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# RETARDATION OF POLYMERIC CARRIER DISSOLUTION BY DISPERSED DRUGS : FACTORS INFLUENCING THE DISSOLUTION OF SOLID DISPERSIONS CONTAINING POLYETHYLENE GLYCOLS

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## ABSTRACT

Molecular weight is an important determinant of polyethylene glycol (PEG) dissolution rate; the rate decreasing as the molecular weight is increased. PEG samples of equivalent nominal molecular weight had different dissolution properties. Intrinsic viscosity and differential scanning calorimetry suggested that the observed differences may be related to molecular weight variation between samples. The dissolution rate of PEG from solid dispersions is retarded, the effect being dependent on the chemical nature of the drug and its concentration. Phenobarbitone was particularly potent in retarding PEG dissolution. Phenobarbitone dissolution rate was retarded from dispersions of high phenobarbitone content. However drug dissolution from solid dispersions low in phenobarbitone were greater than that of pure phenobarbitone. The low dissolution rates were explained in terms of formation



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of the 2 : 1 PEG monomer : phenobarbitone complex during solid dispersion formation. At high PEG weight fractions (i.e. 30:1, 50:1) drug dissolution was carrier controlled and although PEG dissolution was greatly suppressed, it was sufficiently large to transport the drug into solution at a rate greater than that of pure phenobarbitone.

## INTRODUCTION

Solid dispersions containing water soluble polymers, such as polyethylene glycol (PEG) and polyvinylpyrrolidone have successfully enhanced the dissolution rate of drugs of low solubility [1,2]. Polyethylene glycols have an added technological advantage, in that they are crystalline, have relatively low melting points and therefore dosage forms may be processed from the liquid phase [2]. In many soluble polymer based solid dispersions, where the proportion of drug is less than 20% and where the drug is thought to be molecularly dispersed, drug release is expected to become carrier controlled i.e. drug dissolution rate becomes dependent on the product of the carrier dissolution rate and the proportion of drug dispersed[3]. Thus drug dissolution rates in such systems may be predicted from Eq. 1:

$$G_d = \frac{A_d \cdot G_p}{A_p} \qquad (1)$$

where $G_d$ is the dissolution rate of the drug from the dispersion, A is the component concentration in the system and $G_p$ is the dissolution rate of the carrier. As a first approximation the drug

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release rate may be estimated by assuming that the dissolution rate of the polymer $G_p$ is independent of the drug dispersed[3,4]. However limited studies with such carriers as PVP[5], PEG[6], Renix[7] and β-cyclodextrin[8] have generally shown a decline in carrier dissolution rate. In this paper some of the factors influencing polymeric carrier dissolution will be examined with particular reference to the PEG - phenobarbitone systems.

## MATERIALS AND METHODS

### Dissolution Rate and Solubility Determinations

Dissolution rates from constant surface area discs were determined by the modified beaker method[9,10] as previously described[11]. The effect of PEG on the apparent drug solubility was determined by a method similar to that of Shefter and Higuchi[12].

### Assay Procedures

Polyethylene glycols ( 1000, 4000, 6000 as supplied by Brome and Schimmer Ltd., B.D.H. Chemicals Ltd., Union Carbide and Sigma Ltd.) were assayed colorimetrically[6]. Hydroflumethiazide (Leo Laboratories Ltd.) 273 nm, bendroflumethiazide (Leo Laboratories Ltd.) 273 nm, barbituric acid (BDH Chemicals) 257 nm and phenobarbitone 240 nm[13] (prepared from phenobarbitone sodium B.D.H. Chemicals) were assayed by ultra violet spectroscopy.

### Preparation of PEG - drug systems

PEG-drug systems of varying composition were prepared by the melt, coprecipitate and mechanical mix methods, as previously described[14].

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X-Ray Diffraction and Differential Scanning Calorimetry (DSC)

X-Ray diffraction patterns were obtained on powder samples using nickel filtered copper radiation (Philips PW 1050/26). Samples, 2-10 mg, were examined by DSC (Perkin Elmer, Model DSC 1B) at scanning speeds of 2°, 8° and 16° $min^{-1}$.

Diffusion coefficients and viscosity measurements

The diffusion coefficients of PEG 1,000, 4,000 and 6,000 were determined by a modification of the method of Goldberg & Higuchi[15] as previously described[6]. Estimates of intrinsic viscosities and reduced viscosities were obtained from flow times measured in water at 37° using a calibrated Ostwald U-Tube viscometer[16].

