF PHENYTOIN.

Table : 1 - Compositions of various solid dispersion systems & physical mixtures of Phenytoin with the in-vitro method employed to evaluate these.

Systems	Ratio (w/w) (Pheny : Excipient)	USP method II
Solid dispersions		
Pheny-Urea	1:5	*
Pheny-Urea	1:3	*
Pheny-Urea	1:1	*
Pheny-POS	1:5	*
Pheny-POS	1:3	*
Pheny-POS	1:1	*
Pheny-PEG 6000	1:5	*
Pheny-PEG 6000	1:3	*
Pheny-PEG 6000	1:1	*
Pheny-Poloxamer 188	1:5	*
Pheny-Poloxamer 188	1:3	*
Pheny-Poloxamer 407	1:5	*
Pheny-Poloxamer 407	1:3	*
Physical mixtures		
Pheny-Urea	1:5	*
Pheny-POS	1:5	*
Pheny-PEG 6000	1:5	*
Pheny-Poloxamer 188	1:5	*
Pheny-Poloxamer 407	1:5	*
Pheny (microsized)	100:0	*
Pheny (Recrystallized) 250-500 um	100:0	*

* Systems evaluated

Table : 2 - Dissolution rates of Phenytoin from test preparations.

Systems	Average amount of Phenytoin released (mg/500 ml)						
	5	10	20	40	60	90	120 (min)
Solid dispersions							
Pheny-Urea (1:5)	28.66	30.55	29.67	30.78	30.12	29.00	29.00
Pheny-Urea (1:3)	22.44	28.09	28.77	28.11	28.55	29.00	30.55
Pheny-Urea (1:1)	20.44	22.52	24.75	25.65	26.98	26.10	27.66
Physical mixture							
Pheny-Urea (1:5)	5.14	13.08	14.97	13.74	14.90	15.28	14.65
Pheny(micronised)	9.11	12.47	14.27	14.94	14.94	14.94	15.39
Pheny (Recrystallized)	4.00	3.12	6.23	10.46	10.26	12.92	11.82

Table : 3 - Dissolution rates of Phenytoin from test preparations.

Systems	Average amount of Phenytoin released (mg/500 ml).						
	5	10	20	40	60	90	120(min)
Solid dispersions							
Phenyl - POS (1:5)	31.33	31.23	27.23	27.44	24.54	27.20	27.66
Pheny-POS (1:3)	18.44	23.40	24.97	25.42	25.65	23.21	22.98
Pheny-POS (1:1)	16.22	18.95	19.63	18.96	20.51	19.19	20.51
Physical mixture							
Pheny-POS (1:5)	8.54	11.86	13.99	15.05	14.27	14.82	15.29
Pheny(micronised)	9.11	12.47	14.27	14.94	14.94	14.94	15.39
Pheny (Recrystallized)	4.00	3.12	6.23	10.46	10.26	12.92	11.82

Table : 4 - Dissolution rates of Phenytoin from test preparations.

Systems	Average amount of Phenytoin released (mg/500 ml)						
	5	10	20	40	60	90	120 (min)
Solid dispersions							
Pheny-PEG 6000 (1:5)	19.11	23.18	23.27	22.31	23.41	21.86	24.08
Pheny-PEG 6000 (1:3)	15.77	17.17	16.73	17.39	15.62	17.39	15.84
Pheny-PEG 6000 (1:1)	18.00	22.07	19.86	20.74	20.32	19.19	17.63
Physical mixture							
Pheny-PEG 6000 (1:5)	8.82	12.75	13.90	15.41	14.54	14.87	14.50
Pheny(micronised)	9.11	12.47	14.27	14.94	14.94	14.94	15.39
Pheny(Recrystallised).	4.00	3.12	6.23	10.46	10.26	12.92	11.82

Table : 5 - Dissolution rates of Phenytoin from test preparations.

Systems	Average amount of Phenytoin released (mg/500 ml)						
	5	10	20	40	60	90	120 (min)
Solid dispersions							
Pheny-Poloxamer 188 (1:5)	16.00	17.62	17.18	16.28	19.62	16.96	17.40
Pheny-Poloxamer 188 (1:3)	14.22	14.94	14.28	12.94	12.50	12.27	12.49
Physical mixture							
Pheny-Poloxamer 188 (1:5)	7.48	13.31	14.72	14.85	15.40	15.22	14.44
Pheny(micronised)	9.11	12.47	14.27	14.94	14.94	14.94	15.39
Pheny (Recrystallized)	4.00	3.12	6.23	10.46	10.26	12.92	11.82

Table : 6 - Dissolution rates of Phenytoin from test preparations.

Systems	Average amount of Phenytoin released (mg/500 ml)						
	5	10	20	40	60	90	120 (min)
Solid dispersions							
Pheny-Poloxamer 407 (1:5)	13.55	16.27	17.17	14.95	16.06	17.39	18.51
Pheny-Poloxamer 407 (1:3)	16.66	21.17	22.30	22.09	21.64	21.64	21.64
Physical mixture							
Pheny-Poloxamer 407 (1:5)	13.02	21.12	21.37	21.45	20.00	21.24	21.24
Pheny(micronised)	9.11	12.47	14.27	14.94	14.94	14.94	15.39
Pheny (Recrystallized)	4.00	3.12	6.23	10.46	10.26	12.92	11.82

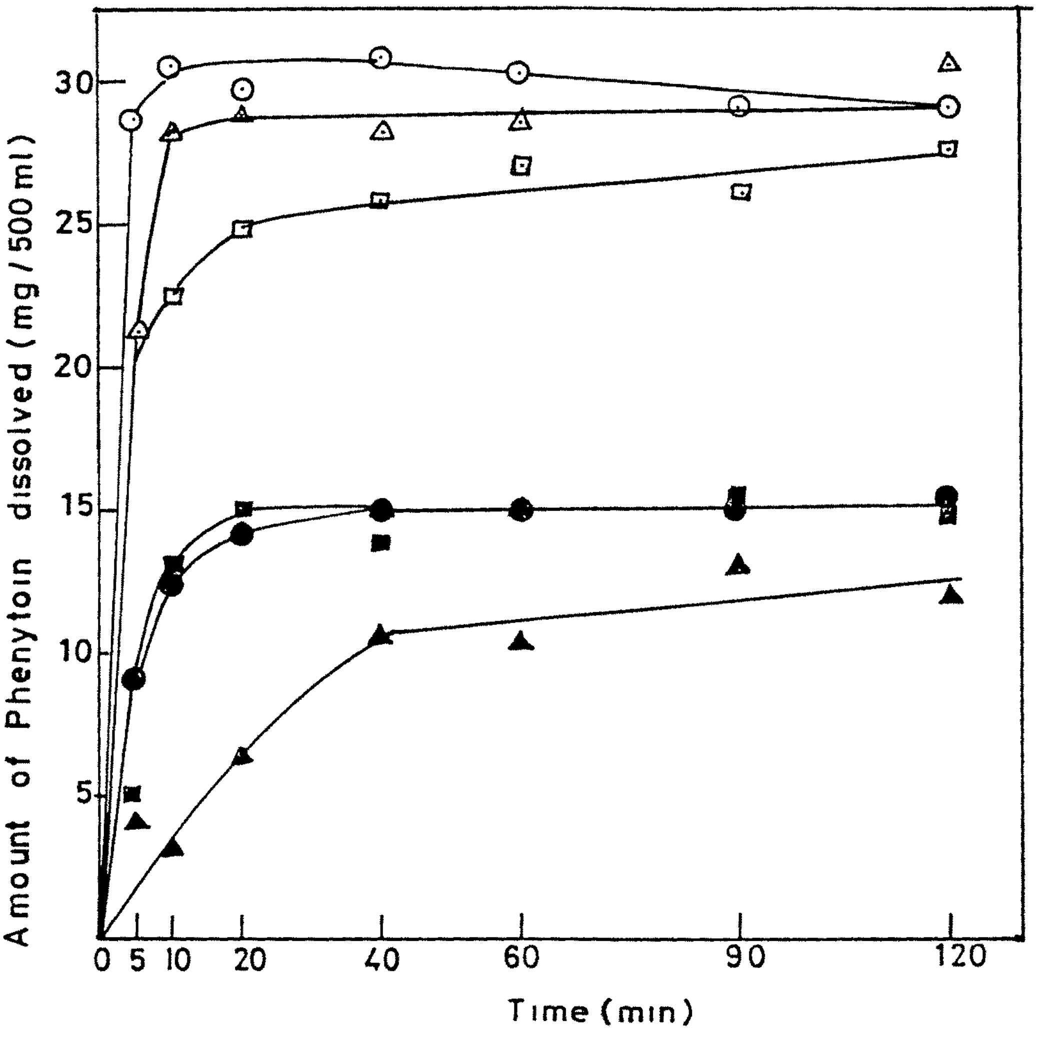

Fig 3 DISSOLUTION PROFILES OF PHENY-UREA SDS, PHENY-UREA PM, PHENY (MSZ) AND PHENY (Recrystallized).

