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Similarities in the release rates of different drugs from polyethylene glycol 6000 solid dispersions

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The dissolution rates (mg min^{-1}) of 10 drugs, solid dispersed by fusion in polyethylene glycol 6000 (PEG 6000) have been examined by rotating disc methodology. The dispersions generally displayed release rates which were linearly dependent upon the drug concentration (% drug) at high polymer content. However the range over which this linearity was encountered varied unduly, e.g. 0–2% for phenylbutazone and 0–15% for paracetamol. The slope of this line (mean value: 0·451 mg min^{-1} $\%^{-1}$) was statistically the same for nine of the drugs studied, the exception being griseofulvin which did not form a true solid dispersion but was a microcrystalline dispersion of the drug within the PEG. During fusion, chain scission of the PEG 6000 occurred in the presence of several drugs. PEG 6000 was incompatible with disulfiram, frusemide, chlorothiazide and chlorpropamide.

The dissolution of drugs from systems containing two components has been described by several mathematical models (e.g. Higuchi et al 1965; Corrigan & Stanley 1982). For non-interacting components, the models predict that the release rate of either component in the mixture is never greater than that of the pure component alone and are consequently inadequate in describing the drug release from solid dispersions where large increases in the dissolution rates of drugs have been claimed (Simonelli et al 1969). The transference of the drug to a higher energy form is a prerequisite for rapid dissolution and is most easily accomplished at high carrier levels when the carrier dissolves rapidly bringing the dispersed drug into solution. Drug release is then dependent upon the product of the carrier dissolution rate and the ratio of the drug present. Corrigan (1984) suggested that when the presence of the drug does not interfere with the dissolution of the carrier, the dissolution rate of different drugs at a given weight fraction should be the same. Ford & Rubinstein (1977, 1978) showed that linear relations exist between the intrinsic dissolution rates of solid dispersed drugs and their drug content (%) at high carrier weight fractions. This communication attempts to verify if the dissolution rates of drugs solid dispersed in polyethylene glycol 6000 (PEG 6000) are independent of the drug by estimating the slopes of dissolution rate versus dispersion content relation for 10 drugs.

Materials and methods

Fourteen drugs (all BP grade except Analar sulphaguanidine) and PEG 6000 (BDH) were used. The influences of heat and PEG 6000 on drug stability were assessed using a TLC method and four drugs (chlorpropamide, chlorothiazide, frusemide and disulfiram) were rejected on the basis of instability.

Dispersion preparation. Preliminary studies involved preparing PEG 6000 dispersions containing 5, 10 or 15% drug which was accomplished by fusion at the minimum temperature required to effect total solution of the two components. 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. The excess was sliced away to produce a smooth uniform surface prior to dissolution studies. Subsequently other dispersions containing 0·5, 1·0, 1·5, 2·0, 2·5, 3 or 7·5% drug were prepared as required.

Dissolution studies. Constant surface area methodology was used similar to that previously described (Ford & Rubinstein 1977, 1978). Dissolution rates were determined using the Copley Computerised Dissolution System series 8000. 1000 ml of distilled water, maintained at 37 °C, was used as the dissolution fluid and the discs rotated at 100 rev min^{-1}, 3 cm above the flat bottom of the flask. The drugs examined and the wavelengths (nm) used to measure their dissolution rates were: chloramphenicol (278), glutethimide (258), griseofulvin (291), indomethacin (320), paracetamol (245), phenacetin (245), phenylbutazone (264), succinylsulphathiazole (260), sulphaguanidine (265) and sulphamethoxazole (257).

Results and discussion

The dissolution profiles of the dispersions were generally linear. Dissolution rates (mg min^{-1}) were calculated by linear regression and are given in Table 1. Supersaturation and subsequent precipitation occurred following the dissolution of the indomethacin and griseofulvin dispersions. Table 1 indicates that at identical drug contents there were marked similarities in the dissolution rates of many of the drugs. The data, when plotted as a function of the drug content, produced a straight line up to an optimum concentration above which decreases in dissolution occurred. The slopes derived from the cumulative data of the individual drugs are given in Table 2, together with the limit of this linearity. The significance of the regression coefficients was $P < 0.001$ with the exceptions of

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Table 1. Summary of the dissolution rates (mg min^{-1}) of drugs solid dispersed in PEG 6000.

