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The properties of solid dispersions of indomethacin or phenylbutazone in polyethylene glycol

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Summary

The effects of molecular weight of polyethylene glycols (PEGs) on the dissolution rates and crystallinity of its solid dispersions with indomethacin and phenylbutazone have been examined. The dissolution rates of both solid-dispersed drugs decreased as the molecular weight of PEG increased. The indomethacin dissolution profiles were essentially linear using constant surface area disc methodology and a limiting dissolution rate of about 10.6 $mg \cdot min^{-1}$ was observed. The phenylbutazone dissolution profiles were, however, generally linear-curvic usually giving lower release rates than the comparative indomethacin weight fractions. A limiting dissolution rate for the linear portions of the profiles was about 1.8 $mg \cdot min^{-1}$. Infra-red spectra indicated that the differences between the two drugs could partly be explained on the basis of PEG crystallinity. Generally bands in the ranges 1100–1130 and 1200–1400 cm^{-1} were poorly differentiated in indomethacin dispersions (PEG 1500, PEG 4000 and PEG 6000) but were better differentiated in phenylbutazone dispersions (PEG 4000, PEG 6000 and PEG 20,000). A greater proportion of amorphousness within the PEG moiety was predicted in indomethacin dispersions by the appearance of a new weak band at 1326 cm^{-1} and by a decrease in intensity of the band at 845 cm^{-1} at the expense of the peak at 960 cm^{-1}. The evidence was supported by differential scanning calorimetry. The heats of fusion were 44.7, 46.4, 47.2 and 39.5 $cal \cdot g^{-1}$ for PEG 1500, PEG 4000, PEG 6000 and PEG 20,000 respectively. Heats of fusion for indomethacin dispersions (2, 5 and 10% drug) were generally lower than for the corresponding values for phenylbutazone dispersions with the exception of PEG 20,000 dispersions. For example, values were obtained of 30.6 and 37.9 $cal \cdot g^{-1}$ for PEG 1500 dispersions containing 10% indomethacin and phenylbutazone, respectively.

Introduction

The dissolution rates of poorly water-soluble drugs may be increased by their prior dispersion in a water-soluble carrier (Chiou and Riegelman, 1971). The most commonly used carriers are long-chain polymers, e.g. polyvinylpyrrolidone or polyethylene glycol (PEG). The increases in dissolution rate from these solid dispersions may be very high and e.g. Ford and Rubinstein (1978) demonstrated that the dispersion containing 15% indomethacin in PEG 6000 provided a 200-fold increase in the dissolution rate of the drug. These increases are composition-dependent and Dubois and Ford (1985) showed that the range over which these large increases were obtained varied with the drug. Linear relationships between dissolution rates and

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the drug content were obtained from dispersions containing 0–10% indomethacin, but only 0–2% phenylbutazone in PEG 6000. Both these systems had been previously studied. Allen and Kwan (1969) demonstrated that rapid release rates were obtained from PEG 6000 dispersions containing 10% indomethacin. Ford and Rubinstein (1978) showed the system was a eutectic containing 13% drug with a solid solution of indomethacin in PEG at low drug levels. Maximum dissolution rates were obtained from the dispersion containing 15% indomethacin but decreased markedly on storage (Ford and Rubinstein, 1979) due to recrystallization (Saboe and Dempski, 1976).

Hoelgaard and Møller (1975) produced a phase diagram for phenylbutazone-PEG 6000 which exhibited a eutectic containing 28% drug. El-Banna and Abdallah (1980) demonstrated that the dissolution rates from dispersions decreased as the phenylbutazone content was increased from 5% to 80%. The rates decreased on storage (Khalil and Mortada, 1978).

In the light of evidence reported by Dubois and Ford (1985) that the composition providing maximum dissolution rate differed markedly for PEG 6000 dispersions containing indomethacin and phenylbutazone, this paper evaluates the influence of PEG molecular weight on the properties of its dispersions containing these drugs using constant surface area dissolution methodology and diffuse reflectance infra-red spectroscopy (IR) and differential scanning calorimetry (DSC).

Materials and Methods

Indomethacin B.P. and phenylbutazone (Sigma Chemicals, U.S.A.) were used without further purification. The polyethylene glycols were of nominal molecular weights 1500, 4000 and 6000 (all B.D.H., U.K.) and 20,000 (Sigma Chemicals).

Solid dispersion preparation

The dispersions of the drugs in PEGs were prepared by fusion at the minimum temperature required to effect total solution of the two components (105°C for phenylbutazone and 120°C for indomethacin dispersions). For dissolution studies the molten dispersions were poured into upturned aluminium vial covers (2 cm internal diameter) so that an excess existed and allowed to solidify at 4°C on stainless steel. For IR and DSC studies the dispersions were cast on glass chilled to 4°C.

Dissolution studies

Dispersions containing 2.5, 5, 7.5, 10, 12.5, 15 and 20% indomethacin or 0.5, 1.0, 1.5, 2.0, 2.5, 3, 4, 5 and 7.5% phenylbutazone were prepared. Immediately prior to a dissolution study, 1 h after preparation, the excess dispersion was sliced away to produce constant surface area discs as previously described (Ford and Rubinstein, 1977, 1978). Dissolution rates were determined using the Copley computerized dissolution system, Series 8000. Distilled water (1000 ml), maintained at 37°C was used as the dissolution fluid and the discs were rotated at 100 rpm, 3 cm above the flat bottom of the flask. Indomethacin and phenylbutazone were monitored at 320 and 264 nm, respectively and PEG did not interfere with either assay. The studies were performed in duplicate.