KEY : ⊙ PHENY-UREA (1:5) SD;
△ PHENY-UREA (1:3) SD;
⊡ PHENY-UREA (1:1) SD;
■ PHENY-UREA (1:5) PM;
● PHENY (MSZ);
▲ PHENY (Recryst).

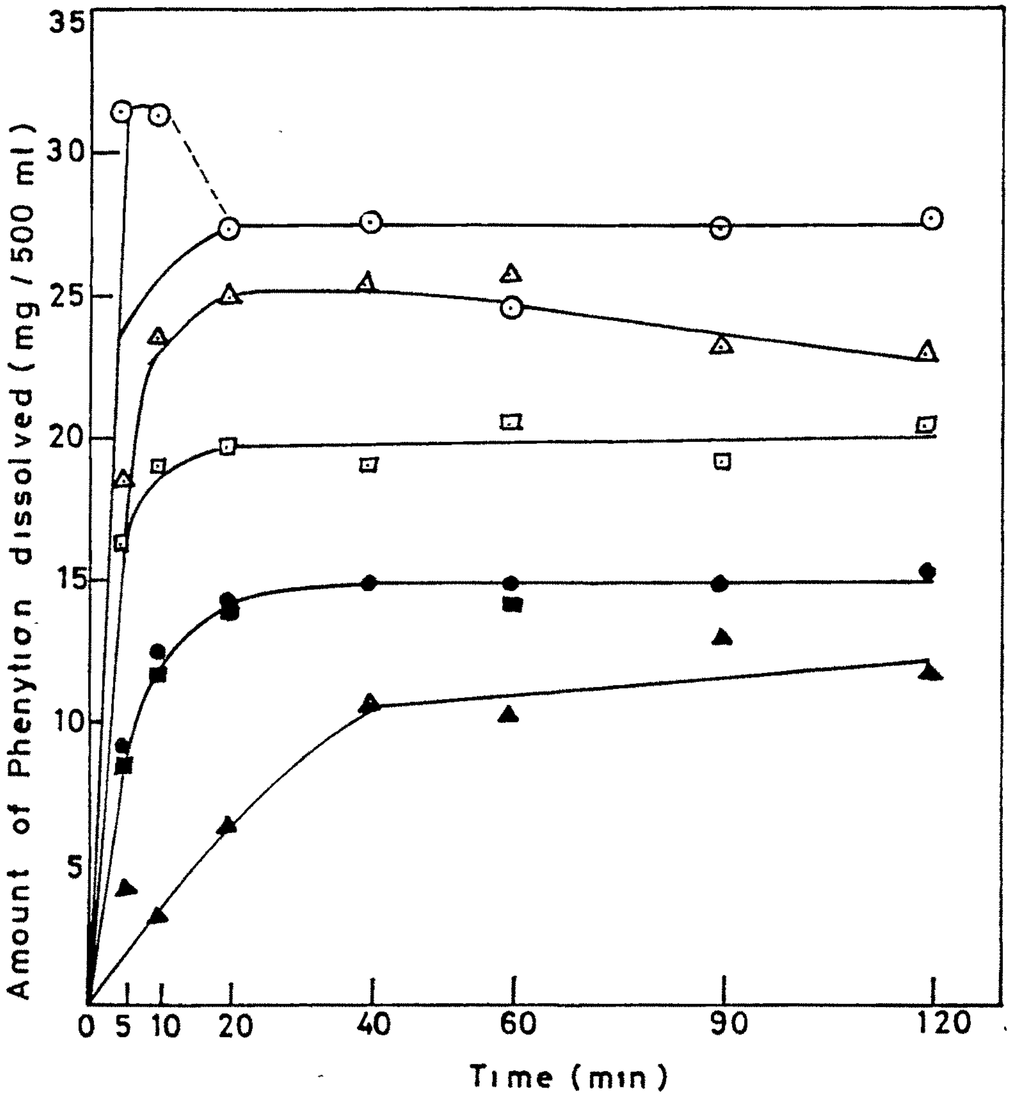

Fig. 4 DISSOLUTION PROFILES OF PHENY-POS SDS, PHENY-POS PM, PHENY (MSZ) AND PHENY (Recrystallized)

KEY : ⊙ PHENY-POS (1:5) SD;
△ PHENY-POS (1:3) SD;
⊡ PHENY-POS (1:1) SD;
■ PHENY-POS (1:5) PM
● PHENY (MSZ);
▲ PHENY (Recryst).

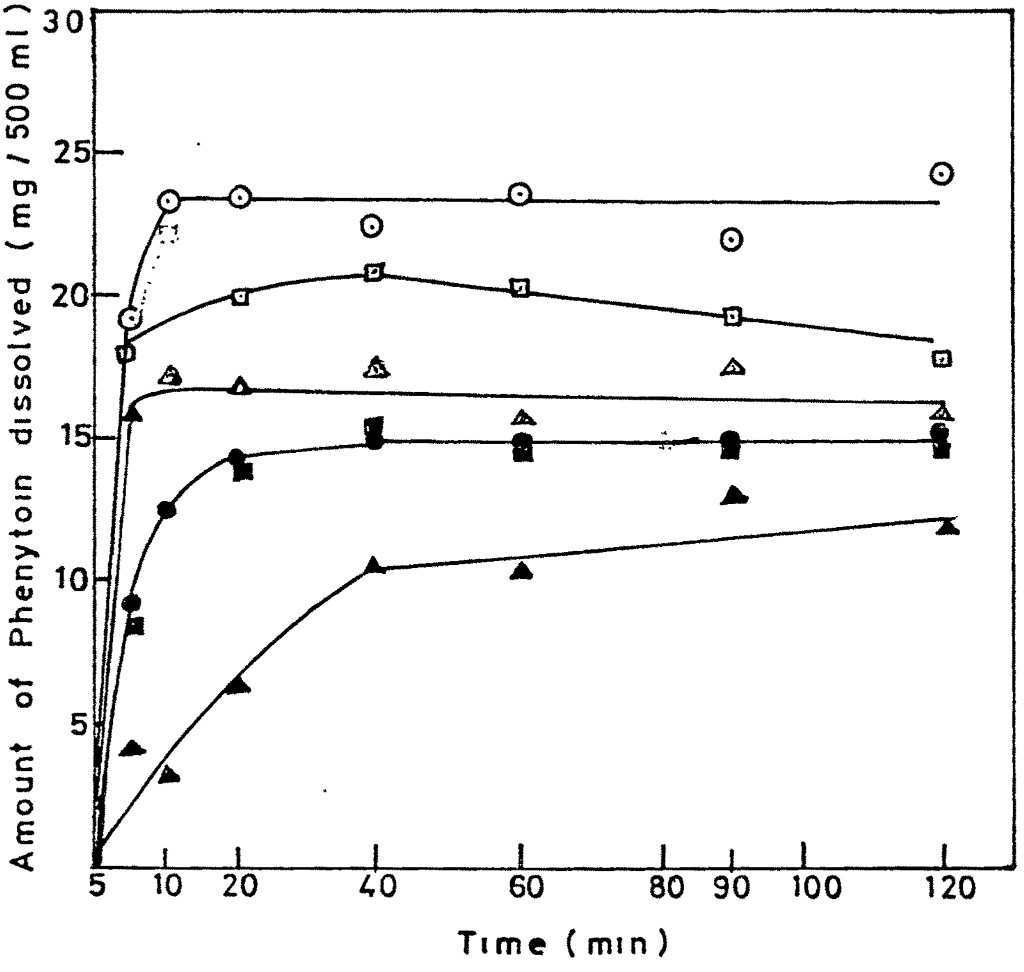

Fig. 5 DISSOLUTION PROFILES OF PHENY-PEG6000 SDS PHENY-PEG6000 PM, PHENY (MSZ) AND PHENY (Recrystallized)

KEY : ʘ PHENY-PEG6000 (1:5) SD;
△ PHENY-PEG6000 (1:3) SD;
⊡ PHENY-PEG6000 (1:1) SD;
■ PHENY-PEG6000 (1:5) PM;
● PHENY-(MSZ);
▲ PHENY (Recryst).