## RESULTS AND DISCUSSION

Physicochemical properties of PEG samples

Previously we have shown that the intrinsic dissolution rate of PEG samples decreased as the nominal molecular weight increased. The molecular weight of poly(ethylene oxide) samples may be estimated from the intrinsic viscosity $[\eta]$[17] by an equation of the form

$$[\eta] = 16.6 \times 10^{-5} M^{0.82} \quad (2)$$

where M is the molecular weight[18]. Values obtained together with aqueous diffusion coefficients and corresponding dissolution rates are summarized in Table 1. The decrease in dissolution rate with increasing molecular weight corresponds with a decrease in diffusion coefficients. In view of the relatively high solubilities, low melting points and relatively constant heats of fusion of the macrogols[17] diffusion rather than solubility considerations are

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TABLE 1

Molecular weights, diffusion coefficients and dissolution rates of PEG samples at 37°C.

| Molecular Weight | | Diffusion Coefficient | Dissolution Rates* |
|---|---|---|---|
| Nominal | Estimated | D $cm^2/sec$ | G $mg/cm^2/h$ |
| 1000 | 1427 | $3.82 \times 10^{-6}$ | 1018.2 |
| 4000 | 3897 | $3.10 \times 10^{-6}$ | 649.2 |
| 6000 | 6328 | $2.47 \times 10^{-6}$ | 486.0 |
| 20,000 | ---- | ---- | 259.7 |

* From Ref. 6

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likely to be dominant in determining the dissolution rate of pure polymer samples.

In polymers, dissolution is critically dependent on diffusion within the swollen surface layer and on the thickness of this swollen layer[19]. Increasing the polymer chain length reportedly decreases the velocity of dissolution due to increased entanglement of the macromolecules[19]. An empircal relationship between molecular weight and dissolution rate of the form

$$G = kM^{-A} \quad (3)$$

where G is the dissolution rate, M the molecular weight, k and A are constants, was proposed for polymers by Ueberreiter[19,20]. Using this relationship, the PEG dissolution rate ($G_{PEG}$) and molecular weight data may be related by Equation 4.

$$G_{PEG} = 4.623 \times 10^4 \ M^{-0.52} \quad (4)$$

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Significant differences in intrinsic dissolution rate between different batches of PEG, nominally having the same molecular weight designation, were observed. A major cause of these differences is molecular weight variations. Molecular weight estimates obtained from viscosity data using Equation 2 for different samples of PEG 4000 and PEG 6000 are summarized in Table 2.

Differences between batches of PEGs were also observed by DSC. Scans for four different lots of PEG 6000 determined at a heating rate of 2° $min^{-1}$ are shown in Fig. 1. Two or three endothermic peaks were evident in these samples. It is likely that these peaks reflect molecular heterogeneity. Differences in DSC scans were rarely evident at heating rates of 8° and 16° per minute. Polymer molecular weight distribution affects rate of crystallization[21], which in turn may influence the solid state characteristics of drugs in solid dispersions[22,3].

Inhibition of PEG dissolution

The dissolution profiles of PEG 4000 from solid dispersions containing 10% barbituric acid, phenobarbitone, bendrofluazide and hydroflumethiazide are compared to that of pure PEG 4000 in Figure 2. Barbituric acid apparently does not complex in aqueous media with PEG[13]. Phenobarbitone forms a complex of reduced solubility[13, 23] while bendrofluazide and hydroflumethiazide form soluble complexes[6]. The presence of 10% drug retarded the dissolution of PEG, the effect increasing in the order bendrofluazide, barbituric acid, hydroflumethiazide and phenobarbitone, the dissolution of polymer in the latter case being negligible. For the first three compounds Eq. 1 was used to estimate the release rate of the drug.