Intra-red analysis

Infra-red spectra were obtained using a Perkin-Elmer Model 1500 Fourier Transform Infra Red Spectrophotometer with a diffuse reflectance accessory and liquid nitrogen cooled narrow band M.C.T. detector. To obtain the diffuse reflectance spectrum an approximately 1 : 10 mixture of the sample and potassium bromide was ground in an agate mortar. The average of 64 scans of this powder in a 10 mm cup was ratioed against the same number of scans of potassium bromide as background. A 19 point smoothing correction was applied to this spectrum which was then absorbance expanded and converted to a Kubelka-Munk spectrum using the data handling function of the attached Perkin-Elmer 3600 Data Station. Spectra were obtained of the PEGs, indomethacin and phenylbutazone together with those of melts and physical mixes of 2% and 5% drugs in the polymers. Additions and subtractions were also made on the spectra of the pure drugs and polymers to produce spectra equivalent to those of physical mixes containing 2 or 5% drug.

Differential scanning calorimetry

Samples, accurately weighed in the range 4–12 mg, were examined using a Perkin-Elmer DSC-1B differential scanning calorimeter. A heating rate of $8°C \cdot min^{-1}$ was used from ambient in an atmosphere of static air using uncrimped aluminium sample pans and lids. The resultant melting endotherms were integrated using a Spectra-physics Autolab Minigrator to determine heats of fusion against indium as standard ($\Delta H_f = 6.80$ cal $\cdot g^{-1}$). The dispersions examined contained 2, 5 and 10% drug.

Results and Discussion

Effect of PEG molecular weight on dissolution

Indomethacin

The dissolution profiles of the indomethacin dispersions were linear (Fig. 1). The dissolution rates are given in Table 1 and generally rank at any given composition as PEG 1500 > PEG 4000 > PEG 6000 > PEG 20,000. This ranking concurs with previous findings, e.g. Ford (1984), Corrigan et al. (1979) and Krasowska et al. (1975), that the dissolution rates of drugs from PEG dispersions decrease as the molecular weight of the glycol increases. Ford (1984) and Ford and Rubinstein (1978) have demonstrated that the dissolution rates of solid-dispersed drugs at high PEG levels are linearly dependent on the drug content. Similar relationships existed for dispersions containing 0–10% indomethacin in the polyethylene glycols examined. The calculated values of the slopes describing these relationships were 0.987, 0.643, 0.415 and 0.157 $mg \cdot min^{-1} \cdot \%^{-1}$ for the dispersions containing PEG 1500, PEG 4000, PEG 6000 and PEG 20,000, respectively.

During dissolution indomethacin precipitated at drug concentrations in excess of 40 $mg \cdot l^{-1}$.

TABLE 1

THE EFFECT OF COMPOSITION AND PEG MOLECULAR WEIGHT VARIATION ON THE DISSOLUTION RATES ($mg \cdot min^{-1}$) OF INDOMETHACIN FROM INDOMETHACIN-PEG SOLID DISPERSIONS

Dispersion composition (% indomethacin)	Dissolution rates			
	PEG 1500	PEG 4000	PEG 6000 *	PEG 20,000
2.5	3.55	1.37	1.26	0.46
5.0	4.78	2.59	2.73	0.77
7.5	8.38	4.06	3.42	1.30
10	10.57	6.24	4.67	1.59
12.5	10.25	7.28	6.71	1.66
15	9.40	9.35	6.09	2.86
20	8.08	4.17	5.07	1.49

* Data from Dubois and Ford (1985).

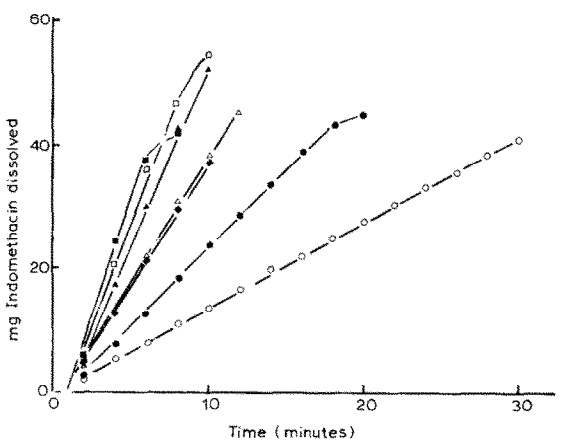

Fig. 1. Dissolution profiles of some indomethacin-PEG 4000 dispersions into distilled water at 37°C. ○, 2.5%; ●, 5%; △, 7.5%; ▲, 10%; □, 12.5%; ■, 15%; ◆, 20% indomethacin.

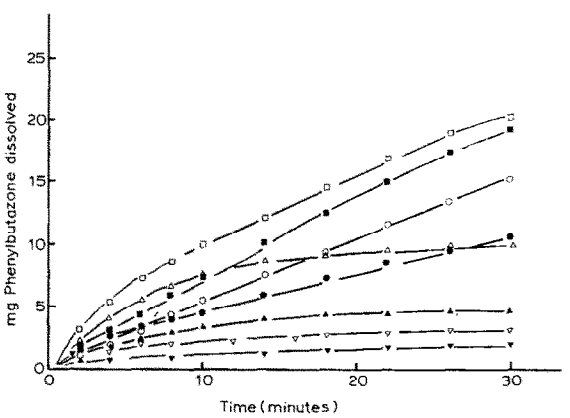

Fig. 2. Dissolution profiles of some phenylbutazone-PEG 6000 dispersions into distilled water, at 37°C. ●, 0.5%; ○, 1.0%; ■, 1.5%; □, 2.0%; △, 2.5%; ▲, 3.0%; ▽, 4%; ▼, 5% phenylbutazone.