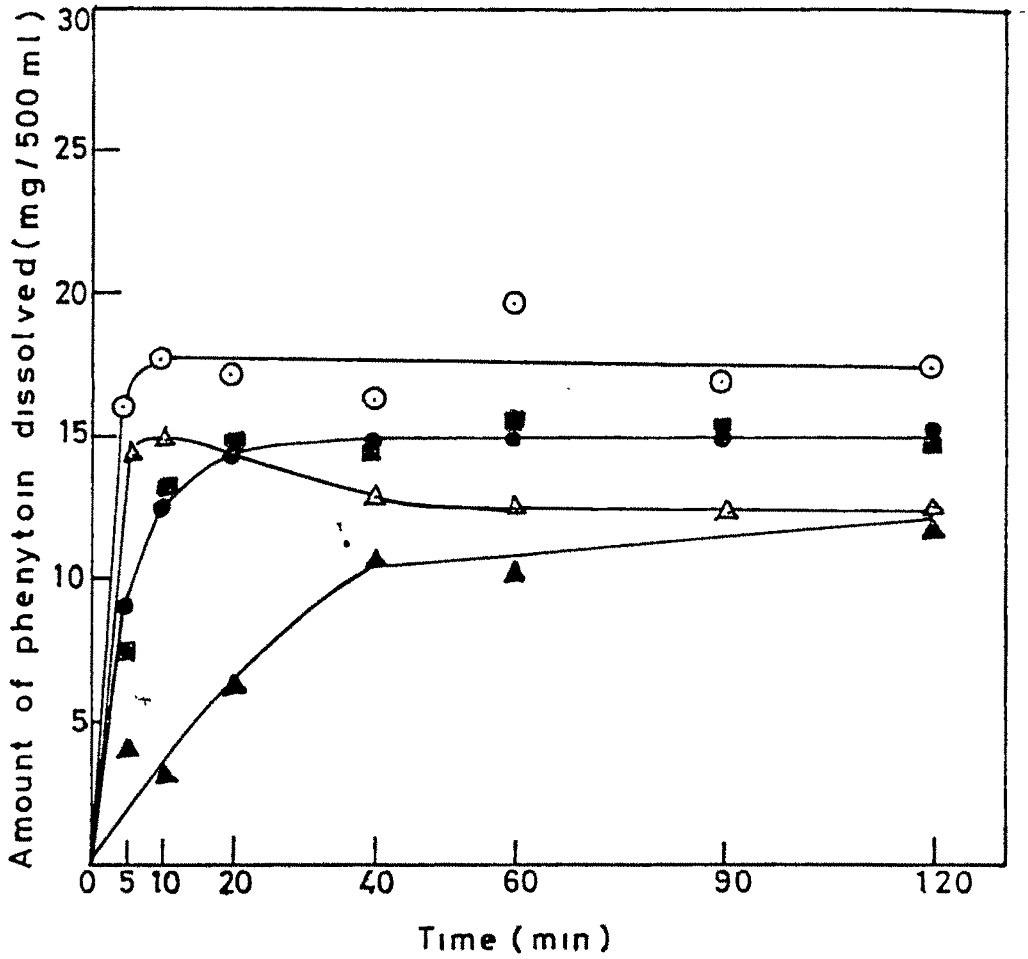

Fig. 6 DISSOLUTION PROFILES OF PHENY-POLOXAMER 188 SDS, PHENY-POLOXAMER 188 PM, PHENY (MSZ) AND PHENY (Recrystallized)

KEY : ⊙ PHENY-POLOXAMER 188(1:5) SD;
Δ PHENY-POLOXAMER 188(1:3) SD;
■ PHENY-POLOXAMER 188(1:5) PM;
● PHENY-(MSZ);
▲ PHENY (Recryst).

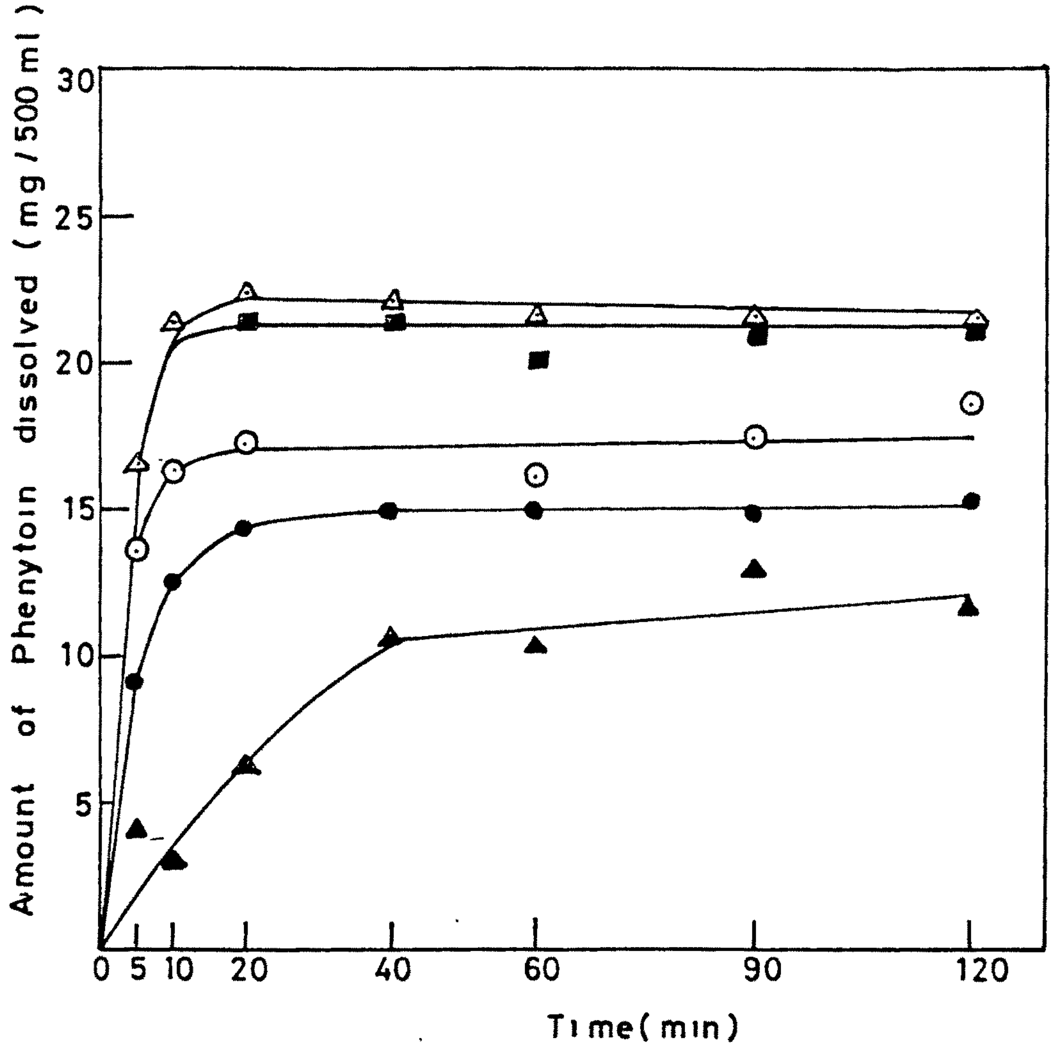

Fig.7 DISSOLUTION PROFILES OF PHENY-POLOXAMER 407 SDS, PHENY-POLOXAMER 407 PM; PHENY (MSZ) AND PHENY (Recrystallized).