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TABLE 2

Batch variations in molecular weight for PEG 4000 and 6000 samples

| Nominal Molecular Weight | Estimated Values* |
|---|---|
| PEG 4000 | 3500, 4293 |
| PEG 6000 | 5126, 5756, 6546, 6910, 7301 |

*Equation 2

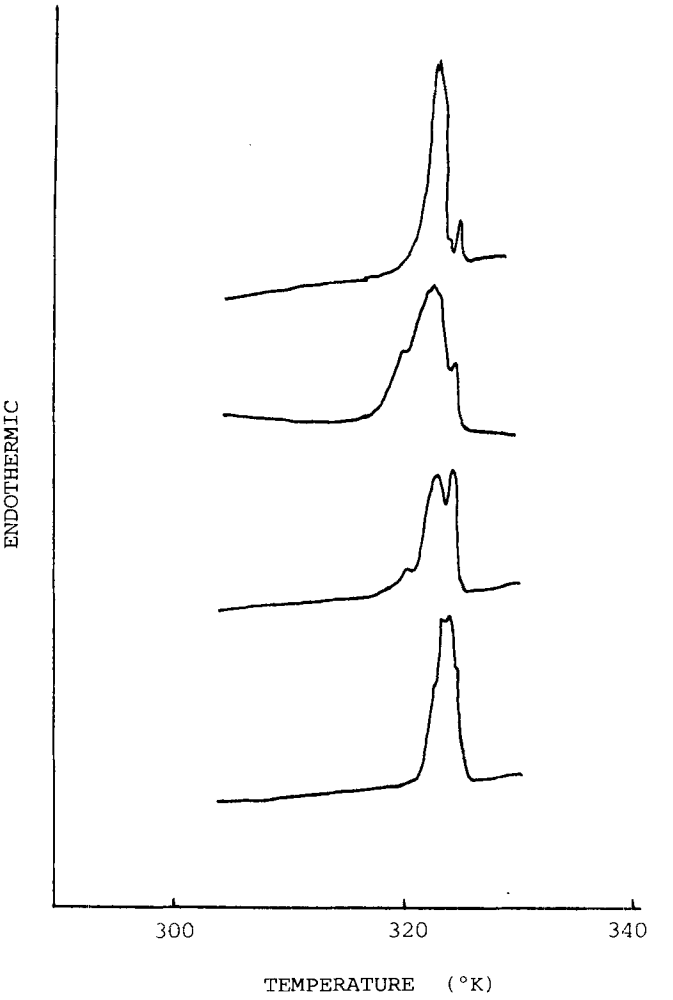


FIGURE 1

DSC Scans of four batches of PEG 6000 determined at a heating rate of 2° $min^{-1}$.

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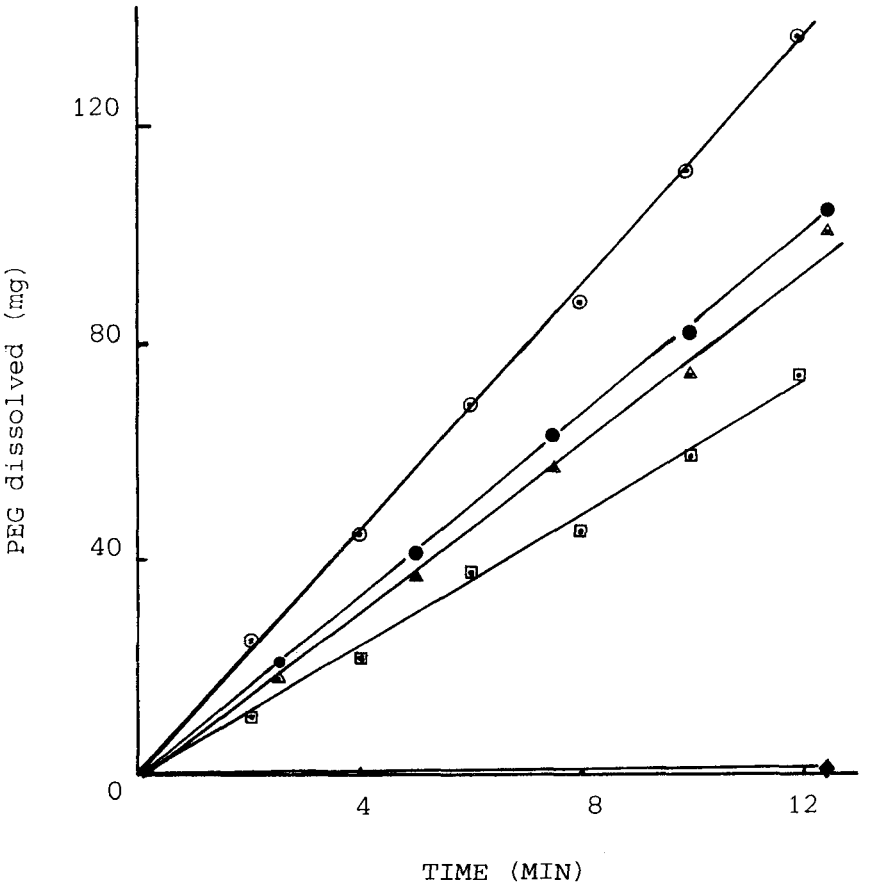