However, the actual concentration at which it occurred was unpredictable, presumably due to inconsistent nucleation.

An interesting phenomenon is the similarity in release rates of PEG 1500 dispersions containing 10–15% indomethacin. The mathematical models describing release from solid dispersions predict a distinct drug concentration that provides the highest release rates (Corrigan and Stanley, 1982). This broad optimum may represent saturation of the processes contributing to the removal of drug from the dissolving dispersion and which is not encountered in the slower dissolving higher molecular weight fractions of PEG which displayed a sharper dissolution rate optimum (Table 1).

Phenylbutazone

In contrast to indomethacin, the phenylbutazone profiles were usually curved giving considerably lower dissolution rates. Fig. 2 displays the profiles of PEG 6000-dispersions which were linear throughout the dissolution period of 30 min for those containing 0.5–1.5% phenylbutazone. At higher drug levels the profiles were lineo-curvic. The PEG 1500, PEG 4000 and PEG 20,000 dispersions behaved similarly and were linear only for drug contents of 0.5–2.5%, 0.5–1.5% and 0.5–1.0% phenylbutazone, respectively.

Consequently the release rates, given in Table 2 were calculated only from initial dissolution data. However, these rates were less consistant than those of indomethacin probably due to their being of a lower magnitude. The curvature probably represents a conversion from a PEG-controlled release to a phenylbutazone-controlled release as the disc surface becomes depleted in PEG.

An analogous situation is apparent in Table 2 to that observed for indomethacin-PEG 1500 dispersions. The release rates of the PEG 1500 dispersions containing 0.5–4% phenylbutazone were similar, representing saturation of the processes involved in the transport of phenylbutazone from the dissolving surface. The influence of PEG molecular weight on the dissolution rate of phenylbutazone was not as clear-cut as for indomethacin, although generally for drug contents of up to 2.5% phenylbutazone the PEGs could be ranked according to their release rates as PEG 1500 > PEG 4000 > PEG 6000 > PEG 20,000. Above this drug level the ranking was less predictable due in part to the low amounts of drug dissolved and the poor reproducibility in the release rates of these systems, a phenomenon noted previously for glutethimide–PEG dispersions (Ford, 1984). It is apparent that the content of the dispersions giving maximum release rates was about 5 times lower for phenylbutazone dispersions than the indomethacin dispersions. Because of the dissimilarities in dissolution rates from the two systems characterization of the physical states of the dispersions at low drug levels was attempted using DSC and diffuse reflectance IR spectroscopy since at high polymer levels the dissolution rates would be controlled by the structure of the PEG rather than that of the drugs. Additionally no evidence was found for the formation of a complex with either drug with PEG. Differential scanning calorimetry has been used previously to quantify PEG 6000 dispersions of indomethacin (Ford and Rubinstein, 1978) and phenylbutazone (Hoelgaard and Møller, 1975) but no interpretation of structure was attempted apart from identifying the existence of a solid solution of indomethacin in PEG 6000. However, since the compositions ex-

TABLE 2

THE EFFECT OF COMPOSITION AND PEG MOLECULAR WEIGHT VARIATION ON THE INITIAL DISSOLUTION RATES ($mg \cdot min^{-1}$) OF PHENYLBUTAZONE FROM PHENYLBUTAZONE-PEG SOLID DISPERSIONS

Dispersion composition (% phenylbutazone)	Dissolution rates			
	PEG 1500	PEG 4000	PEG 6000 **	PEG 20,000
0.5	1.66	0.43	0.31	0.24
1.0	1.70	0.55	0.53	0.33
1.5	1.49	0.69	0.72	0.63 *
2.0	1.79	1.11 *	0.95 *	0.50 *
2.5	1.61	1.08 *	1.01 *	0.40 *
3	1.25 *	1.45 *	0.77 *	0.58 *
4	1.83 *	1.27 *	0.33 *	0.70 *
5	0.65 *	0.75 *	0.07 *	0.85 *
7.5	0.57 *	0.04 *	–	0.20 *

* Calculated from the initial linear portion of the dissolution profiles.

** Data from Dubois and Ford (1985).

amined were to the PEG-rich side of the eutectic composition, the thermograms showed single endotherms only with occasional minor inflections on the up-curve. The areas defined by the endotherms were integrated as representative of heats of fusion.

Infra-red spectroscopy

Although IR analysis has been used to quantify the interaction in solid dispersions between drug and carrier, e.g. chloramphenicol with polyvinylpyrrolidone or PEG (Kassem et al., 1979), few pharmaceutical studies have attempted to interpret the IR spectra of PEG. The spectrum of PEG is already well established. Davison (1955) originally attempted to allocate the IR spectra to a predominantly gauche configuration of the $-O-(CH_2)_2-O-$ portion of the polymer chain. White and Lovell (1959) further confirmed that PEG existed in essentially the gauche conformation in both the liquid and solid phases. However, Miyake (1961) considered that the $-O-(CH_2)_2-O-$ groups existed in both the trans and gauche conformations. This configuration has subsequently been confirmed (Miyazawa et al., 1962; Todokoro et al., 1964; Matsuura and Miyazawa, 1968). Vibrational analysis of PEG in the molten state has also been examined (Matsuura and Miyazawa, 1969). Consequently the assignments quoted in this paper are, unless otherwise stated, the vibrational assignments of Matsuura and Miyazawa (1968) and the vibrations in the range 750–1400 cm^{-1} have been most closely considered since this corresponds to the CH_2 vibrations within the polymer.