KEY : ⊙ PHENY-POLOXAMER 407 (1:5) SD;
△ PHENY-POLOXAMER 407 (1:3) SD;
■ PHENY-POLOXAMER 407 (1:5) PM;
● PHENY (MSZ);
▲ PHENY (Recryst).

Inspecting the results, it appeared that saturation level had been reached in the first 10 min. in most of the systems. The saturation solubility in case of micronised drug was not achieved at the end of 2 hr.

The dissolution rate of drug from these solid dispersions did not vary much as the drug to excipient ratio was increased. In one instance, higher drug to excipient ratio exhibited better dissolution rate than the lower drug to excipient ratio (Pheny-Poloxamer 407 SD). Similar tendency was observed in case of Nfd - Poloxamer 407 solid dispersion. This may be related to the role of viscosity in the dissolution of drug as has also been reported in case of Griseofulvin and Tolbutamide dispersed in PEG 2000 (Kaur et al, 1980).

In order to account for the differences in the dissolution rates of various solid dispersion systems, the effect of excipients on the aqueous solubility of Phenytoin was investigated (Fig. 8). The effect of POS on the aqueous solubility of Phenytoin could not be studied because of some problems associated with the estimations of drug in presence of relatively high concentrations of excipient. Most of excipients showed solubilising capability except PEG 6000. Poloxamer 407 was the most effective followed by urea. In case of Poloxamer 407, the solubilising effect was strong but it could not produce maximum dissolution rate of drug in the drug to excipient ratios employed. However, probably had it been higher drug to excipient ratio (i.e. 1:1), dissolution rate could still be improved.

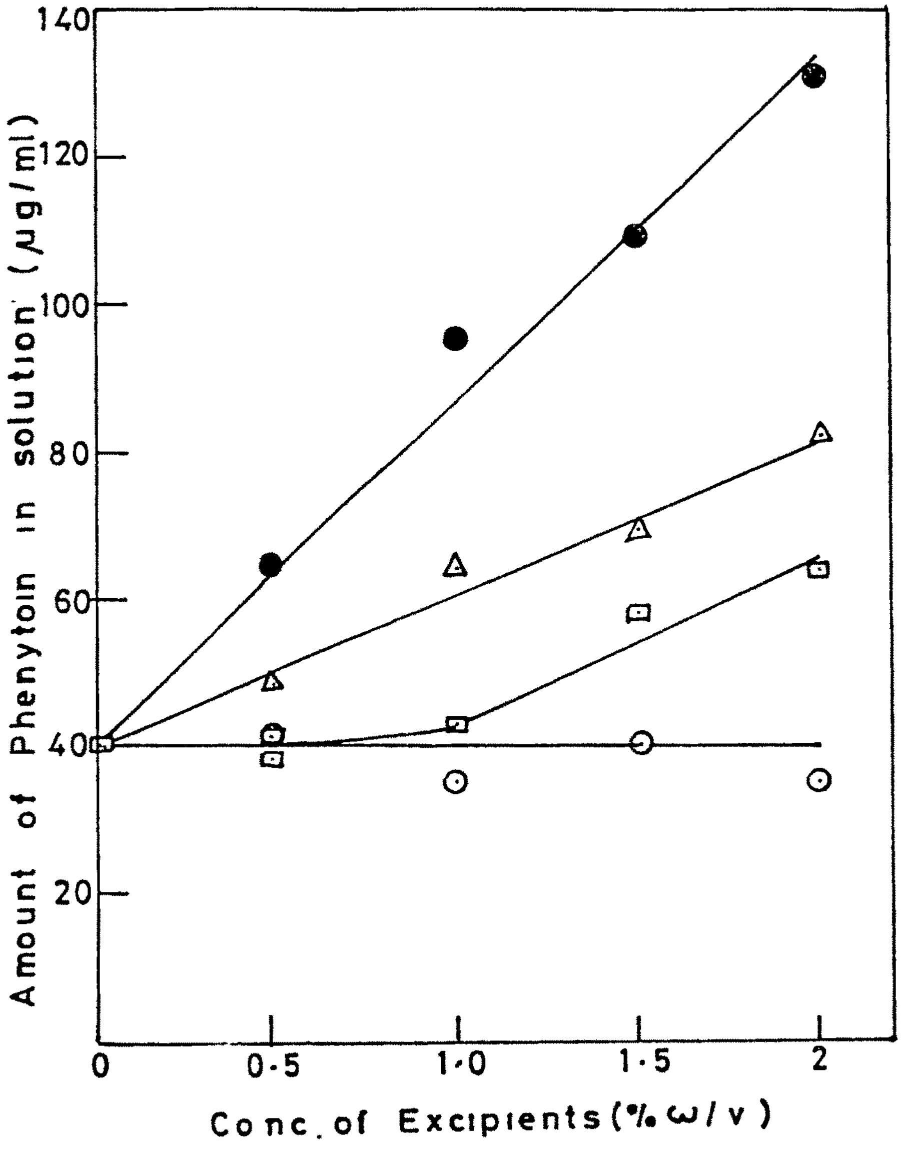

Fig. 8 EFFECT OF EXCIPIENTS ON THE SOLUBILITY OF PHENYTOIN.

KEY : ⊙ PEG6000;

△ UREA;

⊡ POLOXAMER 188;

● POLOXAMER 407.

Because the maximum excipient concentration in the dissolution media became 0.2% w/v and the minimum being 0.04% w/v, the improvements in dissolution rate could not be due only to solubilization. This was also substantiated by visualising dissolution behaviour of the physical mixture of minimum drug to excipient ratio (i.e. 1:5), which reflected no increase in the dissolution rates in most cases, except in case of physical mixture using Poloxamer 407. Other factors which may contribute to the improved dissolution behaviour of Phenytoin from its solid dispersion systems are i) the wettability or affinity of the drug to water is improved ii) the drug crystals dispersed in the excipients are extremely small or the drug may be wholly or partly in amorphous state iii) high concentrations of excipients are formed in the vicinity of drug particles, so that the solubility of Phenytoin at the surface is increased, improving the observed dissolution rate of drug.

Geneidi et al (1980) reported the role of wettability in increasing the dissolution rate of Glibenclamide from its physical mixtures. In the present investigation, however, this should be of limited value as there is no substantial increase in the dissolution rates of drug from physical mixtures in most instances.

Sekikawa et al (1979) proposed as a dissolution mechanism for drug - PVP coprecipitate that high concentrations of both drug and PVP coacervated in the vicinity of the coprecipitate.

This may be one of the contributing factors but needs further substantiation.

On examination of x-ray diffraction patterns of two selected test preparations viz. Pheny-Urea (1:3) SD and Pheny POS (1:3)SD, firstly, the peaks attributed to urea could not be easily differentiated from peaks attributed to drug, as many of peaks overlap. But peaks attributed to POS could be well differentiated from peaks attributed to drug. Phenytoin and urea showed good crystallanity where as POS also had crystalline portion in it.

The reduction in crystallite size of drug in Pheny-Urea SD could not be confirmed due to varying intensities of peaks attributable to Phenytoin (Fig : 9) but in Pheny-POS SD, intensities of peaks attributable to Phenytoin was very much reduced, probably relating to the reduction in crystallite size (Fig : 10). This could be a possible reason for the observed improvement in the dissolution rate of drug from Pheny-POS solid dispersion. The high microenvironmental concentration of urea surrounding the drug particles may be an important factor contributing to the observed improvement in dissolution behaviour of drug from Pheny-Urea solid dispersion.