FIGURE 2

Dissolution profiles of PEG 4000 from solid dispersions containing 10% drug. Key= ⊙ Pure PEG; ● PEG-bendrofluazide; ▲ PEG-barbituric acid; ⊡ PEG-hydroflumethiazide, and ◆ PEG-phenobarbitone.

The predicted and experimental values were in good agreement (Table 3). Decreasing the proportion of drug reduced the inhibiting effect on PEG dissolution, and drug release continued to obey Eq.1. Increasing the proportion of drug however ultimately leads to a cessation of carrier control[3], the point at which this occurs being a function of the drug entity[3,4]. Data on the extent of PEG

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TABLE 3

Summary of percentage retardation of PEG dissolution by added drug together with theoretical and experimentally determined drug release rates.

| Drug | Composition PEG : Drug | Carrier Dissolution as % of pure PEG | Drug Dissolution Rate Experimental | Theoretical[2] |
|---|---|---|---|---|
| Bendrofluazide | 20 : 1 | 83.8 | 26.1[1] | 27.2 |
| | 10 : 1 | 73.8 | 43.9[1] | 47.9 |
| Barbituric Acid | 30 : 1 | 73.4 | 9.5 | 9.5 |
| | 10 : 1 | 70.9 | 26.2 | 27.6 |
| Hydroflumethiazide | 20 : 1 | 60.2 | 18.4[1] | 19.6 |
| | 10 : 1 | 51.7 | 36.3[1] | 33.6 |
| Phenobarbitone | 30 : 1 | 33.2 | 6.9 | 7.2 |
| | 50 : 1 | 51.6 | 6.5 | 6.6 |

[1] from ref. 6

[2] Equation 1

dissolution inhibition and on the theoretical and experimental drug release rates are summarized in Table 3.It is evident that failure to take into account the retardation of polymer dissolution may lead to a significant overestimation of drug release rate.

Dubois and Ford presented release data for 10 drugs from PEG 6000 solid dispersions which strongly support the hypothesis that drug dissolution is controlled by the carrier[4]. Equation 1 was therefore used to estimate PEG dissolution from these systems. The results confirm retardation of PEG dissolution with increased drug content, the the magnitude of the effect being highly dependent on the drug employed.

Phenobarbitone: PEG 4000 systems

In view of the dramatically reduced dissolution properties of phenobarbitone:PEG solid dispersions, this system was selected for more detailed study. Dissolution rates of PEG and phenobarbitone from mechanical mixtures and solid dispersions over a range of weight fractions were determined. The results are summarized in Table 4 . The dissolution rate of phenobarbitone decreased as the proportion of PEG was increased in the range 0 - 90% PEG. PEG dissolution rates increased. At higher weight fractions, the discs of mechanical mixtures tended to disintegrate and intrinsic dissolution rates could not be determined. The dissolution rates of both components from the corresponding solid dispersions were lower than those of mechanical mixtures of similar weight fractions. At a PEGweight fraction of 0.23 the dissolution rate of phenobarbitone was less than 25% that of the pure drug. On further increasing the PEG content the phenobarbitone rate increased

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TABLE 4

Effect of Composition on the Dissolution Rates from Compressed Discs of Phenobarbitone ($G_d$) and PEG 4000 ($G_{PEG}$) coprecipitates and physical mixtures at 37°C.

| Composition | | Dissolution Rates ($mg.hr^{-1}$) | | | |
|---|---|---|---|---|---|
| | | Physical Mixtures | Coprecipitates | | |
| PEG : Drug | PEG (%) | $G_d$ | $G_d$ | ($G_d/G_p$) | $G_{PEG}$ |
| 0 : 1 | 0 | 5.95 | 5.95 | (1.00) | ---- |
| 1 :10 | 9.09 | 2.35 | 2.33 | (0.39) | ---- |
| 3 :10 | 23.1 | 2.31 | 1.36 | (0.23) | ---- |
| 10 : 1 | 90.9 | 5.68 | 2.30 | (0.39) | 0.8 |
| 20 : 1 | 95.2 | ---- | 4.96 | (0.83) | 3.3 |
| 30 : 1 | 96.8 | ---- | 9.09 | (1.53) | 285.9 |
| 50 : 1 | 98.0 | ---- | 8.65 | (1.45) | 444.9 |
| 1 : 0 | 100 | ---- | ---- | ---- | 861.7 |