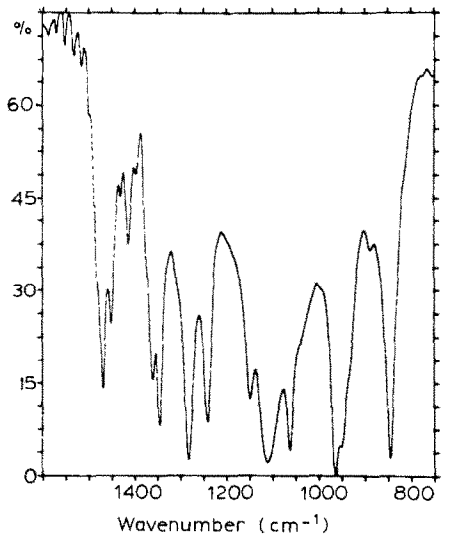

Fig. 4. Infra-red reflectance spectrum of PEG 4000.

Effect of molecular weight of PEG

The major changes occurring in the IR spectra

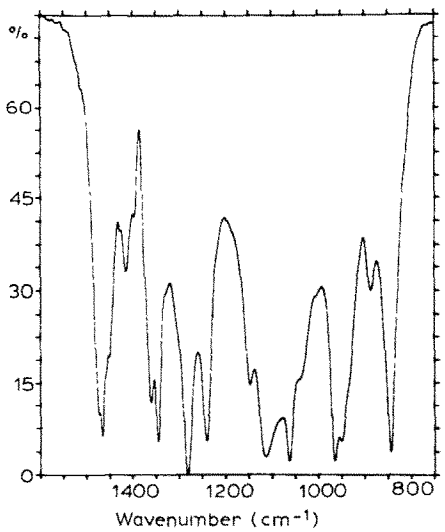

Fig. 3. Infra-red reflectance spectrum of PEG 1500.

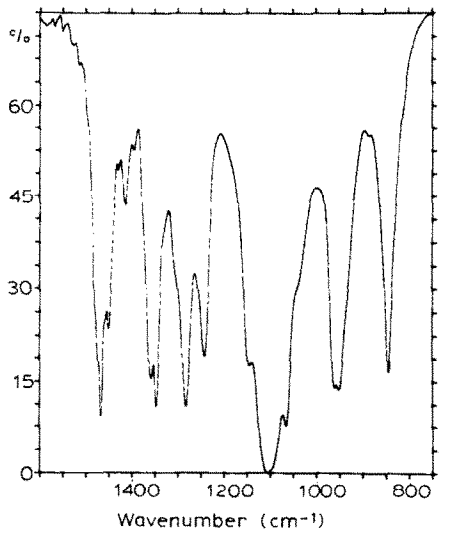

Fig. 5. Infra-red reflectance spectrum of PEG 6000.

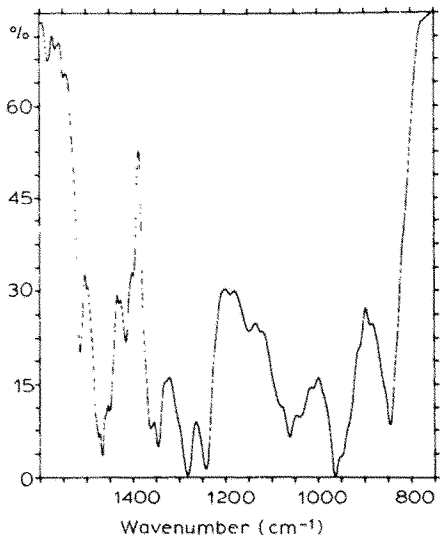

Fig. 6. Infra-red reflectance spectrum of PEG 20,000.

of PEG with increase in molecular weight may be followed in Figs. 3–6. The band at about 886 cm^{-1}, assigned to vibrations in the $-CH_2CH_2OH$ end group (White and Lovell, 1959), decreased in intensity as the molecular weight increased corresponding to a decrease in frequency of end groups with increased molecular weight. The band at 1115 cm^{-1}, of maximum intensity in PEG 4000 and assigned to a hybrid of CO stretching and CH_2 rocking, decreased with both an increase and decrease in molecular weight. The peak at 1360 cm^{-1} (CH_2 wagging), of similar intensity in PEG 1500 and PEG 4000, decreased as the molecular weight further increased. An unassigned peak was apparent only in PEG 20,000 at 1512 cm^{-1}. The differentiation of the peaks in the range 1200–1380 cm^{-1} was less marked in PEG 20,000 and the band at about 1120 cm^{-1} was considerably reduced in this polymer.