Photomicrographs of these test preparations also revealed the existence of crystalline form of drug in both solid dispersions (Fig : 11 - 15). The IR spectra of Phenytoin, urea and Phenytoin-POS physical mixture, are the additional product of the spectrum of Phenytoin and corresponding excipient and are idential to that of corresponding solid

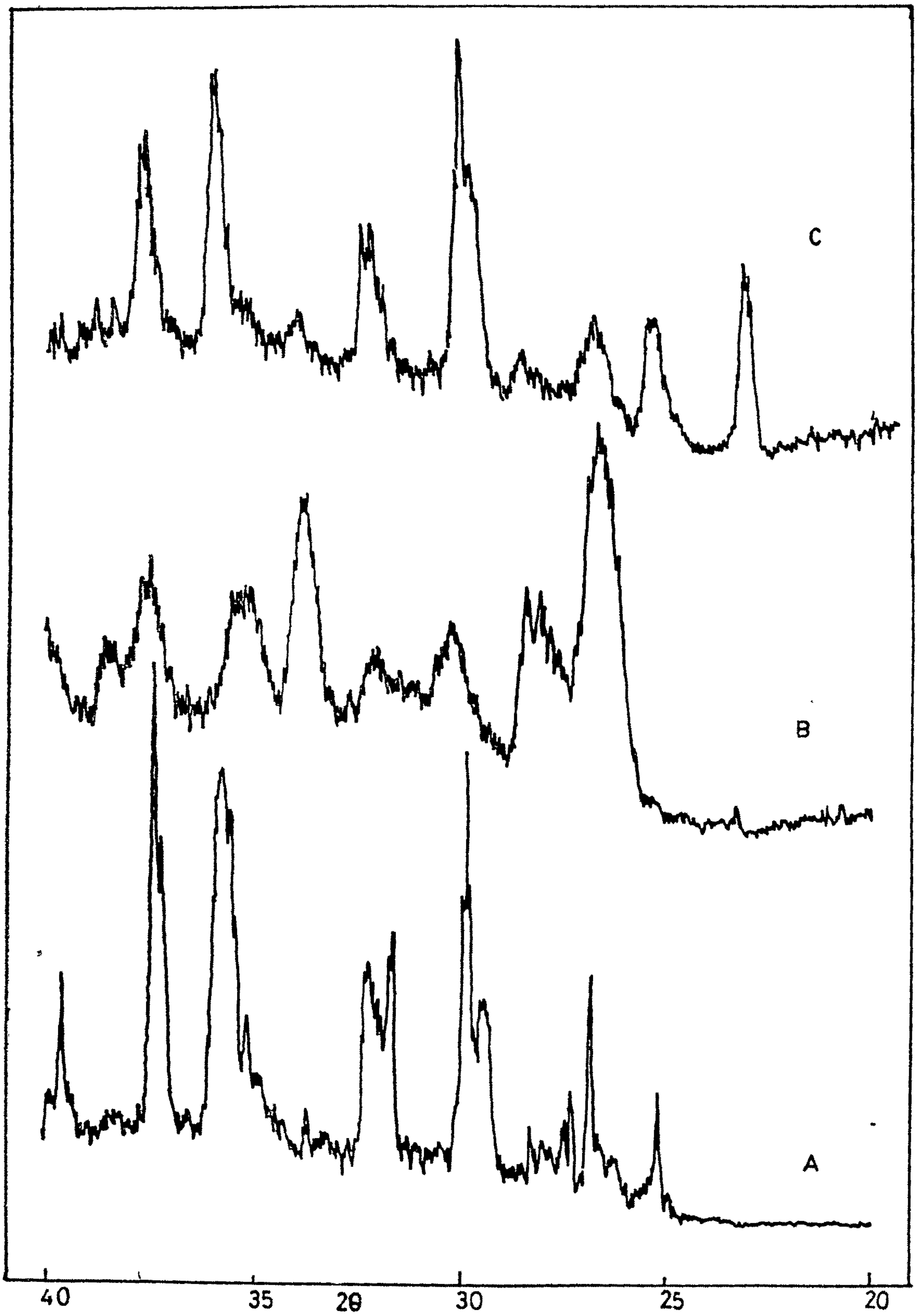

Fig.9 X-RAYF DIFFRACTION PATTEERNS OF (A) UREA ; (B) PHENY ;

(C) PHENY-UREA (1:3) SD

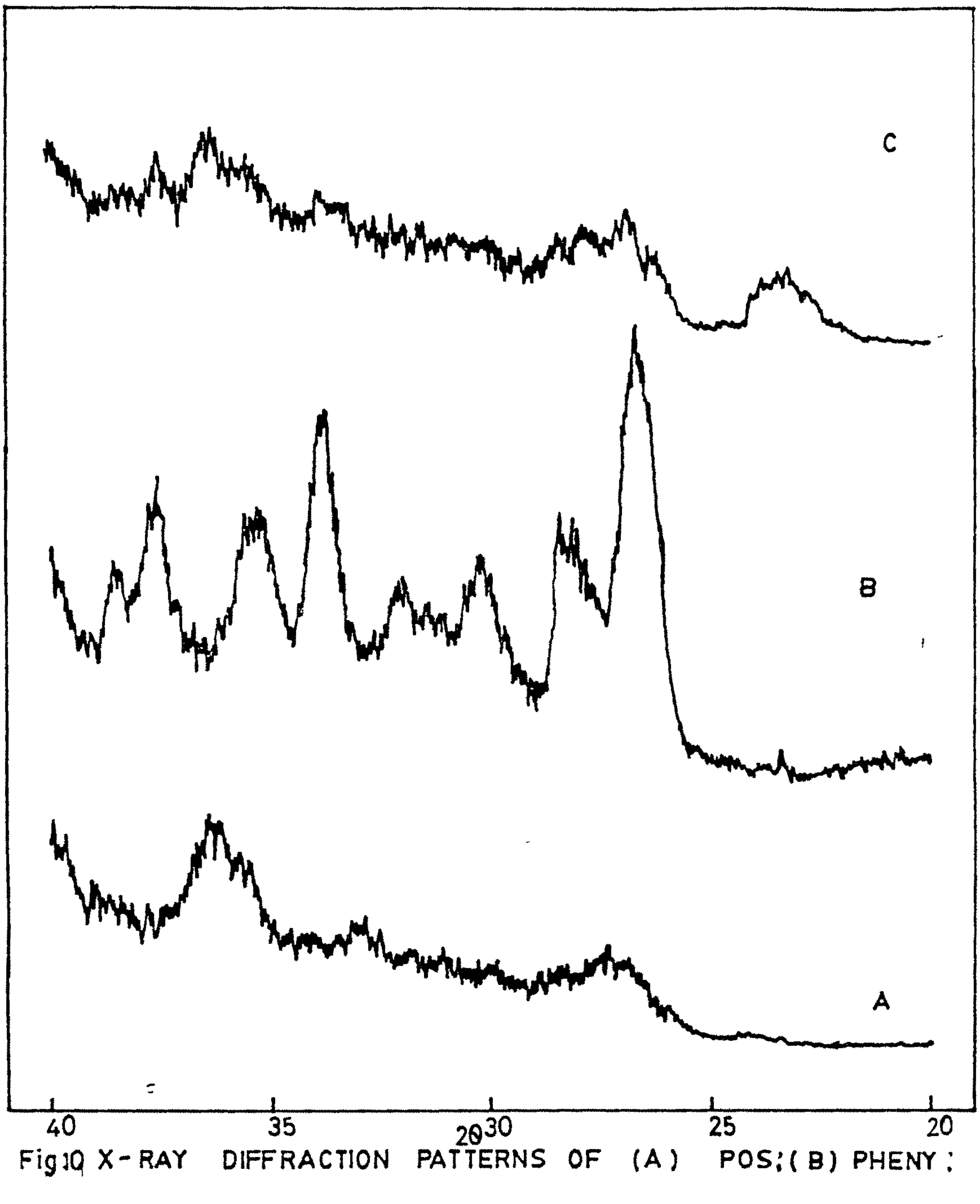

Fig.10 X-RAY DIFFRACTION PATTERNS OF (A) POS; (B) PHENY; (C) PHENY-POS (1:3) DS

Fig 11 PHOTOMICROGRAPH OF UREA (x300)