	Dissolution rates (mg min^{-1})									
Drug (%)	0·5	1·0	1·5	2·0	2·5	3·0	5·0	7·5	10·0	15·0
Chloramphenicol	—	—	—	—	1·19 (2)	—	2·74 (3)	3·37 (3)	4·59 (2)	7·69 (2)
Glutethimide	—	—	—	—	0·90 (2)	—	1·72 (2)	2·94 (2)	2·04 (2)	2·35 (2)
Griseofulvin	—	0·34 (2)	0·66 (2)	0·63 (2)	0·76 (2)	0·78 (2)	2·78 (2)	—	2·42 (2)	1·46 (2)
Indomethacin	—	—	—	—	1·26 (1)	—	2·73 (4)	3·42 (2)	4·67 (3)	6·09 (2)
Paracetamol	—	—	—	—	—	—	2·56 (2)	—	4·49 (2)	7·50 (2)
Phenacetin	—	0·47 (2)	—	0·91 (2)	—	1·20 (2)	2·35 (2)	—	1·70 (2)	1·70 (2)
Phenylbutazone	0·31 (2)	0·53 (2)	0·72 (2)	0·95 (2)	1·01 (2)	0·77 (2)	0·07 (2)	—	0·05 (2)	0·04 (2)
Succinylsulphathiazole	—	—	—	—	1·17 (2)	—	2·21 (2)	3·17 (2)	4·09 (2)	4·98 (2)
Sulphaguanidine	—	—	—	—	1·37 (2)	—	2·37 (2)	3·60 (2)	4·57 (2)	5·71 (2)
Sulphamethoxazole	—	—	—	—	1 30 (2)	—	2·55 (4)	3·49 (2)	*	*

Numbers in parentheses refer to number of replicate determinations. * Too inconsistent for means to be calculated. — Not studied.

glutethimide and griseofulvin. The lower significance of the glutethimide–PEG 6000 data is due to the poor reproducibility of dissolution rates from this system (Ford 1984). No straight line relation existed between griseofulvin dissolution rate data and drug content. Microscopic examination of this system revealed the presence of drug crystallites which were not apparent in any of the other dispersions examined. Although increased dissolution rates of griseofulvin were achieved following its dispersion in PEG 6000 (Chiou & Riegelman 1969) our findings confirm the belief of Simonelli et al (1971) that rapid conversion of griseofulvin from a high energy phase to crystalline drug occurred on storage. The presence of drug crystallites explains the apparent anomolous behaviour of this system.

There is a striking similarity in the derived slopes in Table 2. Using a Null-hypothesis data treatment for the test for parallelism, all the slopes were statistically similar ($P < 0{\cdot}01$). The weighted mean of these slope values was 0·451 mg min^{-1} %$^{-1}$. The data confirms the suggestion of Corrigan (1984) that dissolution rates from solid dispersions at high carrier levels is independent of the drug which they contain. However the range of carrier dominated dissolution rates varied considerably from 0–2% for phenylbutazone to in excess of 15% for paracetamol. The ranges are not related to solubility since phenacetin has an aqueous solubility of 0·77 mg ml^{-1} and a range of 0–5% whereas indomethacin (solubility: 0·04 mg ml^{-1}) was linear over the range 0–10%. The concentrations above those which gave maximum release rates represent the state when excess drug is liberated and forms a discrete drug layer at the dispersion surface which reduces dissolution rates.

Table 2. The effect of drug variation on the slopes (mg min^{-1} %$^{-1}$) of the straight lines obtained by plotting drug dissolution rate (mg min^{-1}) as a function of drug concentration (%).

Drug	Slope (mg min^{-1} %$^{-1}$)	Regression* coeff. (r)	Maximum drug concn used to calculate slope (%)
Chloramphenicol	0·484	0·977 (9)	10
Glutethimide	0·408	0·920 (6)	7·5
Indomethacin	0·415	0·975 (10)	10
Paracetamol	0·494	0·986 (6)	15
Phenacetin	0·466	0·990 (8)	5
Phenylbutazone	0·422	0·960 (8)	2
Succinylsulphathiazole	0·401	0·999 (6)	7·5
Sulphaguanidine	0·433	0·993 (8)	10
Sulphamethoxazole	0·437	0·991 (8)	7·5

* All were significant at $P < 0{\cdot}001$ except glutethimide ($P < 0{\cdot}01$). Numbers in parentheses refer to number of data points used to determine regression slope.

The data presented here suggest that most solid dispersions in PEG 6000 and prepared by the melt method behave similarly. Because the carrier controls dissolution rates at low drug levels, PEG 6000 dispersions are suitable only for low dosage drugs since the amount of PEG required to increase satisfactorily the dissolution rates of high dosage drugs would be prohibitively high. The dissolution rates of dispersions at low drug content are controlled by the dissolution of PEG 6000 only, and are independent of the drug they contain.

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