Effect of fusion and recrystallization on PEG

Fusion only induced marginal changes in the IR spectra of the PEG samples. A weak shoulder at 1040 cm^{-1} increased in intensity in the PEG 1500 spectrum. This unassigned peak was reported by Yoshihara et al. (1964) to increase in intensity in the molten state and would therefore indicate that recently fused samples of PEG 1500 contained more amorphous moieties than unfused samples since the amorphous and molten states show similar IR spectra (White and Lovell, 1959). The broad strong band at 1100–1120 cm^{-1} decreased in intensity to that at 1062 cm^{-1}. Matsuura and Miyazawa (1969) indicated that such changes were typical of the amorphous and molecular states. Fusion in PEG 4000 produced similar changes in the broad band at 1110 cm^{-1} decreasing its wavenumber to 1100 cm^{-1} and reducing its intensity. The band at 947 cm^{-1} (hybrid: CH_2 rock; C–C stretch; CO stretch) increased in intensity whereas the peaks at 1150 cm^{-1} (CO stretch, CH_2 rock) and 1450 cm^{-1} (CH_2 scissor) decreased. For PEG 6000 the broad band at 1110 cm^{-1} decreased in intensity and, whereas prefusion the band at 947 cm^{-1} had a greater intensity to that at 965 cm^{-1} (CH_2 rock, CH_2 twist) fusion reversed this ranking. Matsuura and Miyazawa (1969) showed that the peaks at 947 and 960 cm^{-1} combined in the spectra of amorphous PEG.

The DSC data of the pure PEGs, all showing one broad endotherm, supports the increase of amorphousness following fusion and recrystallization (Table 3), the heats of fusion of the recrystallized materials being lower than the untreated PEGs for PEG 1500, PEG 4000 and PEG 6000. An estimate of crystallinity with the polymers may be based on the theoretical heat of fusion of the 100% crystalline polymer being 51.5 $cal \cdot g^{-1}$ (Beaumont et al., 1966) giving crystallinities for the untreated polymers as 81, 91, 92 and 77% for PEG 1500, PEG 4000, PEG 6000 and PEG 20,000, respectively. Törmälä and Savolainen (1973) have shown that highest crystallinities occur for PEG in the 4000–10,000 region. Only for PEG 20,000 did fusion and recrystallization increase the heat of fusion which is reflected in only small changes in the IR spectrum of this polymer. The 950 cm^{-1} shoulder was transformed by fusion to a weak peak at 948 cm^{-1} and the shoulder at 1075 cm^{-1} (unassigned) was lost.

Generally the spectra of the recently fused PEG samples displayed the same trends with regards to the effects of molecular weight as the unmodified samples. The peak at 886 cm^{-1} decreased in intensity as the molecular weight increased. The ratio of the doublet at 962:947 cm^{-1} decreased as the

TABLE 3

HEATS OF FUSION OF UNTREATED OR RECRYSTALLIZED POLYETHYLENE GLYCOL AND ITS SOLID DISPERSIONS WITH INDOMETHACIN OR PHENYLBUTAZONE

	Heats of fusion ($cal \cdot g^{-1}$) *			
	PEG 1500	PEG 4000	PEG 6000	PEG 20.000
Untreated	44.7 ± 1.5 (4)	46.4 ± 1.8 (4)	47.2 ± 1.0 (5)	39.5 ± 0.7 (4)
Recrystallized	42.5 ± 1.1 (4)	43.4 ± 2.2 (5)	44.9 ± 0.6 (4)	41.6 ± 2.8 (4)
2% Indomethacin	36.8 ± 1.9 (4)	43.7 ± 0.5 (3)	51.3 ± 2.9 (7)	42.2 ± 2.9 (4)
5% Indomethacin	35.8 ± 3.3 (4)	41.6 ± 3.6 (4)	42.6 ± 2.3 (7)	42.2 ± 4.0 (4)
10% Indomethacin	30.6 ± 1.8 (2)	34.6 ± 3.3 (2)	38.9 ± 3.9 (3)	44.8 ± 2.6 (4)
2% Phenylbutazone	39.2 ± 3.1 (3)	43.9 ± 1.2 (4)	47.9 ± 3.7 (6)	41.9 ± 6.6 (4)
5% Phenylbutazone	40.5 ± 4.3 (7)	42.4 ± 3.0 (4)	47.8 ± 2.8 (5)	40.3 ± 3.9 (4)
10% Phenylbutazone	37.9 ± 3.4 (4)	39.8 ± 1.8 (4)	42.9 ± 0.9 (4)	42.7 ± 1.6 (4)

* Mean ± standard deviation (no. of replicates).

molecular weight increased. At 1005 cm^{-1} a weak band was apparent in PEG 1500, a weak shoulder in PEG 4000 but no band for PEG 6000 or 20,000. A band at about 998 cm^{-1} is characteristic of the amorphous or molten state (Yoshihara et al., 1964). The peak at 1115 cm^{-1} showed maximum intensity in PEG 6000, but at lower molecular weights was broader and less intense. The weak band at 1148 cm^{-1} decreased in intensity as the molecular weight increased. The differential in the peaks at 1200–1400 cm^{-1} was less marked for PEG 20,000 than for the other molecular weights. A weak band at 1450 cm^{-1} showed maximum intensity in PEG 6000 and was only a shoulder in PEG 1500 and PEG 4000.

Spectral changes following fusion and recrystallization of drug–PEG physical mixes

The spectrum of indomethacin (Fig. 7) was similar but not identical to Nujol mull spectrum previously reported (e.g. Borka, 1974) presumably because it is a diffuse reflectance spectra. The spectrum of phenylbutazone (Fig. 8), however,

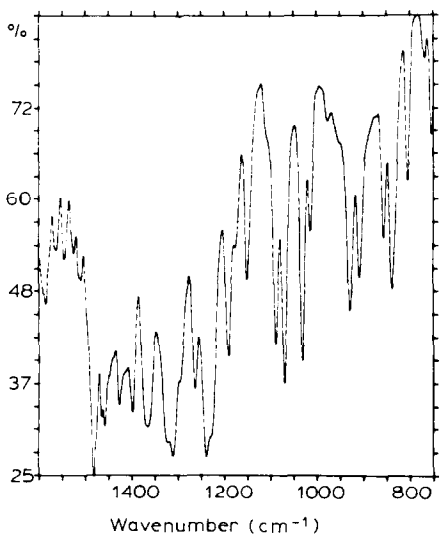

Fig. 7. Infra-red reflectance spectrum of indomethacin.