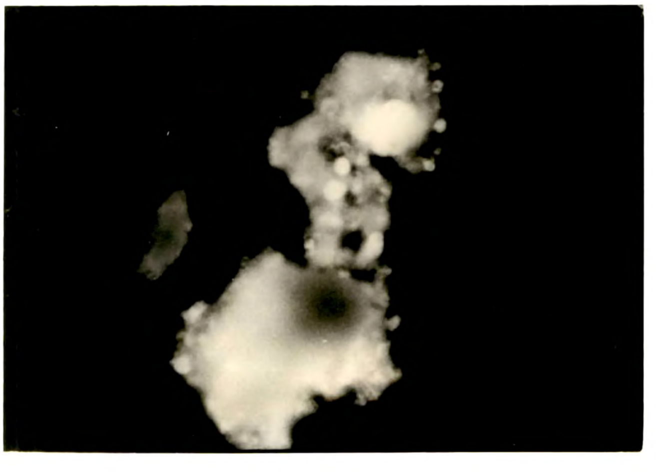

Fig 12 PHOTOMICROGRAPH OF PHENY-UREA(1:3)SD (x300)

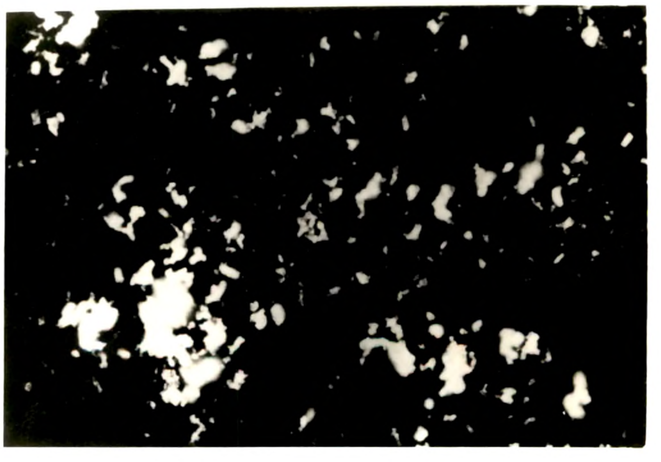

Fig 13 PHOTOMICROGRAPH OF PHENY CRYSTALS (x300)

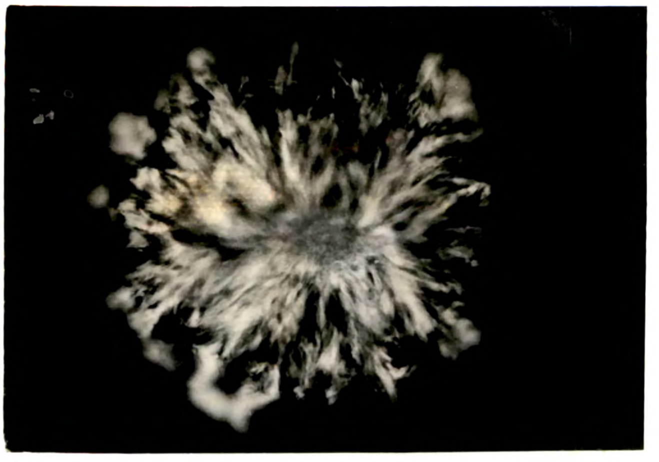

Fig 14 PHOTOMICROGRAPH OF POS (x300)

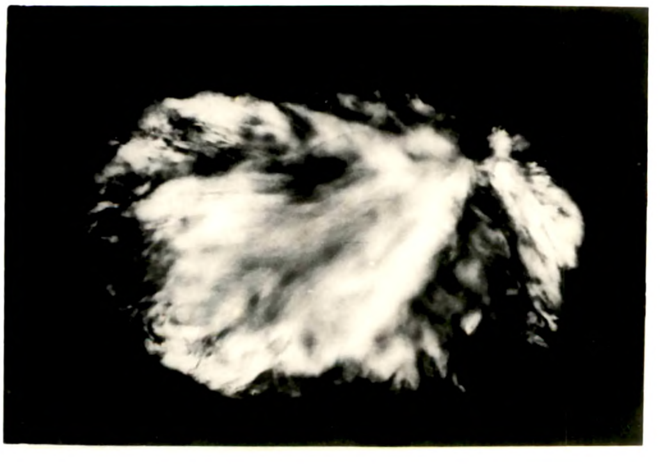

Fig 15 PHOTOMICROGRAPH OF PHENY-POS(1:3)SD (x300)

dispersion, thereby indicating absence of any chemical interaction between drug and these excipients .

Phase diagrams were constructed using Differential thermal analysis, the results of which revealed endothermic peaks of both the excipients i.e. urea and POS and Phenytoin (Fig : 16). Phase diagrams of both the selected systems of Phenytoin, were of the monotectic type (Fig : 17, 18). This type of system has been reported by Kaur et al, (1980) in case of Griseofulvin and tolbutamide.

A monotectic phase diagram has the form of a eutectic diagram in which one arm is missing and the lower melting component replaces the eutectic composition. The rising liquidus curve on the left of each monotectic diagram corresponds to the solubility curve of the drug in the liquid excipient.

Comparision of the phase diagrams show that they do not differ much in terms shape of the rising curve. There is no or negligible solubility of drug in the molten state of excipients.

Role of such monotectic mixtures in improving the dissolution behaviour of drug from solid dispersions is not known.

Chemical stability - Two selected test preparations viz. Pheny-Urea (1:3) solid dispersion and Pheny-POS (1:3)