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reaching a maximum 1.53 times that of pure phenobarbitone at a phenobarbitone weight percentage of 3.2%. At this drug content the PEG dissolution rate was 33.2% that of pure PEG. Decreasing the phenobarbitone content of the dispersion further to 2% resulted in an increase in dissolution rate of PEG to a value 51.6% that of pure PEG. The dissolution rate of phenobarbitone decreased however because of the lower content of drug in the solid dispersion. Interestingly the release of drug from the 30 : 1 and 50 : 1 PEG-drug systems was carrier controlled and the theoretical and experimental rates are included in Table 3 .

To shed further light on the nature of PEG - phenobarbitone interaction, mechanical mixtures over a range of weight fractions were prepared and examined by DSC. The results obtained together with those of the pure materials are included in Fig. 3. As the content of PEG in the mix was increased, the endotherm at 324°K, corresponding to the melting of PEG, increased while the phenobarbitone peak at 448° decreased and became negligible at ~30 - 40% PEG. In this weight range a new endothermic peak developed at 422°. In these mixtures both the endotherms at 324° and 422° were immediately followed by small exotherms. As the PEG content was further increased the peak at 422° decreased in size, becoming negligible at about 80% PEG.

The formation of a phenobarbitone:PEG complex in aqueous media, having a phenobarbitone to PEG monomer ratio of the order of 1 : 2 (i.e.72% phenobarbitone)[23] and 1 : 2 .4(i.e. 68% phenobarbitone) has been reported[13]. In addition this complex was also prepared from pyridine solution by coprecipitation[24]. It appears therefore that the endotherm at 422° is due to the formation, following melting, of the phenobarbitone:PEG complex. This proposition was supported by the

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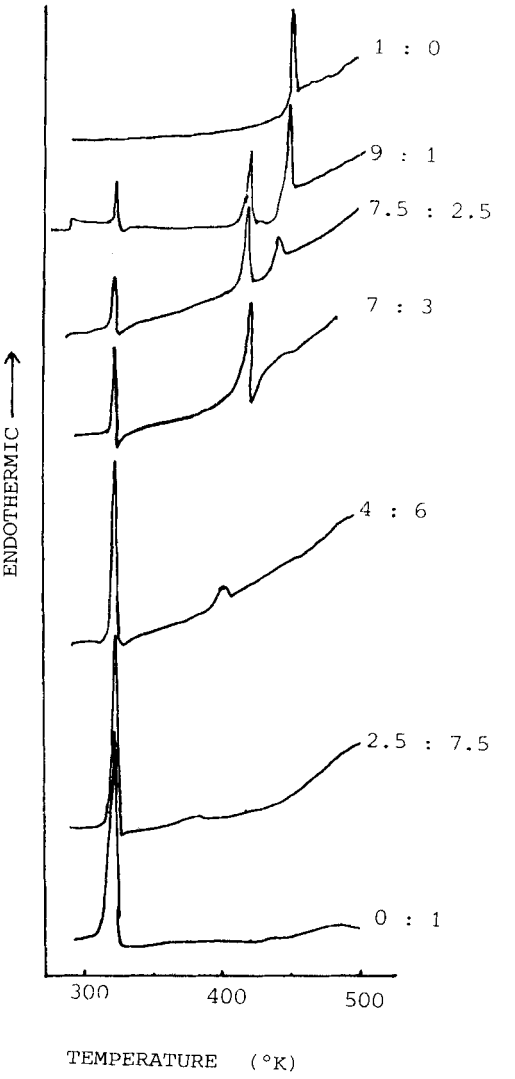


FIGURE 3

DSC Scans of mechanical mixtures of phenobarbitone and PEG 4000 at a heating rate of 8° $min^{-1}$. Key = Ratios refer to the proportion of phenobarbitone to PEG in the mixture.