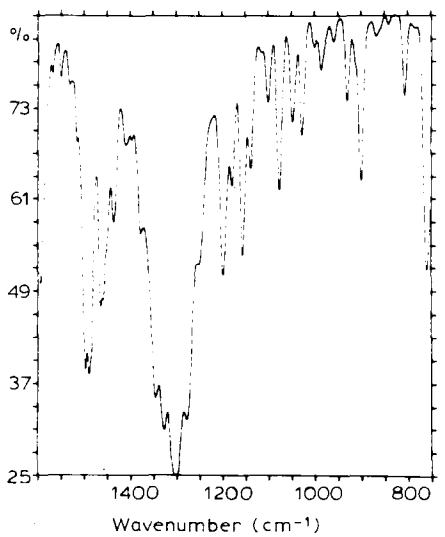

Fig. 8. Infra-red reflectance spectrum of phenylbutazone.

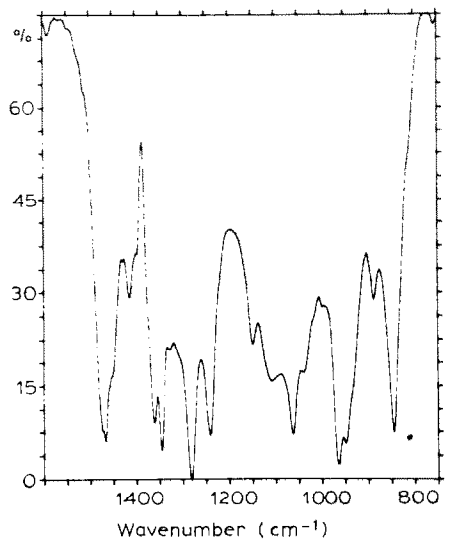

Fig. 9. Infra-red reflectance spectrum of a PEG 1500 solid dispersion containing 2% indomethacin.

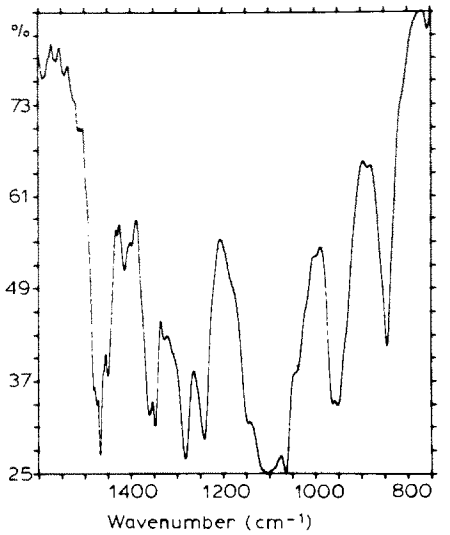

Fig. 11. Infra-red reflectance spectrum of a PEG 6000 solid dispersion containing 5% indomethacin.

corresponds to its KBr and Nujol-mull spectra. Diffuse reflectance IR spectroscopy was, however, used since it was found difficult to prepare successfully Nujol mulls of PEG and it was felt that compression into KBr discs may alter the polymorphic forms of the drugs, especially phenylbutazone for which compression-induced changes have been identified (Ibrahim et al., 1977).

It was initially envisaged that the spectra of the recently prepared dispersions could be compared with those obtained directly from physical mixes. However, the spectra of the latter were very different to those of the dispersions and corresponded to those of mixes containing disproportionally higher drug levels. Consequently the spectra of the physical mixes containing 2 and 5% drug levels

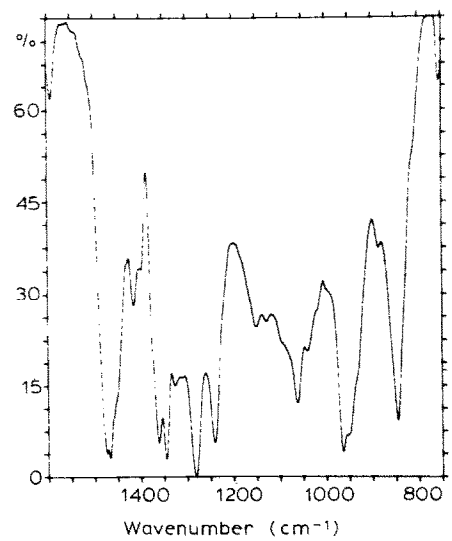

Fig. 10. Infra-red reflectance spectrum of a PEG 4000 solid dispersion containing 5% indomethacin.

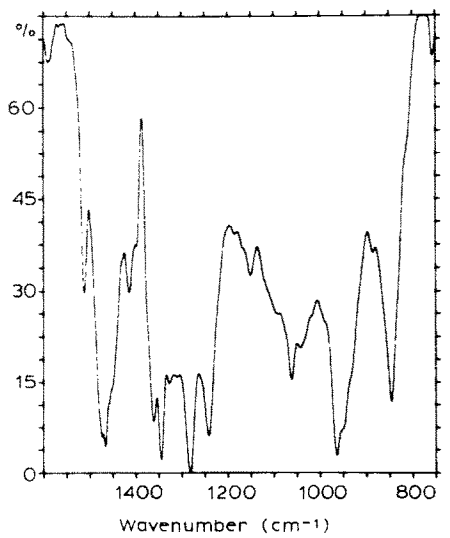

Fig. 12. Infra-red reflectance spectrum of a PEG 20,000 solid dispersion containing 5% indomethacin.