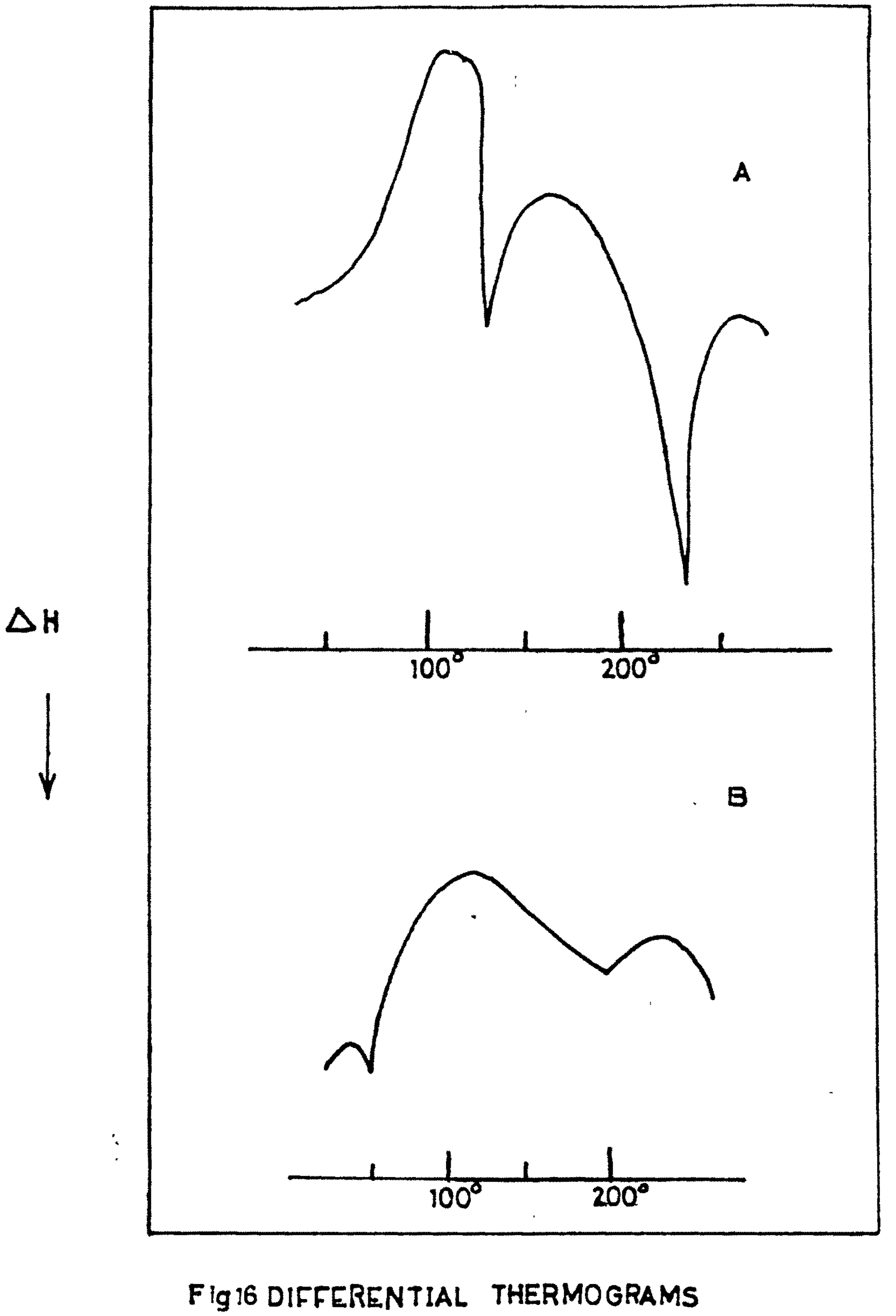

Fig 16 DIFFERENTIAL THERMOGRAMS
OF (A) PHENY-UREA (1:3) S.D
(B) PHENY-POS (1:3) SD

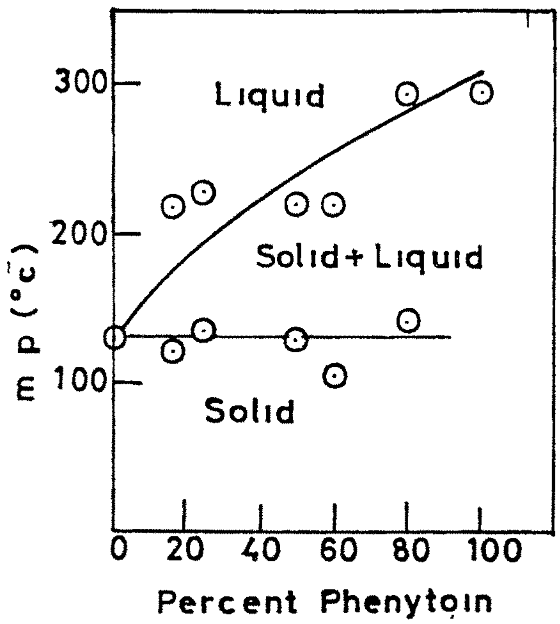

Fig. 17 PHASE DIAGRAM OF PHENY - UREA SD.

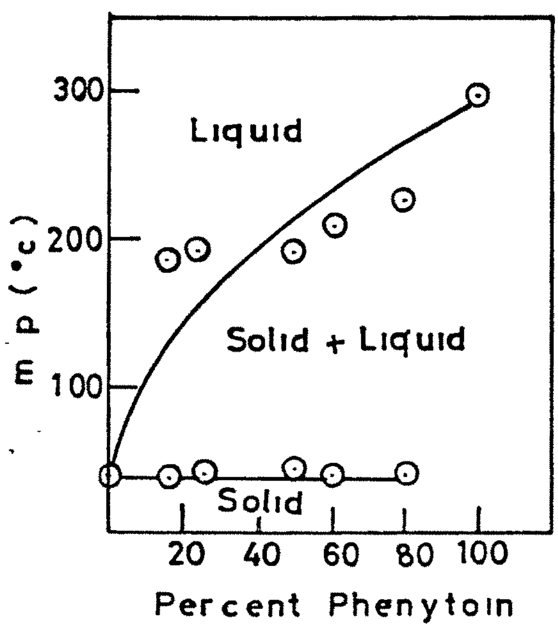

Fig. 18 PHASE DIAGRAM OF PHENY — POS SD.

solid dispersion were stored under ambient conditions for two years. Phenytoin content in the stored samples was determined by uv measurement at 235 nm, as mentioned in the preparation of calibration curve (Table : 7) . There was no significant change in the drug content as well as physical appearance of these test preparations.

Aging study - Two selected test preparations mentioned above were subjected to aging study by storing them under ambient conditions for a period of 12 months. The samples were periodically analysed for any change in their dissolution behaviour (Fig : 19, 20). In case of solid dispersion containing urea, the dissolution behaviour changed on storage (decrease in the dissolution rate with time) and it nearly approached the dissolution behaviour of micronised drug alone at the end of 12 months. On the other hand solid dispersion employing POS did not indicate appreciable change in dissolution behaviour at the conclusion of study period. Therefore the kind of excipients may have some influence on the dissolution behaviour of Phenytoin.

Bioavailability study - The chosen composition (for bioavailability study) of solid dispersions (1:3) was a compromise between good dissolution behaviour and dose volume.

Based on in-vitro dissolution data, initially it was planned to conduct the urinary excretion trial for unchanged

Table : 7 - Stability of Phenytoin (percent residual amount) in samples stored under normal temperature & humidity conditions.

Sample	Storage Period		
	Initial	12 mo	24 mo
Pheny-Urea (1:3) SD	100.00	98.72	104.38
Pheny-POS (1:3) SD	100.00	102.58	98.20

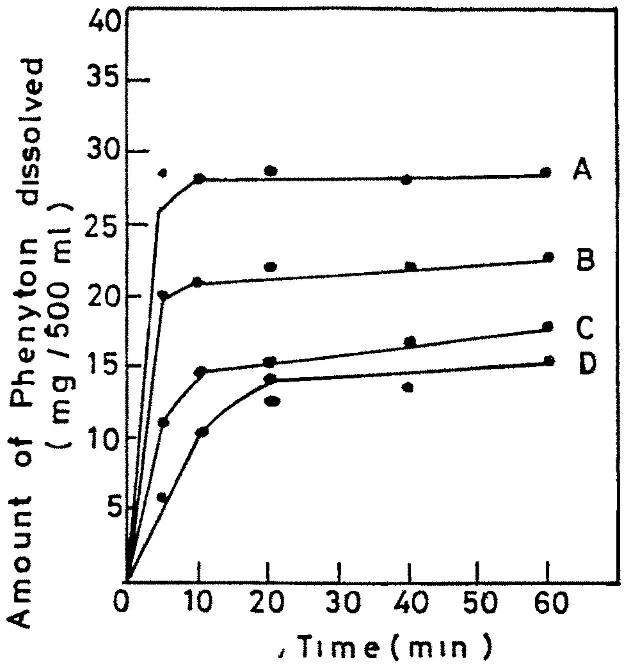

Fig.19 EFFECT OF STORAGE UNDER AMBIENT CONDITIONS ON THE DISSOLUTION BEHAVIOUR OF PHENY - UREA (1 : 3) SD,
STORAGE PERIOD: (A) INITIAL, (B) 3 mo, (C) 6 mo, (D) 12 mo.

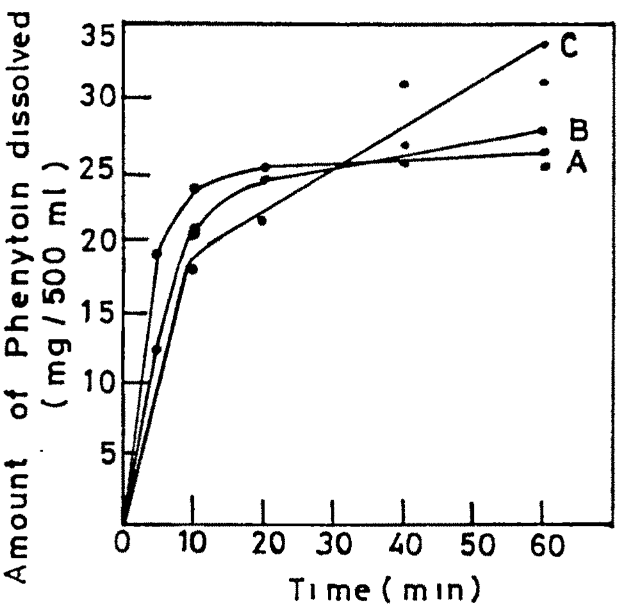

Fig 20 EFFECT OF STORAGE UNDER AMBIENT CONDITIONS ON THE DISSOLUTION BEHAVIOUR OF PHENY - POS (1:3) SD.
STORAGE PERIOD : (A) INITIAL , (B) 6 mo (C) 12 mo .