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observed absence of the PEG endotherm at 324° from melts containing greater than 70% phenobarbitone, indicating that the PEG has formed the complex. X-Ray diffraction scans of pure PEG, phenobarbitone, a PEG-phenobarbitone mechanical mixture and melt are shown in Fig 4 . These scans also support formation of the PEG-phenobarbitone complex and are consistent with published X-Ray diffraction data (25). From these results an explanation can be offered for the very low dissolution rates from systems containing a high proportion of phenobarbitone. Solid dispersions containing up to ~ 30% PEG appear to consist of PEG-drug complex and phenobarbitone. During dissolution the less soluble complex controls dissolution, hence, the limiting dissolution rate of phenobarbitone from these systems was less than that of pure phenobarbitone. The expected relative dissolution rate of the complex (R)[26]

$$R = \frac{G_c}{G_p} \qquad (5)$$

where $G_c$ is the dissolution rate of the pure complex and $G_p$ is the dissolution rate of pure phenobarbitone, was estimated from the data of Singh et al[22] to be 0.337 . Since the complex was 68% phenobarbitone, the expected phenobarbitone relative release rate is 0.23. This value is in agreement with the minimum relative rate of 0.23 observed for phenobarbitone from the solid dispersions (Table 4 ). The higher, though still suppressed, release rates observed for mechanical mixtures reflect the less complete formation of complex during dissolution in these systems.

Phenobarbitone : PEG solid dispersions containing more than 30% PEG consist of PEG and or PEG-drug complex(es) all the free phenobarbitone having been converted to complex. The presence of the com-

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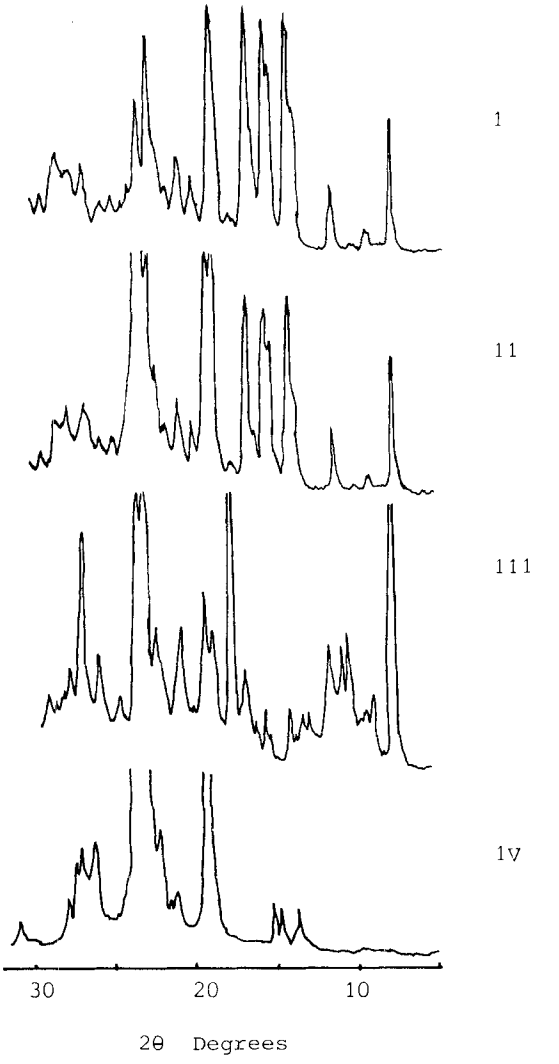


FIGURE 4

X-Ray diffraction scans of phenobarbitone (1), phenobarbitone : PEG 4000 (7:3) mechanical mixture (11), phenobarbitone : PEG 4000 (7:3) melt system (111) and pure PEG 4000 sample (1V).

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plex, having both a lower solubility and diffusion coefficient than phenobarbitone, will shift the critical mixture ratio to a higher PEG weight fraction[3], thus further limiting the weight fraction range over which PEG controls dissolution. Chang et al inferred from IR spectral analysis[24] that the factors responsible for complexation of phenobarbitone with PEG 4000 were hydrogen bonds formed between the $N^1$ and $N^3$ hydrogens ofthe barbiturate ring and the ether oxygen links of PEG. The retardation of PEG dissolution may be related to the hydrophobic nature of the complex. In addition, since the complex involves two ether linkages per phenobarbitone molecule, phenobarbitone may form crosslinks between PEG polymer chains, thereby increasing the effective molecular weight and retarding dissolution as indicated by Equation 3.

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