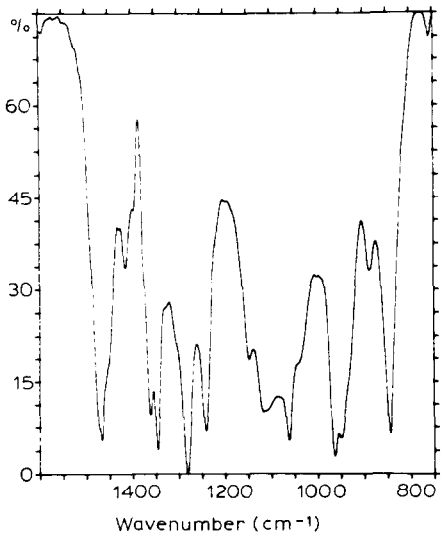

Fig. 13. Infra-red reflectance spectrum of a PEG 1500 solid dispersion containing 2% phenylbutazone.

were obtained by computer aided addition and subtraction of the spectra of the pure drugs and PEGs.

Indomethacin systems

Very similar changes occurred following fusion and recrystallization in the spectra of mixes containing 2 and 5% indomethacin (Figs. 9–12). The

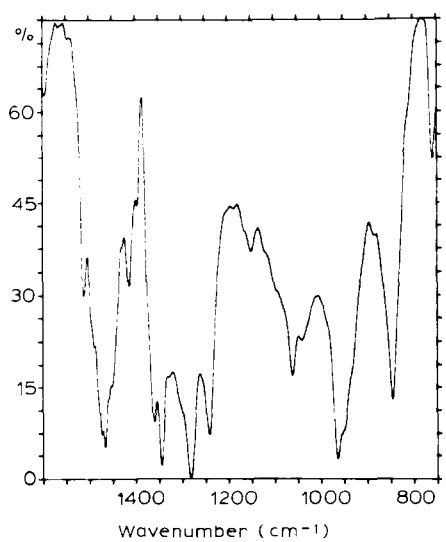

Fig. 14. Infra-red reflectance spectrum of a PEG 20,000 solid dispersion containing 5% phenylbutazone.

presence of indomethacin did not dramatically modify the spectra from those of the pure PEGs. Common to both drug concentrations was the formation of a new, unassigned band at about 754 cm^{-1} and loss of a weak band on PEG 20,000 samples at 910 cm^{-1} (Tables 4 and 5). The appearance of a new band or shoulder at 998–1005 cm^{-1} in PEG 1500 (Fig. 9), 4000 (Fig. 10) and 6000 (Fig. 11) samples may be explained on the basis of an increase in amorphousness since this band is characteristic of amorphous or molten PEG. Conversely, the shoulder in this range was lost in indomethacin PEG 20,000 fused samples (Fig. 12). Similarly a decrease in intensity for the band at 1148 cm^{-1} was observed for PEG 1500, 4000 and 6000 samples but an increase in intensity was noted for PEG 20,000 containing 5% indomethacin.

Additionally, changes occurred in the ratio of the peaks at 845 cm^{-1} (CH_2 rock: CO stretch) and 960 cm^{-1}. The peak at 845 cm^{-1} is regarded as a crystalline band (Kuroda and Kubo, 1959) and broadens in the molten state and increases in intensity in crystalline PEG at the expense of the bands at 947/960 cm^{-1} (Miyake, 1961). For the dispersions in PEG 1500, PEG 4000 and PEG 6000 the bands at circa 960 cm^{-1} increased in intensity following fusion whereas that at the 845 cm^{-1} decreased. This is indicative therefore of increased amorphousness although no similar changes were apparent in the PEG 20,000 system.

Marked changes occurred in the spectra of all indomethacin–PEG samples in wavelength ranges 1000–1130 and 1200–1400 cm^{-1} (Tables 4 and 5). The changes in intensity of the broad band centred at circa 1115 cm^{-1} and shifted to a lower wavenumber are characteristic of PEG in its molten or amorphous state (Matsuura and Miyazawa, 1969), although the changes were less marked in PEG 20,000 samples. Matsuura and Miyazawa (1969) demonstrated changes in the amorphous state of PEG include transposition of bands at 1236 and 1244 cm^{-1} to a liquid band at 1249 cm^{-1} and the band at 1280 cm^{-1} moves to 1296 cm^{-1}. Additionally the bands at 1344 cm^{-1} and 1362 cm^{-1} transpose to 1352 cm^{-1} (CH_2 wagging). Davison (1955) indicated that broader peaks and a decrease in resolution was characteristic of the amorphous

state. Interestingly the PEG 20,000 samples showed an increase in peak separation and resolution in the range 1200–1400 cm^{-1}. All the indomethacin-PEG samples displayed on fusion a weak peak in the range 1325–1330 cm^{-1} (Figs. 9–12). Matsuura and Miyazawa (1969) reported that CH_2 wagging vibrations occur at 1326 cm^{-1} and is characteristic of PEG in the molten or amorphous state.