Phenytoin (as plasma levels of Phenytoin correlate well with excretion of Phenytoin, (Shigeru et al, 1984) on three test preparations namely Pheny-POS solid dispersion, Pheny-urea solid dispersion and Phenytoin alone. But later as the study progressed, it was found that Pheny-urea solid dispersion upon aging resulted in lowering of dissolution rate of drug within relatively short span of time. Therefore, it was decided to exclude it from study and trial was conducted taking Pheny-POS solid dispersion and Phenyton alone as test preparations.

A dose equivalent of 200 mg. of Phenytoin was administered in the case of Phenytoin solid dispersion and 300 mg. in case of Phenytoin alone. Higher dissolution rate of drug and narrow therapeutic range accounted for the reduction of dose.

Mean excretion rate of Phenytoin (Fig : 21) and three parameters used to define the bioavailability; time to peak excretion rate, peak excretion rate and area under time excretion rate curve area recorded in table 8 & 9.

Time to peak excretion rate in both the cases was similar i.e. 0 - 2 hr. The lower time to peak excretion rate for solid dispersion may be anticipated but for Phenytoin alone, it is much lower, perhaps due to small crystal size. There was direct correlation between particle size of Phenytoin crystals and bioavailability in dogs; and AUC was

Table : 8 - Mean excretion rate of Phenytoin from test preparations.

Time (Minpoint in time interval, in hr.)	Excretion rate$^{(a)}$ mg hr^{-1}		
	Phenytoin$^{(b)}$	Phenytoin-POS$^{(c)}$ solid dispersion	Significance of difference between Phenytoin & solid dispersion (d)
1	0.79 ± 0.62	2.53 ± 0.58	$P < 0.05$
3	0.41 ± 0.13	0.93 ± 0.15	$P < 0.05$
5	0.30 ± 0.24	0.54 ± 0.55	NS
7	0.49 ± 0.53	1.03 ± 0.30	NS
10	0.39 ± 0.14	0.67 ± 0.26	NS
17	0.35 ± 0.21	0.54 ± 0.34	NS
28	0.31 ± 0.20	1.16 ± 0.49	$P > 0.05 < 0.1$
40	0.18 ± 0.13	0.58 ± 0.34	NS

a) Mean ± S.D. b) Dose : 300 mg/body c) Dose : 200mg/body

d) one tail test.

Table : 9 - Mean time to peak, peak excretion rate and AUC of excretion data following oral administration of 300 mg. of Phenytoin and Phenytoin solid dispersion equivalent to 200 mg. of Phenytoin.

Test preparation	Time to peak (hr).	Peak excretion rate (mg hr^{-1}) [(a)]	AUC mg. hr [(b)]
Phenytoin	1 hr. (0-2 hr)	0.79 ± 0.62	15.67 ± 6.66
Phenytoin - POS solid dispersion	1 hr (0-2 hr)	2.53 ± 0.58	37.15 ±10.55

(a & b) mean ± SD.

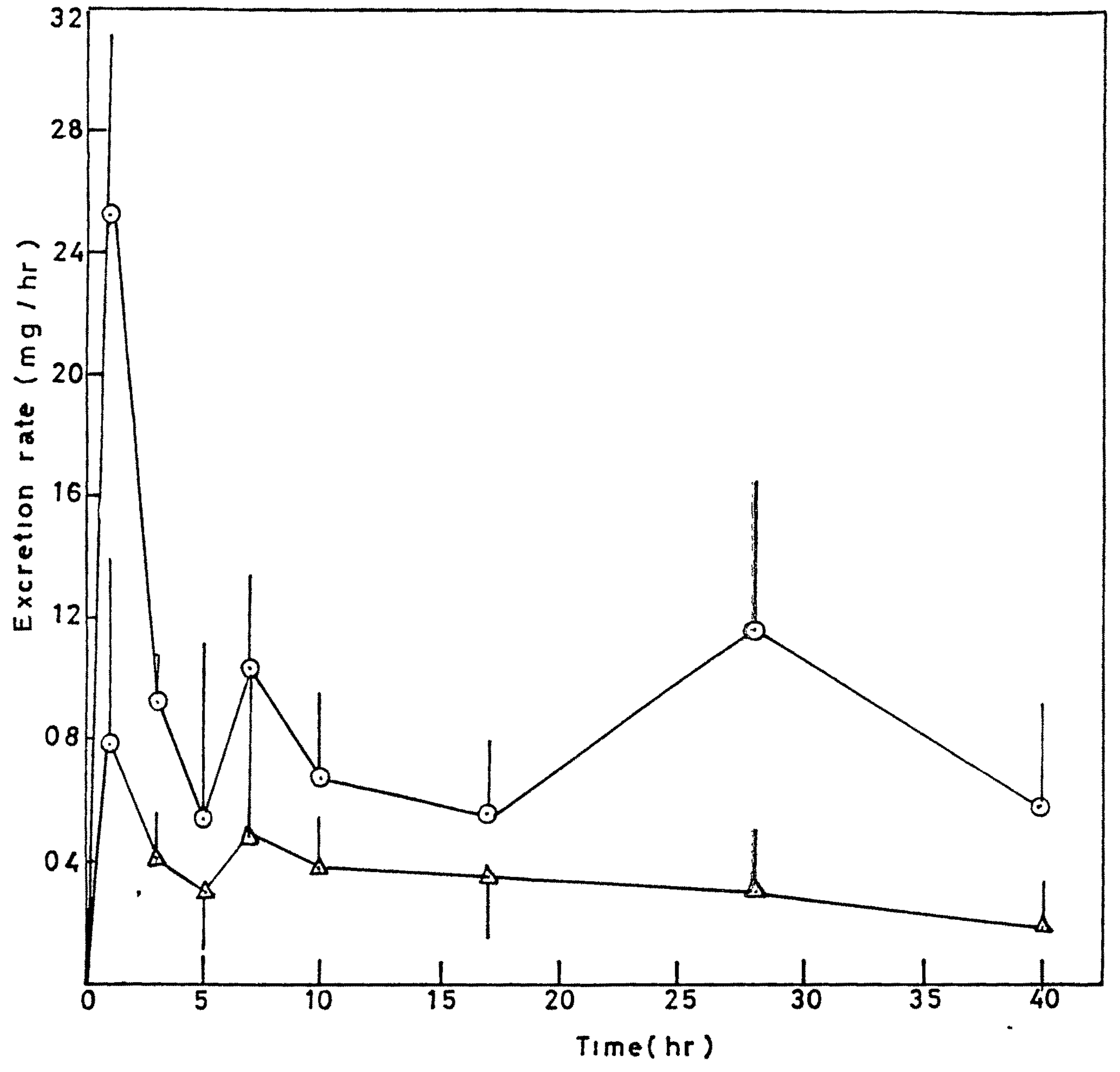

Fig 21 URINARY EXCRETION RATE OF PHENYTOIN FOLLOWING THE ORAL ADMINISTRATION OF 800 mg. PHENY - POS SD (O) AND 300 mg OF PHENY (Δ).

EACH POINT REPRESENTS THE MEAN ± S.D. OF FIVE SUBJECTS.

reported to be inversely related to the particle size (Chakrabarti et al, 1979).

Excretion rate at peak time(of drug) from solid dispersion was 3.2 times the excretion rate of Phenytoin itself and gave about 2.4 times larger AUC than Phenytoin, although the dose (as Phenytoin) was 2/3 of that for Phenytoin crystals.

Analysing the excretion rate data at the midpoint of collection time at 1 and 3 hr, the solid dispersion shows significantly higher excretion rates than Phenytoin itself ($P < 0.05$, one tail test). At 28 hr., solid dispersion exhibits higher excretion rate than Phenytoin ($P < 0.1$) but not significantly higher at $P = 0.05$. At rest of the time intervals, there is no significant difference in excretion rates.

The improved bioavailability of Phenytoin achieved by the solid dispersion should possibly permit to achieve a therapeutic blood concentration with a lower dose. The inter-subject variation of Phenytoin bioavailability in epileptic patients and healthy subjects could be explained by poor absorption due to the low solubility of Phenytoin in the gastrointestinal fluid. Thus, the improved characteristics of Phenytoin from solid dispersion should offer the clinical advantage of quick drug release and excellent bioavailability in Phenytoin therapy.