Additionally, the PEG 1500 samples containing 5% indomethacin displayed a new weak band at 1015 cm^{-1} and the PEG 1500, 4000 and 6000 samples decreased in peak intensity at 1062 cm^{-1} but not in PEG 20,000 samples. Matsuura and Miyazawa (1969) reported that in amorphous states the peak transposes to 1038 cm^{-1} and is assigned to a hybrid of CO and C–C stretching and CH_2 rocking.

Thus the general interpretation placed on these results is that for PEG 1500, PEG 4000 and PEG 6000 mixtures with indomethacin, fusion and recrystallization increased the amorphousness of the PEG. This effect was not as marked for the PEG 20,000 dispersions. The recently fused samples were, however, yellow in colour which can be attributed to the presence of amorphous indomethacin (Borka, 1974; Allen and Kwan, 1969; Saboe and Dempski, 1976).

The DSC data for these dispersions (Table 3) supports the IR in ranking the amorphousness within the dispersions. The heats of fusion decreased as the proportion of indomethacin increased in dispersions containing PEG 1500, PEG 4000 and PEG 6000. Conversely, for PEG 20,000 no decreases in the heats of fusion were observed with increased indomethacin content. The data can be used to estimate the crystallinity of the PEG moiety of the dispersion. Since there was no microscopical evidence for indomethacin crystallites it may be assumed that the melting endotherm corresponds only to melting of PEG. Using therefore the value of 51.5 $cal \cdot g^{-1}$ for 100% crystalline PEG 100% crystallinity within the dispersions would give heats of fusion of 50.5, 48.9 and 46.4 $cal \cdot g^{-1}$ for dispersions containing 2, 5 and 10% drug, respectively. This gives for instance percentage crystallinities of 78, 73 and 66% for PEG 1500 dispersions containing 2, 5 and 10% indomethacin, respectively.

Phenylbutazone systems

The changes induced by fusion and recrystallization of the phenylbutazone dispersions were less complex than those seen in the indomethacin systems (Figs. 13 and 14). Slight modifications at 755 cm^{-1} were noted (Table 6) and weak shoulders were lost at 1010, 1080 and 915 cm^{-1} in PEG 20,000 samples (Fig. 14). The band at 1065 cm^{-1} became more intense in PEG 6000 systems indicating that this dispersion contained more crystalline PEG than the prefused mix, since Matsuura and Miyazawa (1969) indicated that this peak was lost in fused or amorphous samples. The changes in the spectra of PEG 1500, PEG 4000 and PEG 6000 mixes containing 2% phenylbutazone in the range 1100–1130 cm^{-1} were similar (e.g. Fig. 13) to those observed in the indomethacin mixes since the bands became broader and reduced in intensity. Additionally, similar changes were apparent in PEG 1500 and PEG 4000 mixes containing 5% phenylbutazone indicating that for each of these five dispersions a decrease in crystallinity may have occurred. However, the remaining mixes (5% phenylbutazone in PEG 6000 and 2 and 5% in PEG 20,000) displayed an increase in resolution and intensity following fusion, indicating that these systems displayed an increased crystallinity in the PEG portion of the dispersion. Similar supportive evidence for increased crystallinity in some of the phenylbutazone systems was provided by the changes in the 1200–1400 cm^{-1} range (Table 6) predicting increased crystallinity in all the PEG systems except the PEG 1500 dispersions and PEG 4000 dispersions containing 5% phenylbutazone. Other changes included an increased intensity in the band at 1148 cm^{-1} for the PEG 6000 dispersions but a decrease in the same band for PEG 1500 and PEG 4000 dispersions containing 5% phenylbutazone. A new weak band at 1200 cm^{-1} was also apparent in some PEG dispersions containing 5% phenylbutazone (Table 6).

The overall pattern for the phenylbutazone dispersions is that contrary to the indomethacin dispersions, an increase in crystallinity of the dispersions may have occurred following fusion especially for the PEG 6000 and PEG 20,000 dispersions and possibly for the PEG 4000 dispersions. The band changes at 845 and 960 cm^{-1} indicated

that PEG 1500-phenylbutazone dispersions only displayed increased amorphousness since the band at 960 increased in intensity at the expense of the band at 845 cm^{-1}. The PEG 4000 and PEG 20,000 dispersions showed little intensity change at these wavenumbers but PEG 6000 dispersions actually showed an increased intensity at 845 cm^{-1} indicating increased crystallinity.

The DSC data for the phenylbutazone dispersions generally supports those proposed crystallinity changes. The heats of fusion (Table 3) decreased in PEG 1500 and PEG 4000 dispersions below that of the pure polymer as the phenylbutazone content increased and were lower than from the corresponding indomethacin dispersions. Expressed as percentages of the PEG content, values of 78–83, 86–87 and 93–98% crystallinities were obtained for PEG 1500, PEG 4000 and PEG 6000, respectively. The values for PEG 20,000 were, however, similar to those obtained for the indomethacin-PEG 20,000 systems.

General Conclusions

Although theory predicts that dissolution rates from solid dispersions at low drug levels is polymer-controlled (Corrigan and Stanley, 1982), these rates must in turn be controlled by the crystallinity of the polymer. It is apparent from the results reported here that phenylbutazone enhanced the crystallinity of PEG whereas indomethacin in solid dispersion with PEG tended to increase the degree of amorphousness within the polymer. Therefore the drug range over which PEG controlled indomethacin dissolution was wide (up to 15% drug depending on the carrier molecular weight) whereas PEG controlled the phenylbutazone release in the narrow range of 0–2% phenylbutazone. The results imply that the crystallinity of PEG also controls the drug release rate from solid dispersions. The effects on other drug–PEG systems is currently under investigation.

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